

Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 42

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

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**RECOLLECTIONS OF THE HISTORY OF  
NEUROPSYCHOPHARMACOLOGY THROUGH INTERVIEWS  
CONDUCTED BY LEO E. HOLLISTER**

Edited by

Peter R. Martin and Thomas A. Ban



Leo E. Hollister (1920 – 2000)

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## PREFACE

This volume is a compendium of interviews conducted by Leo Hollister as part of a major project of the American College of Neuropsychopharmacology (ACNP). Of the 238 interviews of neuropsychopharmacologists conducted at the close of the twentieth century under the aegis of ACNP and published in ten volumes<sup>1</sup>, Leo Hollister participated as the primary interviewer in thirty-four<sup>2</sup>. These interviews conducted by Hollister provide an unusual insight into the field of neuropsychopharmacology by virtue of the number and diversity of the subjects whom he interviewed. Moreover, this volume assembles in archival form, and thus, may be viewed as another of the many important contributions of Hollister to the field of neuropsychopharmacology—communicating his wide understanding of the actions of pharmacological agents that affect the brain and his wisdom about their potential uses in man for therapeutic purposes. To offer the reader the opportunity to hear Hollister’s own voice, two interviews of Hollister himself, conducted by Frank Ayd on December 9–13, 1996 and Thomas Ban on April 6, 1999 are included to complete this volume.

I was particularly interested in the perspective of Hollister because I very much identified with him. I also began my career as an internist and became interested in psychopharmacology as a result of my training in clinical pharmacology at the Addiction Research Foundation at the University of Toronto. Whenever I encountered Hollister’s work in the early 1980s, I was struck by the clarity of thought and his capacity to explain the pharmacologic actions of psychopharmacological agents. These drugs had become widely used by psychiatrists as the field

<sup>1</sup> Ban TA (Editor). An Oral History of Neuropsychopharmacology. The First Fifty Years. Peer Interviews. (Volumes 1-10). Nashville: American College of Neuropsychopharmacology. 2011.

<sup>2</sup> The edited transcripts of the 34 interviews Leo Hollister conducted were first presented in the following volumes of the Oral History series: Frank Ayd Jr, Joseph Brady, Albert Kurland, Stephen Szàra, and Joseph Wortis in Volume One – Starting Up, edited by Edward Shorter; George G Aghajanian, Irwin Feinberg, and Samuel C. Kaim in Volume Two - Neurophysiology, edited by Max Fink; Julius Axelrod, Frank M. Berger, James V. Dingell, Silvio Garattini, Candice B. Pert, and Fridolin Sulser in Volume Three – Neurophysiology, edited by Fridolin Sulser; Joseph Autry III, Thomas A. Ban, Jonathan O. Cole, Donald F. Klein, Douglas M. McNair, Allen Raskin, George M. Simpson, Oldrich Vinar, and David Wheatley in Volume Four – Psychopharmacology, edited by Jerome Levine; Bernard J. Carroll, Angelos E. Halaris, and David S. Janowsky in Volume Five – Neuropsychopharmacology; Jack Blaine, Jerome H. Jaffe, Donald R. Jasinski, Charles P. O’Brien, and Roy W. Pickens in Volume Six – Addictions, edited by Herbert Kleber; and Roger M. Maickel and Alexander M. Mathé in Volume Eight – Diverse Topics, edited by Carl Salzman. The text of the interviews in this volume is based on text in those seven volumes. Yet, because of further editing, the interviews in this volume are not identical to the interviews in the “oral history” series.

transitioned from psychoanalysis. However, psychiatrists possessed remarkably little understanding of the emerging discipline of clinical pharmacology which could greatly clarify psychiatric pharmacotherapy (at least that was my opinion, as I was transitioning from clinical pharmacology training in internal medicine to a residency in psychiatry). Hollister often served as an interpreter to psychiatrists to help them better utilize psychopharmacological agents and did so with talent and good nature. He viewed the effects of psychopharmacological drugs on the entire body, not simply the mental state, and that appealed to me very much. He felt equally comfortable expounding on the effects of lithium on glomerular function, as on the effects on the thyroid, and the efficacy of lithium in bipolar disorder.

Leo Hollister was an astute clinician who was there at the introduction of psychotropic drugs in the United States. He was among the first to note the beneficial effects of chlorpromazine and reserpine on aspects of psychotic mental state and behavior. Hollister's clinical focus is quite apparent from his quotation: "If you watch your patients, you can learn a lot." He became expert in the clinical psychopharmacology of many of the medications used by psychiatrists without ever becoming trained as a psychiatrist; rather, he was a clinical observer and consultant in the great tradition of internal medicine.

Hollister was born and raised in Cincinnati where he became interested in drugs while working in a pharmacy as an undergraduate at the University of Cincinnati. After completing his residency in internal medicine, in 1951, he began work at the Veterans Administration (VA) Hospital in Palo Alto, California, where he would spend the majority of his career. Here he served as the internist working at essentially a psychiatric hospital. Hollister's work at Palo Alto, while he was chief of the medical service, abruptly transitioned into psychopharmacology after he introduced reserpine as an antihypertensive at the VA and recognized antipsychotic effects of this agent in the psychiatric patients under his care. At Palo Alto, he pioneered designs of clinical trials and eventually served in a leadership role in the VA Cooperative Studies Program, which conducted large multi-center trials confirming the effectiveness of the new psychotropic agents, the use of which he pioneered in his own clinical work.

His interest in drug addiction and bringing to this field the perspective of clinical pharmacology were very attractive to me at the time of my own entry into the field via clinical pharmacology and internal medicine. In particular, I read with interest Hollister's seminal observations of withdrawal reactions observed after prolonged high-dose use of central nervous

system depressants like meprobamate and chlordiazepoxide. This description of hyperactivation of the central nervous system as a result of drug discontinuation truly fascinated me and became the focus of my earliest research and my thesis.

Leo Hollister's incredibly broad knowledge base is amply demonstrated in the interviews he conducted as part of the ACNP project. Not only did he understand the key historical issues—the precursors and consequences of each discovery—he seemed to have personally met and knew well all the protagonists in each of the stories related by the neuropsychopharmacologists he interviewed. He seemed to have valuable opinions in all these conversations, opinions that were fascinating and enlightening for those interested in history of the field of neuropsychopharmacology. He, himself, seemed truly to find historical developments compelling—this appreciation of the history of the field of neuropsychopharmacology is clearly shown by this short exchange that Hollister had with Tom Ban many years before Ban formally proposed the publishing of what was to become the “oral history” series<sup>3</sup>:

*Hollister:* I think these kinds of interviews are very good, historically, but I'm still a print man. This project with all the visuals is important but I still would like to see something in print.

*Ban:* We seem to have the necessary information in these interviews to present in print a coherent account on the history of the field. Do you think it would be a worthwhile undertaking?

*Hollister:* I think it's a worthwhile undertaking, yes. Many organizations start off with no concept that they are going to want someday to know what their history was, and so they ignore it for the first decade or two. And then, all of a sudden, someone says, "Gee whiz, we've got a history!"

*Ban:* We are ready to do it. That's all I can say.

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

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<sup>3</sup> Interview by Leo Hollister of Thomas Ban, on December 9, 1996.

assemble this volume of the interviews conducted by Leo Hollister which were initially published under the imprimatur of American College of Neuropsychopharmacology.

Peter R. Martin

Nashville, Tennessee, U.S.A.

January 3, 2014.

## 1. GEORGE K. AGHAJANIAN

LH: Las Croabas, Puerto Rico, where we are about to interview an old hand in the field, George Aghajanian.\* I'm Leo Hollister and I'm joined by Tom Ban in doing this interview with George. George, how did you get started in medicine and pharmacology? What influence persuaded you to make a career this way?

GA: Well, actually, I was interested in engineering first and all through high school that was my leaning. There is one branch of my family, especially an uncle who was involved in engineering in the early part of the century pioneering the development of machine tools. So, I had an interest there. But, once I got to college, I started veering more toward medicine and became a pre-med, and finally went to medical school.

LH: Now, you went to Yale for both of your, undergraduate and postgraduate studies?

GA: No, I went to Cornell for my undergraduate studies. My postgraduate work was at Yale Medical School.

LH: And then, once at Yale, you stayed?

GA: Pretty much, except for a year of internship, and a tour in the army. In those days, there was a doctor's draft, the Berry plan. I had to put in my two years' service in the army.

LH: Well, didn't you already start your training in psychiatry?

GA: Yes, I had postponed the army requirements until after I finished not only residency but also two years of post-doctoral studies. I went in the army when I was about thirty, when they finally caught up with me.

LH: But, by that time you had a lot of training under your belt. Did the army make use of them?

GA: Yes, they did. I was trying to switch out of the Army into the Public Health Service and go to NIH. But in the course of this attempt, when the Army heard I had experience in psychopharmacology research and, particularly, with LSD, they said, "Oh, we want this guy."

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\* George K. Aghajanian, M.D. was born in Beirut, Lebanon in 1932. He graduated from Yale Medical School in 1958 and he joined the department of pharmacology in 1970. He is professor of psychiatry and pharmacology at Yale School of Medicine. His research contributed to the discovery of some of the essential properties of serotonergic, noradrenergic, and dopaminergic neurons. He was interviewed by Leo E. Hollister and Thomas A. Ban.

They sent me directly to Edgewood Arsenal, the Army Chemical Center, to work on incapacitating agents that might be used in warfare. That was their idea at the time but no longer is.

LH. I'm reminded of when I was first starting to work with reserpine, one of our staff in the hospital had the idea that we could store the reserpine in Russian reservoirs and tranquilize them. So, both sides were thinking the same thing.

GA: People had some pretty odd ideas about that at the time. First, the Army had the lethal agents program with the acetylcholinesterase (AChE) inhibitors. But later, they also had an "incapacitating agents" program that included very high potency antimuscarinic compounds.

LH: The BZ series.

GA: Yes. That was the code name for the most potent one. They also had the LSD program.

LH: I would say that outside of botulinum toxin, LSD is the most powerful biologically active substance known.

GA: Certainly, at the time, it was one of the most potent substances known.

LH: Well, it's hard to beat that. One milligram a day is all you need and that's pretty good. OK. What did you do after the two-years in the army?

GA: After I came out of the army in 1965 I returned to Yale and got an NIMH career development award. It made it possible for me to learn certain basic sciences. I started in electron microscopy and histochemistry, but in two or three years I shifted into electrophysiology.

LH: So you were preparing for a research career in neuropsychopharmacology.

GA: In that regard, the person, who had probably the biggest influence on me, was one of the founders of ACNP, the late Daniel X. Freedman. Incidentally, I understand it he was the person who influenced ACNP to have their meetings in Puerto Rico. He was my thesis advisor when I was a medical student.

LH: So, Danny was in the department of psychiatry at the time.

GA: Yes. When I was a medical student in the late 1950's, he was a young faculty member in a department that predominantly was psychoanalytically oriented.

LH: That was when Mort Reiser was chairman?

GA: Before that.

LH: When Fritz Redlich was chairman?

GA: Yes, Fritz Redlich was the chairman at the time and his interests were quite eclectic, although he came from an analytic background. But there were Ted Lidz, Steve Fleck and many others in the department who had a dynamic, analytic orientation. It was a very interesting department; they were quite good in psychodynamics. It was Danny Freedman in the late 1950s who came along and started the biological program in the department.

LH: He was working on it, primarily with Nick Giarman.

GA: That's quite right. Your memory on that is very good. Nick Giarman was in the pharmacology department and it was through Nick Giarman that Dan Freedman was able to get a program going in neuropsychopharmacology. It was very much a joint program of the departments of pharmacology and psychiatry. So, Dan really was responsible for getting quite a number of people started in the field. I think that was one of the first training programs in neuropsychopharmacology.

LH: Who were some of the others in the program?

GA: Herb Meltzer and Jack Barchas were medical students like me at the time. Jack Barchas was in the class behind me in medical school.

LH: So the program was quite an incubator for neuropsychopharmacologists.

GA: Yes, Dan Freedman was a magnet for people who were interested in neuropharmacology and psychopharmacology.

LH: Was he always as nice a guy as I know him?

GA: That was my entire experience with him. He was always very encouraging to young people.

LH: He was really a fine gentleman.

GA: That was very important in the late 1950s and early '60s for someone starting out in the field of neuropharmacology to have encouragement because that was not the accepted way in psychiatry at that time. I was actually told that there would be no future for someone like me in academic psychiatry without getting analytic training. In fact, Dan did that even while bringing forth his neuropharmacology training program.

LH: Well, he had a degree in psychology, as well, didn't he?

GA: Yes, I think at a college level. I don't think he had a PhD in psychology.

LH: So, do you suppose then that Nick's interest got you into research?

GA: Yes, along with Danny. I did my medical school thesis on LSD. People today wouldn't believe that LSD was not a controlled substance at that time.

LH: You could order it from the drug company.

GA: From Sandoz. Sandoz would send it out to any physician who wrote in a request for it. There were ampoules of LSD lying around all over the place.

LH: I've still got some 100 milligrams of LSD powder to make a solution. You could order it from biochemical supply houses without any control.

GA: Dan left a supply of LSD with me when I was a medical student, between my junior and senior years. I was doing a behavioral study on LSD when he went for sabbatical to NIH for a year. So he just left with me a large supply of ampoules.

LH: What year was that?

GA: That would have been the summer of 1957.

LH: That was pretty early in the game, wasn't it?

GA: Yes, it was.

LH: It's pretty amazing that from 1943, or whenever the accidental discovery was made, how the number of papers on LSD started to escalate.

GA: It was only in 1953 and 1954 that the interaction between LSD and serotonin was discovered and the possible relevance of this interaction to the biochemistry of mental illness raised. The structure of serotonin had been discovered only a relatively short time before that. So, it was only about three years later; Giarman had just come back from a sabbatical in Gaddum's laboratory in England. Gaddum was one of the co-proponents of the serotonin hypothesis of LSD's action mechanism.

LH: He developed a hypothesis about schizophrenia based on the antagonism between LSD and serotonin. Now, who was the other guy who got the same idea from New York?

GA: Woolley.

LH: Woolley, Woolley and Shaw.

GA: Right, they started in with their research in New York about the same time as Gaddum was doing his work in England. Gaddum first published on this work in 1953 and Woolley and Shaw in 1954.

LH: Well, but they weren't using it as a neurotransmitter.

GA: They had no idea about its role of a neurotransmitter. The serotonergic systems had not been discovered until 1965.

LH: It was probably all done in platelets.

GA: By 1953, it was known that serotonin was present in the brain. Nick Giarman thought of it as a neurohumoral substance. He referred to it as a substance that was present in the brain. There was no specific knowledge that it was actually within a specific set of neurons and might be a transmitter used by those neurons. That wasn't really known until 1965.

LH: Well, I suppose that Brodie and his crew established prior to that that serotonin has an important role in the action of reserpine.

GA: Certainly. Levels could go up and down; reserpine could deplete serotonin in the brain, but it wasn't known where the serotonin was in the brain. They were working with whole brain, with brain homogenates. At that time, nothing was known about the neurotransmitter role or localization of serotonin. All those classical studies of Brodie, Carlsson, Freedman, and others were done on brain homogenates. It was Freedman who found in those days, that LSD affected the levels of serotonin and its metabolites in the brain.

LH: I think it was also Danny Freedman and Nick Giarman who came up with the idea first that LSD produces a model psychosis by affecting serotonin.

GA: Well, I think by the time they suggested that in the 1950s the model psychosis idea was around quite widely.

LH: I used to have friendly arguments with Danny about just how good the LSD model was for schizophrenia. But, regardless, he certainly started you out on a trail of neurotransmitters. You've studied them over the course of a long time.

GA: I started as assistant professor in the department when I got back from the army. It was at the time when the discoveries of the Swedish histochemists were published showing for the first time that the origin of serotonin is in the raphé neurons of the brain stem and the fibers from those cells containing serotonin projected to all other parts of the brain. The information on the release of serotonin came just a little bit later. In one of my first studies I was showing an increase of serotonin metabolites in different parts of the brain after electrical stimulation of the raphé neurons in the brain stem. This was indicative that serotonin had been released.

LH: Did you measure it chemically or histochemically?

GA: I measured it chemically. That was about 1966 or '67.

LH: That was when fluorescence made the scene.

GA: Fluorescence measurements were already on the scene. That was the time when I switched to electrophysiology because I thought that the activity of these neurons might be very important

for determining what their function was. I had no background in electrophysiology, but I was able to make interested a post-doc in the neighboring laboratory of the late John Flynn from Yale, in starting some studies of this nature. We did our research at night. On the basis of Danny Freedman's findings that LSD raises the levels of serotonin but decreases its metabolites, I hypothesized that LSD might be inhibiting the firing of serotonergic neurons and as a result the released neurotransmitter would back up but its metabolites would go down.

LH: Well, that's one of the possibilities, isn't it?

GA: We did the first experiment one night in the winter of 1967, and it did work. Nine out of ten, or ninety-five out of a hundred of my hypotheses do not pan out, but that one did. So, I became a confirmed electrophysiologist from that time.

LH: Well, over the years, I noticed, you published papers with three ACNP presidents: Danny Freedman, Floyd Bloom, and, more recently, Steve Bunney.

GA: Yes. Floyd Bloom and I were in the same laboratory studying electronmicroscopy in the 1960s. Steve Bunney was one of the first post-doctoral students in my laboratory. He was a resident in our program in the early 1970s.

LH: And, that's where he learned his electrophysiology?

GA: Yes. His older brother, William Bunney or Biff Bunney, whom I had known for some years because we overlapped in residency at Yale, Biff steered Steve my way. Steve started with no experience, whatsoever, as a post-doc in my laboratory.

LH: The first time I ever heard Steve Bunney give a paper it was at the ACNP meeting in Phoenix I think. I was impressed and afterward I asked him, "Why don't you get your older brother to nominate you for membership of this organization"? And he did. Well, if you had to pick out of your many papers, two or three that you think it represents your best work which ones would you pick?

GA: The papers describing the recording of the electrophysiological properties of the monoaminergic neurons; it was made possible after the Swedish histochemists published maps showing where they were. The first recording of this kind were of the effect of LSD on the firing of serotonergic neurons. Then, within the next two or three years in my lab, we went on to record from the dopaminergic neurons and noradrenergic neurons at a locus coeruleus. That series of studies and the ensuing papers represent my best work. They were the first recordings from monoaminergic neurons and described their basic electrophysiological properties and the effects

of drugs on their firing rate. So, that started off many studies in this area of research and, as you know, became a major industry.

LH: Oh, yes.

GA: We did that early work in a period of five years starting in 1967 and running until about 1973. We did the LSD studies and described the electrophysiological properties of serotonergic neurons in 1967 and '68 and published our findings in *Science*. We did the first studies on noradrenergic neurons in 1971 with a medical student working for the summer in the lab. Then, when Steve Bunney came along, his project was to record from dopaminergic neurons - that was in '73.

LH: Was he doing it in a single neuron?

GA: Yes, in single neurons. Many, many of the properties of the monoaminergic neurons that are well known today were discovered in those studies. We learned in those studies that serotonergic neurons are releasing serotonin at all times in very slow tonic firing; that the tonic firing of noradrenergic neurons is very reactive to sensory stimuli; and that the firing of dopaminegic neurons is affected by amphetamines and antipsychotic drugs. One of the main principles derived from those studies is that monoaminergic neurons have autoreceptors in the somatodendritic region for their own transmitters and that these autoreceptors serve as a negative feedback regulating their activity.

LH: Well, that's an established principle now.

GA: Yes, that principle was derived from findings in these early studies.

LH: That's landmark work.

GA: It had a major impact for many years on the development in that field through the work of many, many investigators.

LH: Did you ever think that serotonin would be as versatile as it seems to be?

GA: I certainly did not.

LH: I don't think anybody did.

GA: I remember when Eli Lilly was developing fluoxetine in the early 1970's; they were not very confident that they were working on a drug that had any future. But there were a few people who did.

LH: More in Europe than in America.

GA: You're absolutely right there. In Britain, there were those who were inclined toward thinking that serotonin would have a role in affective disorders. Also, in Sweden, Arvid Carlsson believed that serotonin might be important for depression. In fact, Arvid Carlsson was involved in the development of a serotonin reuptake inhibitor, zimelidine.

LH: That looked pretty good for some time, didn't it?

GA: Yes but it had certain toxicities and was dropped. Meanwhile, Eli Lilly was developing fluoxetine, but because the developers were not very confident about the prospective marketing of the drug, the basic science work went on for some years before fluoxetine got into clinical testing.

LH: You know if you look back, though at both, imipramine and amitriptyline were also serotonin uptake inhibitors, but they, also, had an effect on norepinephrine. I always used to joke that in this country we bought more norepinephrine than in Europe, whereas in Europe they had bought more serotonin.

GA: In recent years, because of many atypical antipsychotic drugs block the 5HT2A receptor, interest in serotonin everywhere was reawakened.

LH: Do you think that has anything to do with their antipsychotic action?

GA: The most critical test of this is currently ongoing. The atypical antipsychotic drugs that we had in the past have also other actions. Of course, it's difficult to sort out the 5HT2A blocking component in their action from the other components. Among the currently used drugs, risperidone, comes the closest to testing the relationship between blocking 5HT2A and antipsychotic action. It has a very high potency in blocking 5HT2A receptors. It is about ten times more effective blocking 5-HT2A receptors than D2 receptors. Risperidone has now been clearly shown to be an effective antipsychotic, and that it has antipsychotic effects in a dose range where primarily it occupies 5HT2A receptors without occupying D2 receptors. In higher dose range, risperidone will occupy D2 receptors and produce extrapyramidal side effects.

LH: Oh.

GA: There is a drug, which was originally called MDL 100907 and, after the takeover by another corporation, is called now M100907 because the new company couldn't get that many digits into their coding system. It has just gone through Phase-III clinical trials.

LH: Now, is M100907 solely a 5HT2A blocker?

GA: It doesn't touch D2 receptors.

LH: Well, we shall see. I've been of the opinion that all of the atypical antipsychotics have in common a weak D2 antagonism and that D4 or D1 antagonism doesn't mean a damn thing.

Probably serotonin antagonism doesn't mean anything, but I may be completely wrong on that.

GA: That's why this new drug, MDL 100907 is so important.

LH: Well, was not ritanserin blocking selectively serotonin receptors?

GA: Ritanserin does block 5HT2A receptors, but it also blocks 5HT2C receptors, and it also interacts with a number of other receptors, so it is not quite as suitable for testing the relationship between blocking 5HT2A and antipsychotic effects.

LH: It bombed out as an antipsychotic.

GA: It was said to be useful in improving negative symptoms, but maybe not the positive symptoms. It's quite interesting that ritanserin doesn't seem to do the trick, even in animal models.

LH: So, it's not a true test of the idea?

GA: MDL will be the true test and the results are being analyzed now. But the question in my mind is that being so selective, as we believe it is whether it would work, and if it works would it be in just a subset of patients? Probably, all schizophrenias are not the same and it might pick out a subset of schizophrenias where the 5HT2A receptor is important in the pathophysiology; whereas, it might not have an effect on other schizophrenias where the 5HT2A receptor is not involved. But, that could bring me to the topic of a recent research of mine. I'm inclined to think these days that it's really not the monoamine receptors that are primarily involved in antipsychotic effects, although they may have some impact. I don't think the existing antipsychotic drugs are so effective anyway. We know that schizophrenic patients are not going to pop back to normal living after they are given an antipsychotic drug. So, in our recent research we are studying whether an abnormality of glutamate release might also be involved. We were led to this hypothesis by studies on the mechanisms of 5HT2A receptor activity, and the recognition that the 5HT2A receptors are concentrated in the cerebral cortex. It makes a lot of sense that they are concentrated in the cerebral cortex because psychedelic hallucinogens that work through the 5HT2A receptor and, possibly, to some degree also through the 5HT2C receptor, produce not only hallucinations and illusions but have an effect on all cortical functions, including cognitive and affective. In recent years we've been studying, electrophysiologically, the role of 5HT2A receptors in the psychoses induced by hallucinogens.

We found that that hallucinogens work as partial agonists of 5HT2A receptors in that they don't have serotonin's full effect. What makes a hallucinogen we believe that they lack the other actions of serotonin that counterbalance the dramatic increase in 5HT2A receptor activity. In other words, they leave the increase of 5HT2A activity unopposed. However, it is not necessarily the overactivity of 5HT2A receptors that produces the hallucinogenic effect but rather, as our studies show, it is an abnormality of glutamate release that might be responsible for endogenous psychoses. If over activity of 5HT2A receptors were responsible, then drugs that block 5HT2A receptors should work right away. However, they don't. Even with MDL 100907, there seems to be a two, three or four week delay in the onset of therapeutic effects. Currently there are also ongoing studies with the ketamine model of psychosis. Ketamine is an antagonist of one type of glutamate receptor, the NMDA receptor. The ketamine-model of psychosis at first glance seems to be a completely different model from the LSD, or psychedelic hallucinogen model of psychosis.

LH: I thought it was a much more realistic model.

GA: People have debated that because there's some overlap between the two models. One obvious difference is that NMDA receptors are blocked with ketamine but not by the psychedelic hallucinogens. Recently, however, Bita Moghaddam, a member of ACNP, found that ketamine induces an increase in glutamate release in the cortex and since the effects of psychedelic hallucinogens have also been attributed to an increase of glutamate release, the two models seem to share a common mode of action. There are also findings in PET imaging studies in Europe that have shown hypofrontality, similar to that seen in schizophrenia, after the administration of mescaline, a psychedelic hallucinogen, and also after the administration of ketamine. During the past few years the so-called metabotropic glutamate autoreceptors have been discovered and it has been shown that glutamate can act on these autoreceptors to suppress glutamate release by a negative feedback mechanism. In this respect the glutamatergic system is analogous to the monoaminergic system where monoamines can act on their autoreceptors to suppress monoamine release. At this time, agonists of these metabotropic autoreceptors have been developed that can block the effect of psychedelic hallucinogens. This fits with the idea that the effects of psychedelic hallucinogens are mediated through an excessive release of glutamate. Furthermore, Bita Moghaddam has also shown that the same metabotropic receptor agonist that blocks the excessive release of glutamate induced by ketamine or PCP, also blocks the

behavioral effects of these substances. So, we have at this time two glutamate models of psychosis, a psychedelic hallucinogen model and a ketamine/PCP model.

LH: I would have thought so because, clinically, the differences are substantial.

GA: That's quite true. One of the major differences is that there is blockade of NMDA receptors in the ketamine PCP model.

LH: Then there's also a glutamatergic-dopaminergic link.

GA: Where that fits into the picture is a little unclear. Bita Moghaddam has shown in her studies, that PCP and ketamine increase dopamine release, but metabotropic receptor agonists don't interfere with that effect. So, we've got a new ball game here.

LH: How exciting! I'd given up on hallucinogens.

GA: It's so exciting that Eli Lilly has become the leading developer of metabotropic receptor agonist drugs. These drugs are analogs of glutamate with different side groups. It had been believed that such drugs would not enter the brain, because they are too polar. But, Lilly has succeeded in developing very highly potent agonists, with nanomolar potency, that can be given systemically and enter the brain.

LH: Are they actually bioavailable or do they just overwhelm you with their potency?

GA: They have surprising bioavailability. They may be, actually, transported into the brain, but that's not been established yet.

LH: I think they are transported into the brain.

GA: They might be transported through amino acid transporters, but that has not been shown yet. These drugs are effective in animals in very reasonable doses. They were originally developed for use in treatment of anxiety disorders and are being used currently in clinical trials in these disorders. But now, because of the new findings that implicate excessive glutamate release in both the ketamine/PCP and psychedelic hallucinogen models of psychosis, Eli Lilly, through Bita Moghaddam's and our efforts, is contemplating clinical trial in schizophrenia with these substances. We're anxiously awaiting the inception of those trials. I've just brought you right up to the present.

LH: This is exciting because, I guess, we've been desperately trying to get off the dopamine hypothesis.

GA: This even gets us off the serotonin hypothesis and gets us to the glutamate hypothesis, because all roads lead to either glutamate or GABA. One can think that monoamines are interacting

with their G-protein coupled second messenger pathways influencing gene expression, but in terms of their immediate electrophysiological effects the main function of monoamines is the modulation of excitatory and inhibitory amino acid transmission.

LH: GABA and glutamate are far more abundant in the brain than monoamines, aren't they? We talk so much about the amines, but they are there in relatively small amounts.

GA: Right. So one can think of a defect downstream of the monoamines and a defect, let's say, in the glutamate release mechanisms. Monoamines through their action via monoamine pathways may have some influence on a defective glutamate release mechanism. Perhaps the influence will not be great enough and will be too slow in coming to translate into optimal efficacy. So, we are hypothesizing that the monoamines have a rather indirect and distant influence on what may be the core pathology, which would be downstream, involving glutamatergic or GABAergic transmission. What might provide specificity is that the metabotropic receptors which modulate glutamate release and transmission are expressed differentially in the different parts of the nervous system. There's one type of metabotropic receptor that's very strongly expressed in the cerebral cortex in fibers that, we think, are involved in the action of the psychedelic hallucinogens.

LH: This isn't history. This is bringing us up to date. I never realized all these things are going on.

GA: I would say there are a good dozen posters on studies dealing with metabotropic glutamate receptors at this meeting.

LH: Well, out of five hundred posters it's hard to find a dozen.

GA: Eli Lilly has already shown that one can make highly selective drugs that hit predominantly one or another subtype of metabotropic receptor. So it's going to be very exciting in the coming years to see how these drugs, with an action on different subtypes of metabotropic receptors, will affect mental functioning and, ultimately, to see what therapeutic benefit their use might have. The first of these drugs, LY354740, as I mentioned earlier, has already been tested in anxiety disorders and does seem to have anxiolytic properties. Moreover, these drugs should work very rapidly because they reach to the heart of the matter rather than influencing it indirectly as the monoamines have been doing.

LH: Well, there are lots of surprises. So, you come from monoamines all the way up to glutamate and all the other transmitters.

GA: To me, the connection with glutamate was a surprise. We started only three years ago with these studies looking at the effect of 5HT2A receptors on glutamate transmission and, at that time, we had no idea how the metabotropic agonists might fit into that scheme. Nor did we have any idea that there were drug companies developing selective agonists of metabotropic receptors that would block the effects of hallucinogens.

LH: Well, that's a novelty in itself.

GA: This has all happened in the last two or three years.

LH: Well, you've had a really exciting career.

GA: Yes, it's very exciting. One difference between the way things were in the 1960s, when I got started, and are now is that there was very little knowledge about brain systems at the time. It would take years to follow up any findings, but now things happen very quickly. The base of knowledge is expanding so much that it makes one envious of the people who are starting out now. The knowledge basis is so now much greater and the tools one has to work with are so much better than they were. The one way I would not be envious is that people starting out now have a tougher road, because there's greater competition. There are so many more people in the field. When I was starting out, there was hardly anyone doing what I was doing. In fact, there was no one doing what I was doing. But now, that's not the case. A young investigator comes up with some novel finding, and in no time at all, ten of the labs will be doing it.

LH: One of the sad developments is the fact that people are reluctant to share their new information for fear that it will be co-opted by somebody else.

GA: When I started recording from monoaminergic neurons, no one else was doing it, and it took, actually, several years before other people started doing that.

LH: Now, it would be several weeks.

GA: Yes, I think so.

LH: Well, thank you, George, for coming by and sharing parts of your most interesting career. I think we're going to have you back in another ten, or fifteen years to bring the history really up to date.

GA: Well, I don't know about that because I've developed another interest, which might have a higher priority in the next ten or fifteen years. That's a game that one plays with a funny looking stick with a head at the end of it and there's a little white ball and you kind of hit it down a fairway. Well, I've been corrupted.

LH: See, he makes you think that you've got a few good shots and he makes you think that you can do that. Well, thanks for spending some time tracking the electrophysiology of neurotransmitters and I wish you a lot of luck. And I'm sure that Tom does, too, because, as clinicians, we feel very deprived, not being on the forefront of things and not having as many things to offer patients as we would like.

## 2. JOSEPH AUTRY, III

LH: Today is April 15th, Tuesday, 1997. We are in Washington, DC, and doing a series of tapes, sponsored by the American College of Neuropsychopharmacology. I'm Leo Hollister, and my guest today is Dr. Joseph Autry.\* Welcome, Dr. Autry.

JA: Thank you.

LH: First of all, I detect a somewhat different accent from the usual American accent and in looking over your CV I found that you graduated from the University of Rhodes, which I didn't recognize as an American University. Is that Rhodesia?

JA: No, it's Rhodes University in Memphis, Tennessee.

LH: Really?

JA: It's a small private Presbyterian college.

LH: I'll be damned. That really surprises me. So, Memphis, TN, and then you went to the University of Tennessee for your MD degree.

JA: That's correct.

LH: And how did you get into psychiatry?

JA: Well, I guess it started in undergraduate school. I started out majoring in chemistry and math; got bored with math and picked up a second major in psychology. I became interested in doing experiments in psychology and realized I could combine chemistry and psychology if I went into medicine and into psychiatry. I wanted to be able to use medications to help treat psychological disorders.

LH: So, your interest primarily was in the psychological area, but you figured medicine was a better entry into what you wanted to do in it.

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\* Joseph Autry was born in Pine Bluff, Arkansas in 1943. He graduated from the College of Medicine, University of Tennessee and trained in psychiatry at National Institute of Mental Health. He participated in research on schizophrenia and bipolar disorder at NIMH and subsequently joined the Extramural Research Program of NIMH where he helped implement the NIMH Treatment of Depression Collaborative Research Program, the Behavioral Medicine and Psychobiological Processes Program, and the Mental Health Clinical Research Centers Program. He was interviewed in Washington, DC on April 15, 1997.

JA: Right.

LH: And then what did you do?

JA: I went to the University of Tennessee Medical School, got involved in research there in the early days of using lithium to treat bipolar illness and then started on a NIMH fellowship and worked in the area of immunoglobulin research in schizophrenia for a couple of years.

LH: Was that also at Tennessee?

JA: That was also at the University of Tennessee. Then I did a straight medicine internship at Baptist Memorial Hospital; came to the National Institute of Mental Health in their old model residency training program; went from there into the Center for Studies of Schizophrenia, and into research.

LH: So, early in your career, then, you were involved in both, treating bipolar illness and later schizophrenia.

JA: That's correct.

LH: What were the drugs in use at that time for schizophrenia?

JA: The primary ones we had were the phenothiazines, most notably, Thorazine or chlorpromazine, and Stelazine or trifluoperazine.

LH: What date was that?

JA: That would have been in the late 1960s, early '70s. Haloperidol was one of the key drugs that came on the scene late in that period of time.

LH: Chlorpromazine was really the first landmark. I guess haloperidol was in a lesser way.

JA: Right.

LH: As all of them are lesser. The difference between having chlorpromazine and not having chlorpromazine was a major change.

JA: That was night and day. It certainly changed the treatment for schizophrenia in that period of time.

LH: And then what did you start doing?

JA: After my residency, I became chief of psychiatry at the Naval Operations Base in Norfolk, Virginia, for two years, and then came back to NIMH in 1975. I headed the depression section in the extramural research program, started the behavioral medicine and psychobiological processes program, and then the mental health clinical research centers program.

LH: I see. Can you tell me a little more about each of those?

JA: That's ancient history now.

LH: I'm not too familiar with them.

JA: In the depression program and the clinical research program, we were looking at the etiology of depression, working to diagnose and categorize mental illnesses better, including the affective disorders. We looked at the genetics underlying the depressive disorders and developed instruments for measuring change in depressive symptomatology in conjunction with the psychopharmacology program of Al Raskin and Jerry Levine. And in the behavioral medicine and psychobiological processes program, we were interested primarily in disorders like anorexia nervosa, bulimia, looking at behavioral correlates of these disorders, and for sequelae of physical disorders such as diabetes mellitus and cardiovascular disorders. The mental health clinical research centers program was the first program that NIMH sponsored that funded both basic and clinical research at the same institution trying to form a bridge between the basic sciences and the clinical sciences. It has been a very, very successful program over the years.

LH: Very necessary, too.

JA: Yes.

LH: Now, were these intramural or extramural programs

JA: These were extramural programs. I did some research of my own in that period of time looking at the influence of drugs in the treatment of depression, and then comparing drug treatment with psychological treatment in depression, working with Morris Parloff and Irene Waskow.

LH: Was this part of the emphasis on depression that occurred when Gerry Klerman was director of ADAMHA?

JA: That was part of it. Gerry was one of the investigators working with Myrna Weissman, who worked in the program where we had two short-term forms of psychotherapy, cognitive behavior therapy and interpersonal psychotherapy, compared to drug treatment, looking at the benefits in depression. And to everybody's surprise, we actually found that they both worked very well, the short-term psychotherapy interventions as well as the drugs. We now know, of course, that the combination of psychotherapy and medication works better than either one of them on its own.

LH: That makes sense.

JA: Yes, it does. But sometimes you have to do the research to prove what makes sense.

LH: I think that report was criticized. The drugs worked better in more severe depression.

JA: That's correct.

LH: And the psychological treatments were more effective in the less severe depression. I suppose in practice that might be translated to say that when someone is seriously depressed the first line of treatment should be with drugs, and as patients come out of depression, to get long lasting effect, one should try the interpersonal and social kind of therapy that Gerry and Myrna were interested in. Is that a correct interpretation?

JA: I think it is a correct interpretation, but I also think that what we have seen in clinical practice is that there is an evolution to using medication more frequently in more patients so that even for moderate depression or even fairly minor depression now, a number of people use drugs as part of their first line of attack on depression.

LH: Yes, but despite all the emphasis that NIMH has placed on depression, I recently ran into Bob Hirschfeld's article in JAMA about the under-treatment of depression. It still exists.

JA: It still exists. You have to remember that tertiary specialists, like psychiatrists only see about 20% of the people who are depressed and, hence, they prescribe only about 20% of the medication that is used for depression. Most treatment for depression is still carried out by primary care physicians. I think as newer generation antidepressants have come on line that have less side effects than the ones of the older generation, you are seeing more and more primary care physicians using pharmacological treatment. Unfortunately, I think they tend to under prescribe or under dose when they use medication. And a lot of times they just flat out miss the diagnosis of depression.

LH: As you said, they probably under diagnose.

JA: That's correct.

LH: It's so subtle because hardly anybody comes in and says, gee, I feel depressed, you know. They come in with a variety of somatic complaints that can lead you down a lot of blind alleys.

JA: In talking to my internist friends, they say that probably 40 to 50% of the patients that they see have some significant component of depression or anxiety disorder.

LH: It is interesting that you have mentioned the two together, because for many years John Overall and I were doing studies in depression, and we found that anxiety was just as frequent and just as severe in depressed patients as depression.

JA: I think that's absolutely correct. I think you also are seeing that many of the antidepressants have, in turn, been used to treat anxiety disorders over the past several years.

LH: I think Ron Lipman did a study some years back in which he showed that imipramine was equivalent to one of the benzodiazepines, I forget which one, in anxious patients. The only trouble is it's much easier to take the benzodiazepine.

JA: Absolutely.

LH: Tricyclics are not too pleasant to take for patients who are not depressed. So, now you've covered depression, schizophrenia and anxiety. What else have you been into?

JA: Well, we worked on post-traumatic stress disorder (PTSD) for a while with Jack Masur. That was at a time when there was very little research on PTSD. We actually found that it was a very definable syndrome and one that was amenable to treatment, both with psychotherapy and also with medication. I think probably the biggest advance we made was not in the psychopharmacology area, interestingly enough, but in the area of diagnosis and eventually developing DSM-III, DSM-IIIR and DSM-IV. I think that has really revolutionized psychiatry in this country.

LH: Yes. PTSD is certainly not limited to Vietnam War veterans.

JA: Absolutely not.

LH: It can occur in everyday life, that some terrible thing happens, and people get involved in it. So what is the drug treatment of choice for that?

JA: It depends on the symptomatology. Many times you can use an antidepressant or a combination of an antidepressant and a benzodiazepine, and it works quite effectively for those folks.

LH: Speaking of benzodiazepines and depression, have you ever been convinced that alprazolam has any special benefits in depression?

JA: I have read the studies, but I have not seen it happen clinically when I've tried to use it that way.

LH: Another thing that I have always been puzzled about is panic disorder that Don Klein first started talking about in the 1960s, which I think is a new name for an old phenomenon. It was not until 1980 or so, that panic disorder became epidemic. It happened to coincide with the development of alprazolam that was looking for a niche in treatment and came up with panic disorder. But that is probably blind speculation.

JA: Well, I don't know that it is necessarily speculation. I sometimes think that disorders do follow the availability of drugs rather than the other way around.

LH: That's a good way to put it. So, God, you've had your hand in a lot of different things. Now, your role in these was to put out contracts or just put out word that grants would be available in these areas.

JA: When you develop a program, what you have to do is to specify the kind of applications that you are interested in. So you set some general guidelines or general parameters, and then solicit grant applications in that area through what is called a request for applications. We also have a program called a cooperative agreement program in which extramural program staff is working as intramural program staff with investigators in the field. And then if you want something very specific, such as you want to have better diagnostic criteria, you can put out a contract that spells out the terms of what you want. What we are interested in doing is trying to find emerging areas, or areas that have been under researched, and stimulate research in those areas. Sometimes that is done by soliciting applications for a cooperative agreement or research grants, and sometimes by working with colleagues in a mentoring program to help them develop interest in a particular area.

LH: A lot of it seems to follow the early philosophy of Jonathon Cole's Psychopharmacology Service Center that identified an area, say, newly admitted schizophrenics, and solicited grants for their study in that area, and then later identified another area, say depression, and so on. What are the newer programs of interest now?

JA: I think probably the newest development has been the development of the clinical neuroscience centers, which are under Steve Koslow. There has been emphasis on trying to stimulate basic research that is specifically related to disorders such as schizophrenia or depression or anxiety disorder. There has been more funding toward the molecular biology end of the spectrum as opposed to the clinical end of the spectrum. And then, of course, the development of newer generations of drugs has been a startling phenomenon over the past five to seven years.

LH: I had occasion last year to write Steve and ask him for a copy of the wonderful 2nd edition of his book on neurosciences and psychiatry. I was involved in the first edition, but the field has passed me by.

JA: It's a rapidly advancing field. There are techniques that are out there now that neither you nor I learned about in medical school or our training.

LH: Oh, you have to run like hell just to keep up with the pack these days. It is not easy. Well, do you think the federal government, especially the Institutes of Mental Health and Drug Abuse,

will continue in the future to try to identify areas of needed research and stimulate them by the mechanisms that you have described?

JA: Yes, I think that is absolutely essential. Even though grant money has gotten a lot tighter in recent years, I think there are numerous fields in which knowledge still needs to be developed. We don't have any perfect treatment for any disorder at this point in time. I think as long as we are dealing with disorders and we don't have ways of preventing them and we don't have perfect treatments for them, there is going to be continuing need for research. I also think that the basic research arena, which is just burgeoning with new knowledge, is going to change the face of modern psychiatry in the next 5 to 10 years.

LH: The genetics of many disorders has been a very difficult area?

JA: It has and continues to be.

LH: I have come to the conclusion that no two of us, even of clones or twins, identical twins, are alike, and especially in our brains. Every one of us has a unique brain, and that may explain the complexity of trying to tie down genetics or specific genes to mental disorders. But, again, that's just a hunch.

JA: Well, I think one of the things that we do know is that all of us process information differently.

LH: Yes.

JA: And even if we are looking at the same phenomenon and we have had the same amount of training, we are going to see it a little bit differently. Even in identical brains you are going to have slightly different processing, and when you process input differently it changes your behavior. It changes how you react to those things. So, it is a very complex area.

LH: The old story of witnesses of the same event coming up with different versions.

JA: Right.

LH: Sometimes it has occurred to me that although the programmatic emphases of the Institutes have generally been pretty timely, the grant structure is set up so that you have to come in with something that almost is certain to be proved, and that's not the way to get really new knowledge. I would sometimes prefer seeing much smaller grants, but many more that were given to people whose ideas were crazy but have got enough logic behind them and the necessary ways to test them that you could get an answer. What do you think of that approach?

JA: I think you are quite correct, that there is always a tension between innovative or, as you put it, sort of cutting edge crazy kind of research, and incremental research where you go from one

incremental step to another incremental step. I think what has happened as grant money has become more scarce, you've seen people wanting to fund more safe research where we can make incremental gains. I think that, from my own perspective, you really need to have a small amount of money set aside just to fund people who have really new and innovative ideas that may have, you know, some rational basis behind them, but don't have the pile of data or the research to back them up. I think we sometimes miss a lot of things by funding incremental research only. That's sort of like the story of the drunk who lost his car keys. He's wandering around under the street lamp looking for his car keys, and they're saying, "Well, why are you just wandering around under the street lamp?" And he says, "Because that's where the light is." I think research is like that. A lot of times peer review committees want to look where the light is, or at best around the edges of that light, rather than going off into the dark and looking for the keys.

LH: In fact, you are almost naive to come in with a new grant proposal without at least some preliminary work that shows it's feasible and there might be some promise to it, which almost makes it a fait accompli when you do the research.

JA: Right.

LH: Well, are you planning to continue your career in mental health administration?

JA: For a while, yes. I've got a few years left before I want to retire. And right now I'm working with a program that oversees drug testing.

LH: For what?

JA: For 120 federal agencies, and we are developing and evaluating new testing technology, and that's kind of exciting. It's one of the few places in the federal government where you can actually take research and turn it into public policy in a matter of months.

LH: Well, that is unusual. Yes, indeed. Is this regarding drug abuse?

JA: Right, regarding drugs of abuse.

LH: So, what do you think of the war on drugs? Are we seeing the light at the end of the tunnel?

JA: I think we are with the war on drugs, like we are with any epidemic. Right now the epidemic is winning, and it's going to take a while before we can get it turned around in this country. It's much like we were in the early days with mental illness. We have even less effective treatments for drug abuse in this country, and I think until we can develop better ways of treating drug abuse we are going to have an ongoing problem. When you talk about biological processes and social processes interacting, I think, drug abuse is a prime example of that. What starts out as a

sociological or behavioral phenomenon very rapidly turns into a biological or addictive phenomenon, and I think we have a lot to learn about that process and how to treat it.

LH: And it takes about a generation to change habits. I remember in the early 1960s I had a young fellow working in my lab who had been on the track team at the University of Oregon, and he used to do a lot of running. And people would see him running, and they would make the kind of motion, like he was crazy. And now, of course, you see runners all over the place, and people who don't run almost have to feel embarrassed because they are not part of it. I think that came about after President Kennedy had a President's Council on Physical Fitness that gave some cache to doing this sort of thing. So it takes a while to change what is in and what's out.

JA: I think one of the things that we are seeing now is that, at least in a number of areas, drug use is beginning to be an out phenomenon that it is not socially acceptable, and I think that is a phenomenon that we have to promote.

LH: Well, it has been most successful, I guess, with nicotine addiction. I predicted many years ago that the best way to go about it would be if it is made socially unacceptable by putting on pressures. The pressure has now been graduated to limiting spaces for smoking, looking down on smokers, ridiculing them, making them feel sort of ostracized. In my house, anyone who wants to smoke has to go outside to the deck and smoke there, but not in the house. So I guess social persuasion is the way to go.

JA: I think that can be very effective, but I also think you have to sort of inoculate each new generation that it's unacceptable. We are now seeing that the junior high school kids are starting to smoke again, and it has become acceptable in that population. So you have to go and work in that population to make it socially unacceptable again.

LH: Well I think the administration's effort to curb the promotion of smoking among young people is very laudable, and I hope it's successful.

JA: Yes, I think that nicotine is a perfect example of where the science has been known for years, and yet it took decades to get that science put into public policy.

LH: It is very discouraging to hear a very prominent politician denying that nicotine is addictive.

JA: It's discouraging to hear tobacco-company executives to deny it too.

LH: And, of course, there are a lot of senators from your area who still think that it is not addictive. We still have a long way to go in educating the public.

JA: Yes, we do.

LH: In looking over the entire field of drugs of abuse, everybody says that treatment is the way to go, and I think there is a lot to commend treatment over interdiction, but the evidence for the effectiveness of treatment, if you take away the effect of methadone and those kinds of treatments, isn't all that persuasive really.

JA: It's gotten better in recent years. There are three studies out now. One in Minnesota, one in California, and a national study called the National Treatment Improvement Evaluation Study (NTIES), which show that regardless of what form of treatment you administer that all of them can be effective in reducing the amount of drugs used, reducing the use of the primary drug, getting people back into employment, and reducing the social consequences of crime associated with drug use. I think we will see more of that kind of data emerge as new treatment studies come about. I think the area that we are the weakest in is the area of prevention for substance abuse.

LH: Well that gets back to the social change that we were talking about.

JA: Right.

LH: Well, the recent study though on the MATCH program, for instance, wasn't very satisfying.

JA: No.

LH: If we use the right program for the right person we should expect to get a good result.

JA: I think, again, that's a problem. It reminds me of where we were back in the late 1960s and early '70s when we were looking at findings with psychological treatment for depressive or anxiety disorders. What we found was that the nonspecific factors of psychotherapy tended to be the most predictive of outcome and that if you tried and individualized the therapies and took out all the nonspecific stuff, you got less effect. I think we are in the same place with substance abuse. These days it's the nonspecific things that you do in therapy that tend to be the most effective.

LH: Just like making a suit of clothes. You have to tailor the measurements to the individual.

JA: That's correct.

LH: Well, do you have anything you want to predict about the future of psychopharmacology from your own point of view as overseeing the broad picture.

JA: I've long since given up my crystal ball about predicting what's going to happen in the future, but I do see some very encouraging signs. I think that some of the newer molecular biology techniques are going to lead to newer drugs that are going to be much more specific in terms of their therapeutic actions and much less problematic in terms of side effects. I think that will be a real step forward in the field.

LH: We may be getting drugs that affect more basic mechanisms than the current ones do. Well, there's hope. I think, say 35 years ago when I began in this area, we all hoped we'd be further along than we are now, and yet by the same token, we haven't done too badly. I've got a project in mind to compare the advances in treatment of hypertension, say, versus treatment in mental disorders.

JA: Oh, I think mental disorders are hands down ahead of that.

LH: You think so?

JA: I really do.

LH: Well, I don't know. I think it's a fairly even match. But, of course, hypertension is so ridiculously simple compared with mental disorders in terms of how to diagnose it and how to explain the pathogenesis. What actually prompted me to think of such a project was that in the early 1950s one of the foundations put out a book called America's Health in Mid Century, and they identified a dozen problems one of which was schizophrenia and one was hypertension. And I thought it might be a good exercise to see where we are by trying to compare the progress in these areas. We have made a fair amount of progress, I think, comparable to other areas of medicine.

JA: I think if you look at the number of clinical trials and the number of new medications that have been developed, and if you look at the amount of research that has been done to understand the basic underpinnings, then I think mental health comes out way ahead.

LH: Well, I'm glad to hear that. That's a really encouraging note. Well, thank you very much for giving us your viewpoint on where we have been, where we are going, and how to get there.

JA: It's been a pleasure. Thanks.

### 3. JULIUS AXELROD

LH: Today is April 14, 1997, and we are in Washington doing another tape in our series of the history of psychopharmacology. I'm Leo Hollister, the interviewer. Our guest today is a man who needs no introduction, Julius Axelrod.\* Welcome, Julius, and thank you for coming.

JA: It's a pleasure.

LH: Your life began in New York.

JA: Yes, on the lower east side of New York. It couldn't be more deeply in New York.

LH: A typical American saga.

JA: Well, I suppose so. My parents came from Austrian Poland, at the beginning of the century. They met and married here.

LH: Were they fleeing a pogrom?

JA: No. In the Russian part of Poland there were pogroms, but not in the Austrian part. It was a little bit more liberal. Franz Joseph was the emperor there, and he was a little bit more tolerant towards Jews. It was mainly poverty.

LH: They just wanted to get to the land of opportunity.

JA: Yes, the golden land.

LH: Well, unfortunately they didn't find the streets paved with gold.

JA: No, not at all. But they talked to people who came from the same area of Poland and they informed them what to expect.

LH: They networked.

JA: Yes, networked.

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\* Julius Axelrod was born in New York, New York in 1912. He received his bachelor's degree in biology from the College of the City of New York in 1933. He worked briefly as a laboratory technician at New York University, then in 1935 he got a job with the New York City Department of Health and Mental Hygiene testing vitamin supplements added to food. While working at the Department of Health, he attended night school and received his master's in sciences degree from New York University in 1941. In 1946, Axelrod took a position working under Bernard Brodie at Goldwater Memorial Hospital. In 1949, Axelrod began work at the National Institutes of Health (NIH). Realizing that he could not advance his career without a PhD, he took a leave of absence from the NIH in 1954 to attend George Washington University Medical School. Allowed to submit some of his previous research toward his degree, he graduated one year later, in 1955. Axelrod then returned to the NIH and began some of the key research of his career. Axelrod received the Nobel Prize in 1970, along with Bernard Katz and Ulf von Euler, for his work on the release, reuptake, and storage of the neurotransmitters epinephrine and norepinephrine. He died in 2004 in Bethesda, Maryland, USA. He was interviewed in Washington, D.C. on April 14, 1997.

LH: Were you the only child?

JA: No, I have two sisters. I was the oldest. I was born in 1912.

LH: You know there's a current idea about birth order.

JA: Yes.

LH: David Healy tells me that most of the people he interviewed have been either first born or an only child.

JA: Oh, really. I don't know whether there is anything to it, but it's interesting.

LH: So, you have two sisters. Are they both alive?

JA: No, they both died this year. I'm the only surviving member of my siblings. We lived in a part of New York that was almost all Jewish. We stayed in a certain area because otherwise we were either beaten up or called all kinds of names. But I enjoyed that life. We were very poor.

LH: I guess that was common, though, wasn't it?

JA: Yes, it was. We were very poor, but I didn't know any better. That was life. Amongst the Jewish people there was quite an intellectual foment. There were theaters and libraries, and a lot of talk and lot of politics. Most of those living in that area were socialists. Actually, we had a socialist congressman, Pankin.

LH: Yes, I remember him. That was not a bad idea in those days.

JA: No, it wasn't. The Russian revolution occurred around 1917 and people there were split on the basis of whether they were reading the socialist or the communist newspaper.

LH: Well, you know socialism in a democracy, as done in the Scandinavian countries, is pretty benign.

JA: Yes, but the discussions in our area were sometime very emotional.

LH: Political discussions can get pretty emotional.

JA: For me they were very interesting.

LH: You went to the New York public schools?

JA: The first public school I went to was built before the civil war. There was one famous alumnus: Isadore Robbie, a physicist. He graduated long before me. And in high school, I went to Seward Park on Hester Street. I wanted to go to Stuyvesant, a school fairly close by where all the smart kids went to, but I couldn't get in. I wasn't that smart.

LH: What a paradox.

JA: Well, I wasn't a bad student, but I wasn't in the top of my class. But I enjoyed going to Seward Park. We had a lot of interesting alumni. Most of them were entertainers: Walter Matthau, Zero Mostel, and Tony Curtis were all graduates of Seward Park. And also the songwriter, Hip Haburg; *Over the Rainbow* was one of his songs.

LH: A lot of talent came from that area.

JA: Oh, yes.

LH: Where did you go to college?

JA: I went to City College. That was a tuition-free college. It was sort of a poor man's Harvard. It was not easy to get in. It was one of the fortunate things for me because if it weren't for a tuition-free college, I never would have gone to college. We couldn't afford it at all. And I really got a high quality education there. We had some world-class teachers. In philosophy we had Morris Rayfield Cohen.

LH: He wrote a textbook.

JA: Yes, he was a famous philosopher. We had good teachers in chemistry, biology and some other subjects. I wanted to get into medical school and majored in biology and chemistry. When I graduated I applied to several medical schools, but I could not get into any.

LH: You think that was due to the quota system?

JA: Well, to the quotas they had at the time. The only graduate I know who got into medical school was Arthur Kornberg. He wasn't my classmate. He was about three years behind me. He was a smart kid.

LH: He was an MD, wasn't he?

JA: He got an MD, yes. I graduated from college in 1933.

LH: Ooh, bad time.

JA: It was a bad time to graduate, especially from City College. Fortunately a stroke of luck determined my whole career. I heard of a position to work in a laboratory as a volunteer for \$25 a month and I applied for the position. I could have worked in the post office for more than \$25 a month, but I accepted the position at the Harriman Research Laboratory of NYU. Making that choice was very crucial to my career. I was a technician in the laboratory of Dr. K.G. Falk, a biochemist. He was fairly well known by chemists because he wrote a textbook on the mechanism of enzyme action. He worked on enzymes in malignant tissues, and I got my first taste of research by assisting Dr. Falk.

LH: So that was the door to biochemistry in your career.

JA: Yes. I became very much interested in biochemistry. Well, after two years I decided to get married. My wife was a student at Hunter College, and we just couldn't live on \$25 a month.

LH: That old saying that two can live as cheaply as one is not true.

JA: Fortunately, the city of New York opened up a laboratory to test vitamins, and food supplements. It was a non-profit laboratory. This was in the 1930s. Vitamins were just being developed and they became a big thing. Still are to a degree. They added vitamin A and D to milk, and various supplements to bread. My job was to set up assays to measure the vitamins in foods, in milk, in bread and in pills. I didn't develop my own methods but had to modify the existing methods. For this I had to read the original literature. It was a very good experience for me because methods are so crucial to research. If you have a hypothesis or an idea, you wouldn't get very far, if you can't develop methods for testing it. Well, I learned a good deal about devising methods, and not only chemical or microbiological methods. They were using a spectrophotometer, and I got a great deal of experience working with it that was very useful for me. I thought I would stay in that lab for the rest of my life. The salary wasn't bad. The work was fairly interesting. And I kept up with the literature. The laboratory subscribed to The Journal of Biological Chemistry that I read, and so I had a feel for what was going on in those days, mainly in enzyme research, vitamins and nutrition. I was working there for 11 years. In 1945, the head of this vitamin-testing laboratory was George Wallace, the former chairman of pharmacology at NYU. He was editor of The Journal of Pharmacology. And one day a group of people from an institute for the study of analgesic drugs, a consortium of manufacturers involved in selling drugs like acetanilide, came to Dr. Wallace with the problem that some people became habituated to bromoseltzer...

LH: That had bromine in it.

JA: Yes. But it also contained acetanilide and many people taking the drug got methemoglobinemia. They were very concerned about this and wanted to find out why people get methemoglobinemia on acetanilide. They came to Dr. Wallace for advice, and Dr. Wallace asked me whether I would like to work on this problem. I said yes, but I told him also that I had no experience in research at all. So he said, well, I can send you to one of my associates, Dr. Bernard Brodie, at NYU.

LH: Oh.

JA: You probably know him. They called him Steve Brodie.

LH: Your name has been intimately connected with his ever since. Two giants of...

JA: Well, anyway, I called Brodie one day and he asked me to visit him. He was then at Goldwater Memorial Hospital, that was on an island now called Roosevelt Island. I remember that day. It was in 1946, a very fateful day for me. It was Lincoln's Birthday, February 12. Brodie was a magnetic man with a great deal of presence. We talked about the problem I was supposed to address. I was fascinated just talking to somebody like him. He had a way of talking that I found stimulating. The first thing he told me that anytime one takes a chemical or drug, the substance changes in the body, it's metabolized and transformed. He asked me to put the structure of acetanilide on his blackboard. And I did. Then he said, let's look and see what kind of changes this molecule can undergo. Acetanilide consists of an aminobenzene ring with an acetyl group. One possible change is the removal of the acetyl group that should result in aniline. And I vaguely remembered that aniline could cause methemoglobinemia. So I learned right away the importance of asking the right questions. The second question to be answered was whether aniline was really formed from acetanilide. In order to answer that question one has to develop methods to measure aniline in the blood and the urine. Brodie was a great methods man, and we developed a specific and sensitive method to measure aniline in the urine, plasma, and blood. And I took some acetanilide and found some aniline in my urine. So we knew we were off.

LH: Self-administration, huh?

JA: Yes. There were patients at Goldwater Memorial Hospital. We gave them acetanilide and found aniline in their urine. I don't remember whether they gave informed consent but we definitely told them that the powder they were given was harmless and used for treating headache. Then I took some aniline myself. I thought I'd turn blue.

LH: Prove it beyond any question, huh?

JA: It was really crazy.

LH: Did they have the methylene blue treatment for it then?

JA: No. I didn't take that much. I became a little woozy but found a lot of methemoglobin in my blood. We did show that there was a direct relationship between methemoglobinemia and aniline in the blood. And so we solved that problem.

LH: This was the first demonstration, I guess, that a toxic effect of a drug could be due to the metabolism of the compound.

JA: One of the first demonstrations.

LH: Did you do this work at Goldwater?

JA: Yes. I have forgotten to tell you that Brodie asked me to come and work with him there, although the laboratory I worked for at NYU paid my salary. And we also found that when one takes acid anilide, aniline represented only about 4%, a very small amount of the entire drug. So, there was also some other pathway for the metabolism of the drug. Well, within three months we identified acetanilide's major metabolic product. It was acetyl-para-aminophenol. Dr. Brodie checked it for analgesic activity and it was just as good an analgesic for headache as acetanilide. It had the advantage that it wasn't toxic. It did not cause methemoglobinemia. We suggested that it should be used instead of acetanilide. It was used mainly by pediatricians, because it was soluble. This work led to the publication of my first paper.

LH: Now this was phenacetin?

JA: No. Acetanilide metabolized by hydroxylation to acetyl-para-aminophenol and phenacetin, and phenacetin metabolized by de-ethylation to acetyl-para-aminophenol. I think that Squibb had a concoction that consisted of aspirin, phenacetin and acetyl-para-aminophenol. They called it acetaminophen because of the acetyl-para-aminophenol it contained. But then the company sold the compound to McNeil. Acetaminophen puttered along until Johnson & Johnson bought McNeil in 1970 and had a very powerful marketing campaign for Tylenol. It was their name for acetaminophen.

LH: A very successful drug.

JA: Very successful. All we got for it was a \$10,000 grant. But I got out of it much more, the beginning of a research career. I was pretty good at research, and I loved it. At the time all I had was a master's degree in chemistry from New York University that I earned by taking night courses while I worked in the vitamin testing laboratory. So that was the beginning of my career as an investigator.

LH: So you found that acetanilide metabolized to phenacetin and phenacetin metabolized to acetaminophen?

JA: Both acetanilide and phenacetin are metabolized to acetyl-para-aminophenol. We didn't call it acetaminophen.

LH: I think that was probably the first time that sequence has ever been used.

JA: Yes, it was. We showed that a drug could be metabolized to a toxic metabolite as well as to a nontoxic metabolite. Actually there was a precedent for this before when in the early 1930s

Gerhard Domagk developed prontosil (for which he received the Nobel Prize), a very toxic substance that metabolized to sulfonamide.

LH: Well, sulfonamide was the first really effective antibacterial drug.

JA: Yes, and it revolutionized medicine. Antibiotics, penicillin came later. People think that drug metabolism is not in the mainstream of science. But it certainly was, at least in these cases. Well, let me talk to you about Goldwater Memorial Hospital. During World War II malaria was very prevalent in the troops fighting in the Pacific and the Japanese cut off the supply of quinine. There was a need for new anti-malarial drugs and Shannon, a renal physiologist, was asked to test clinically some synthetic anti-malarial drugs at Goldwater. This happened before Shannon went to Bethesda to become the founding director of the NIH. Shannon had a good nose for picking people and he had at Goldwater a group of young people who, instead of fighting in the Pacific, worked with him on the clinical testing of anti-malarial drugs. The group included Bob Berliner, Bob Bowman, who was to develop the spectrophotofluorimeter, Sidney Udenfriend, Stu Broad, the cancer man, Tom Kennedy, David Earl Steele, an internist, and several others. It was a stimulating group of people. They had a great influence on my thinking. Well, after working for four years at Goldwater, I knew that I didn't have a chance for an academic appointment without a PhD. I had no inclination at the time to take a PhD. And then I saw an advertisement in The New York Times that Shannon was appointed director of the NIH. I wrote to him and he hired me. Well, the NIH then was not like it is now.

LH: No, but, let's see, that was 1949?

JA: Yes, that was when congress established the National Institutes of Health. It was not just the Heart Institute but also the Cancer Institute, the Arthritis Institute, and various other institutes. The Mental Health Institute was started with Bob Felix as the director. And Shannon persuaded Steve Brodie, Bob Berliner and Sid Udenfriend to join him. He recruited a remarkable group of people. In building three, there were 3 people who ultimately became Nobel Prize winners, Kornberg, Anderson and myself, and there were 20 people who became members of the National Academy of Sciences. It was just a small building of three stories. Well, a secure job meant more than anything else to me, and particularly a job doing research. When I joined NIH, I worked first under Brodie. He recruited a lot of people and had a very large team and I wasn't happy after a while working in a large group. I was offered a position by one of the drug companies, and I told Brodie that I would like to leave. But he asked me: "Well, what would it take for you to stay?"

And I answered: "Well, if I could be completely independent to do my work I would stay." I didn't have a PhD yet. Still he said: "Fine." So my first project was to study the fate of caffeine in man. There was no study on it in spite of the fact that caffeine was the most widely used drug.

LH: Still is.

JA: Yes, it is. I did that work all myself but got only one senior-authorship in 15 to 20 papers we have written. I became interested in sympathomimetic amines, amphetamine, ephedrine. They interested me primarily because they affected behavior. They also raised blood pressure and being in the Heart Institute, I thought it would be a good idea to work on the metabolism of sympathomimetic amines. I worked out the metabolism of amphetamine and became very curious why the body can metabolize thousands of synthetic compounds it never saw before. I thought I would like to tackle the problem how the body can do this. My lab mate, the man who occupied the bench next to mine, was Gordon Tompkins, a post-doc then with Brodie.

LH: He died early, didn't he?

JA: Yes. He was a brilliant fellow. I used to have wonderful times with him. He was a very great raconteur. He also used to play the clarinet in the evenings at a nightclub. Knowing my interest in drug metabolism, one day Gordy Tompkins asked me: "Julie, why don't you find out what enzymes there are?" I told him that I have no experience in enzymology. But he said all you need is a liver where the enzymes are and a razor blade. One used to work making slices of the liver in those days to study metabolism. By that time I had a method for measuring amphetamine and learned that amphetamine was not deaminated by monoamine oxidase, because it did not have the right structure for it, but by another enzyme. And I was curious to find out what part of the cell carried out amphetamine's metabolic deamination. Just around that time Pauletti had described methods to separate the various sub-cellular fractions, such as the mitochondria in the liver by differential centrifugation in sucrose. I learned these methods and found that when the various sub-fractions were separated amphetamine couldn't be metabolized. It was metabolized only when I used cofactors like TPN or APN. At the same time Bert La Du was working in Brodie's laboratory on a similar problem, and he found that TPN could cause the metabolism of one of the drugs I was working on. I think it was antipyrine, or something, I forgot, that required ATP to metabolize. Well, anyway, when I added TPN to the mitochondria, amphetamine was metabolized. But I wasn't very careful and didn't wash the mitochondria.

Fortunately Bernard Harke, a very good biochemist, who was working on the pentose phosphate shunt in the laboratory below mine, loaned me many of the substrates he used, and I found that any time I added a substrate like isocitric acid or gluconic acid to the unwashed mitochondria, amphetamine was metabolized. That is amphetamine was deaminated. And when I added isocitric acid and TPN to the mitochondria, it generated reduced TPN. So when I then washed the mitochondria and added reduced TPN, amphetamine was metabolized. So I knew I had something there. I was also working at the same time on ephedrine and when I added ephedrine to the mitochondria it was demethylated. So here were two different metabolic pathways using common cofactors, reduced TPN and oxygen. One pathway led to the deamination of amphetamine, and the other pathway to the demethylation of ephedrine. I knew we had something. We called the enzyme responsible for the two pathways of metabolism, the microsome. It was this discovery that led to the parting of Brodie and I. I wrote two abstracts based on my findings for the pharmacology meeting in 1953. When Brodie saw these abstracts he became very upset.

LH: Was he upset about the order of authorship?

JA: No, he wasn't a co-author at all. He didn't do anything. He was upset that I solved the problem because there were other people working in the lab trying to solve the same problem. He put the whole laboratory to work on this line of research and it worked on almost any drug they tried. And they wouldn't allow me to publish my paper until the rest of the laboratory did all of their work. And he called us all together and said: "Let's publish this in Science and let's do the authorship alphabetically." I realized that I would be cursed. They just put my name first. So I knew then that I had to leave. I had to get my PhD.

LH: Well, by that time, you had more than enough work for a PhD.

JA: Of course I did. I applied to George Washington University, a local school. I knew the chairman. He told me: "Well, since you have a master's degree, you will not have to take any courses, but you will have to pass very tough exams in five subjects: physiology, biochemistry, drug metabolism, and some other fields. And as far as your thesis is concerned, you can use the work you did on the sympathomimetic amines and the enzymes." I had already published four papers by then and I just put them together in my thesis. I was also asked to give a course in drug metabolism while working for my PhD. Although I didn't have to do it, I decided that I shouldn't take a chance and took the courses for the medical students on the various subjects. Shannon, the

director of NIH, was very generous. He said I could take a year off for my PhD and will still get my salary.

LH: It seems paradoxical that you would be taking courses on drug metabolism.

JA: Well, let me tell you, I had to take the exams on drug metabolism after I gave the course because it was required. I didn't pose the questions so, somebody else did.

LH: Now, when you started working on the sympathomimetic amines, had epinephrine been already discovered?

JA: Epinephrine was discovered way back in 1897 by John Abel. He isolated it from the adrenal gland.

LH: But it wasn't identified as a transmitter.

JA: Well, there was a big controversy about the neurotransmitter of the sympathetic nervous system. Walter Cannon thought it was epinephrine. He called it sympathin A. And then von Euler actually isolated the substance and showed that it was norepinephrine.

LH: Was he the one who called it sympathin first?

JA: No, that was Cannon. It's a pity that Cannon didn't get the Nobel Prize. He certainly deserved it.

LH: Oh, he was a giant.

JA: Yes, he did so much work on stress and behavior; how stress affected the various organs.

Well, I left the Heart Institute and sent my application to the Cancer Institute and to the Mental Health Institute. At the time Seymour Kety was the director of the intramural program of the Mental Health Institute. He called me for an interview and seemed to be very pleased with it. He thought I had a good chance for a position at the Institute and sent my application to the heads of several laboratories. One of the people he sent it was Ed Evarts. I don't know whether you know Ed?

LH: Evarts? Yes. He was billed as a physiologist, wasn't he?

JA: Yes, but he was a psychiatrist and neurologist. He was working on LSD then. He saw my application and asked me if I would join his laboratory. I said of course and after I got my PhD I was working in his lab on developing a method for the detection of LSD. LSD at that time was a big thing in psychiatry. They thought it was a good tool to study. LH: Model psychoses.

JA: Actually a nurse can recognize the difference between LSD and amphetamine.

LH: That's what we found.

JA: Yes, I know. I remember when you did that work. Anyway, I developed a method for the detection of LSD. Bob Bowman at the time was developing a fluorometer, and I asked him whether I could use it. He gave me one of his experimental models, and I developed a method for the detection of LSD. And Ed Evarts and I studied the metabolism and distribution of the substance. We found that it went into the brain in incredibly small amounts. It must have been a very potent drug. Anyway, I got my own laboratory. I was working alone by 1955. I had no experience in neuroscience at all. I know very little about the brain. I thought that neuroscientists had to be very gifted theoreticians and experimentalists working on this very complicated electronic apparatus. I was worried that Kety would want me to work on schizophrenia or depression. But he said: "Julie, you can work on anything you want as long as it's important and its original." So I started to work on the metabolism of drugs that I knew best, on morphine and the conjugation of morphine. I also collaborated with Jack Strominger, a very good biochemist who is now a noted immunologist, on how glucuronide conjugation was a major mechanism for detoxifying drugs. There was a paper just published showing that glucuronides were formed by a cofactor, uridine diphosphate glucuronic acid, when Jack and I met at NIH, and since I had a good method for measuring glucuronides, Jack suggested that we should study glucuronide conjugation. To do our research we required uridine diphosphate glucose that we could convert to glucuronic acid either by TPN or DPN. Herman Colcott happened to be at the NIH. He was a very distinguished Danish biochemist. I don't know whether you know him. He had uridine diphosphate glucose. So we all collaborated and showed that DPN, NADP plus uridine diphosphate glucose would form morphine glucuronide. At that time I had to leave the laboratory to get my PhD but Strominger purified the enzyme and published it. When I returned to the Mental Health Institute, I noticed a paper by Rudy Schmidt, the former dean of the San Francisco medical school, who found that bilirubin was detoxified by forming a glucuronide and if this glucuronide didn't conjugate one gets jaundice. I called him and told him that I think I can find the enzyme that makes bilirubin glucuronide. We collaborated on this project and found the enzyme that forms bilirubin glucuronide. Then Rudy Schmidt told me about a mutant strain of rats, the Gunn rat, studied by Castle at Harvard that has jaundice. He thought it would be a good idea to see whether or not they developed jaundice because they couldn't form bilirubin glucuronide. Sure enough, we found that there was a defect in these rats in their liver, an inability to form glucuronides. I told Rudy Schmidt that we found that

acetaminophen was formed from phenacetin by glucuronidation and that we got some patients who had Crigler-Najjar disease and gave them acetaminophen.

LH: And they couldn't conjugate that either.

JA: Exactly. Well, they could, but very, very weakly. I felt little guilty not working on the brain. Well, around 1956 Ed Evarts stepped down from his position of lab chief, because he didn't like to be an administrator, and Seymour Kety stepped down from the directorship of the Institute, to become the head of the Laboratory of Clinical Science. During his tenure we had seminars every week. And on one of these seminars we had a report from two Canadian psychiatrists who found when they left adrenaline in the air it turned pink.

LH: Oh, the famous pink spot.

JA: Well, that comes later. What they claimed was that they started to hallucinate when they took the pink adrenaline.

LH: Oh, this was adrenochrome.

JA: Right. Yes, you remember that one.

LH: Was this Hoffer and Osmond?

JA: Yes. They had a great impact on my life. Let me tell you what happened. They claimed that schizophrenia, possibly, would be caused by an abnormal metabolism of adrenaline. I was fascinated by this report. And I looked through the literature but all I could find was that there was an enzyme, monoamine oxidase discovered many years before by Blaschko that deaminated adrenaline.

LH: Would that be the same enzyme you were using for deaminating amphetamine?

JA: No, that was the microsomal or P450 enzyme. It is one of the most studied enzymes in the world. Well, anyway, I thought, I might as well work on the metabolism of adrenaline since it is so closely related in structure to amphetamine. First I tried to look for the enzyme that converted adrenaline to adrenochrome. I spent four frustrating months but couldn't find that enzyme. Then, one day there was an abstract published by McMillan and Marvin Armstrong showing that patients with pheochromocytoma excreted a lot of a compound called vanillylmandelic acid. It was a methylated compound and by looking at its structure I knew that it must be coming from adrenaline or noradrenaline. And I suspected that it was formed first by the methylation of adrenaline or noradrenaline and then by the deamination of the resulting substance by monoamine oxidase. I thought the methyl donor was adenosylmethionine. I didn't want to ask Cantoni who discovered

that the methyl donor was adenosylmethionine, so looking for this methylating enzyme I added a cofactor that contained adenosylmethionine, magnesium, liver extract, methionine and ATP. I found that when I added all these ingredients, adrenaline disappeared. It was metabolized. So I knew that I had an enzyme there that transferred the methyl group of adenosylmethionine to one of the hydroxy groups of adrenaline. We called the methylated substance metanephrine.

LH: Of course, to do all this work, the Bowman spectrophotofluorimeter was indispensable.

JA: Well, yes, that's what I used. We didn't have radioactive isotopes. And I had a new enzyme. We called it catechol methyl transferase. And at the time there were only two neurotransmitters recognized: one was acetylcholine and the other was noradrenaline that was discovered by von Euler a few years before. There were a lot of other putative neurotransmitters, e.g., serotonin, dopamine. Well, Nachmansohn and Leary discovered that acetylcholine was inactivated by choline acetyl transferase. So I thought that the catecholamines, noradrenaline and adrenaline would be inactivated by catechol methyl transferase. But just around that time, Zeller discovered an inhibitor of monoamine oxidase.

LH: Iproniazid.

JA: Yes, but when they injected iproniazid to inhibit the activity of monoamine oxidase, it didn't affect the metabolism of norepinephrine sufficiently to be reflected in blood pressure changes. And we found an inhibitor for catechol methyl transferase. It was called copaline or something like that. But when Dick Crout, who worked at the Heart Institute, inhibited both enzymes, i.e., monoamine oxidase and catechol methyl transferase, and injected norepinephrine, the action of norepinephrine on blood pressure was still rapidly terminated, in spite of the fact that the functioning of both of the enzymes responsible for the metabolic breakdown of norepinephrine were blocked. So we knew that they were not these enzymes alone that inactivated norepinephrine.

LH: So you didn't stop at the enzymes.

JA: Well, then, of course, it really became an intriguing problem, what was happening. Well, just about the time I was conducting these experiments, Kety ordered some tritium-labeled adrenaline to study the metabolism of adrenaline in schizophrenics to see whether the adrenochrome hypothesis is true. I asked him for some tritium labeled adrenaline. By then Irv Kopin and I already identified several metabolites of adrenaline and noradrenaline, e.g., normetanephrine, MHPG, so that Kety could study the metabolism of adrenaline in schizophrenics. Well, when I worked on drug metabolism I used to study the tissue distribution of the drugs and their metabolites. So we

studied the tissue distribution of tritium-labeled adrenaline, and found that it persisted in many tissues unchanged, long after the physiological actions of the substance were over. I realized that the highest concentrations were found in organs that contained a lot of sympathetic nerves, such as the heart and the spleen. So we suspected it must be sequestered in sympathetic nerves. And that was an important finding.

LH: That was a revolution.

JA: Yes, what it led to...

LH: The reuptake mechanism.

JA: Right, exactly. Let me tell you how we did the rest of it. Around that time I was attracting post-docs. One was George Hertting. He was a real classical Viennese pharmacologist, and when I was discussing with him how we could prove that norepinephrine is taken up in sympathetic nerves, he came up with a very brilliant idea. He said, well, what we can do is, take out the superior cervical ganglia unilaterally. When we do that, the nerves will degenerate on one side and we will have a unilaterally denervated animal. And when he did what he suggested and injected radioactive noradrenaline he found that the radioactivity was localized only on the innervated side. So we knew that it was going into the nerves. We also realized that we had something very important. So we were thinking of other experiments. In one of these experiments we perfused norepinephrine in the spleen, and when we stimulated the nerves to the spleen there was a release of noradrenaline from the spleen. And we knew that noradrenaline was not only taken up but that it was also released from the sympathetic nerves of the spleen. We called this process reuptake. In the next experiment we did autoradiography. It was carried out by Lincoln Potter, one of my first post-docs, who worked together with Keith Richardson and David Wolf, who were autoradiographers. I happened to be working on the pineal then that is very rich in sympathetic, noradrenergic nerves. And when we injected radioactive noradrenaline to do autoradiography, Wolf told me that it should take weeks before we will get the films ready. I was very impatient and asked him to try to have it in two days. And we had it in two days. All radioactivity was in the sympathetic nerves, localized over dense core granules in little vesicles. We suspected that these little vesicles were the storage place of noradrenaline. We also studied the distribution of noradrenaline with Weil-Malherbe, a German biochemist who did a lot of work on the biochemistry of mental illness. He left Germany during the Nazi regime and he developed methods, while he was in England, for measuring adrenaline. Well, I thought, let's measure the

effect of drugs on the uptake. We couldn't do it in the brain because the noradrenaline we administered didn't cross the blood-brain barrier. The first drug Hertting and I tried was cocaine and found that it blocked the uptake of noradrenaline into the tissues of the heart and the spleen. And we tried a whole bunch of drugs. Amphetamine did the same thing as cocaine. But we wanted to get into the brain. At the time I had another post-doc, Jacques Glowinski, who is now vice-president of the College of France. Most of my young people turned out very well.

LH: You've had so many distinguished graduates.

JA: Well, Glowinski developed a technique of introducing radioactive noradrenaline right into the third ventricle. And we tried antidepressant drugs, a whole series of tricyclics. We got them from Geigy. We gave these various tricyclics and then we injected radioactive noradrenaline into the brain and measured the amount of radioactive noradrenaline in the nerves before and after the drug injection. And we found a reduced level of radioactivity in the nerves only when we gave a clinically effective tricyclic drug. Later on one of my post-docs, Joe Coyle, found that not only were the antidepressants blocking the reuptake of noradrenaline, but they also blocked the reuptake of dopamine. Then Sol Snyder found that the antidepressants blocked the reuptake of serotonin as well. Antidepressant development was based on the employment of simple methods of reuptake inhibition. Thousands of synthetic drugs were screened with these simple methods rather than giving the drugs to humans. That's why it was so easy to develop these antidepressant drugs.

LH: Those methods are probably still used.

JA: They still are, of course. In fact they call these drugs serotonin reuptake inhibitors or whatever.

LH: After you discovered that the action of neurotransmitters was terminated by reuptake, did you ever have the idea that this was going to be important enough to win a Nobel Prize?

JA: Well, we all think we'll win a Nobel Prize. But, you know, at the time the catecholamines, norepinephrine, dopamine, were hot subjects and there was von Euler, and there was Carlsson...

LH: Did Carlsson work in your lab too?

JA: No, he worked with Brodie. Carlsson, Blaschko, Butterworth and I, we all worked with Brodie. I thought that I might have a chance to get the Nobel Prize, but there were those other people deserving it also.

LH: Crowded field, huh?

JA: Yes. I got it with von Euler and Bernard Katz. There were a lot of other things I did. One, of course, was the discovering of catechol methyl transferase. We also found the enzyme that makes adrenaline, noradrenaline, phenylethylamine. Well, the PNMT story is an interesting one. Dick Wurtman got his MD from Harvard and when he came to my lab as a post-doc, he pointed out that in the adrenal gland of the rabbit, the cortex is separate from the medulla, and the catecholamine in the medulla is noradrenaline exclusively. Since in animals in which the cortex and medulla are not separated, the medulla contains also adrenaline, we suspected that the cortex has something to do with the formation of adrenaline from noradrenaline by methylation. Evidently the glucocorticoids were somehow affecting the synthesis of adrenaline. To study this further we hypophysectomized rats and found that it caused a decrease in the synthesis of cortisol and a decrease in the activity of PNMT. But we also found that when we gave dexamethasone to hypophysectomized animals, PNMT activity was increased.

LH: Nature made sense putting the adrenals where they were.

JA: Exactly. And we also showed that the brain can stimulate tyrosine hydroxylase, the enzyme that is required to make dopamine and also the rest of the catecholamines, trans-synaptically. We've done a lot of experiments with Hans Thoenen and Bob Muller in this area of research, but when Dick Wurtman came I was working on the pineal gland. I don't know whether you want to hear that story?

LH: Oh, yes, sure. I had a little adventure with the pineal gland myself.

JA: Yes, I know. And I think Altschule thought that the pineal gland was involved in schizophrenia. I came across that story in 1958 in an article by Aaron Lerner, a dermatologist and biochemist at Yale, who found that when he took an extract of the pineal gland and added it to a tank where tadpoles were swimming, it blanched the skin of the tadpoles and affected their melanophores in some way.

LH: Did Lerner use the term melatonin?

JA: Well, that's what he called it. He isolated the active principle that was responsible for blanching the skin of tadpoles and that was melatonin. It's a methylated serotonin. And I saw that abstract. I became very much interested in how melatonin was made because of the methyl group it has. Herb Weisbach together with Sid Udenfriend worked out the metabolism of serotonin. Since melatonin was a serotonin analogue, I asked Herb whether he wanted to collaborate with me to find the enzyme that makes melatonin. And he wanted to collaborate. I don't want to go into the

details. We found two enzymes: one, acetyl transferase, that acetylated serotonin, which later became a very important enzyme, and another, that methylated acetyl serotonin to melatonin. And what Dick Wurtman and I had found was that light would affect the synthesis of melatonin. That is, in the dark there was more melatonin synthesized than in the light.

LH: Was more melatonin synthesized in light or in darkness?

JA: It was more in the darkness. Well, anyway, I love working with the pineal gland. Usually when I was working with catecholamines, many experiments didn't work and that made me feel a little depressed. But every time I did an experiment on the pineal gland, it worked, and it sort of lifted my spirit. It was a good antidepressant. It was a wonderful gland to work with. Well, anyway, Dick and I called the pineal gland the neuroendocrine transducer. It was in '63 or '64 and we couldn't measure melatonin directly then. What we could measure was serotonin, its precursor. Then, when Sol Snyder came to work in my lab, and he came just around that time, Sol and I developed a very sensitive method to measure serotonin in the pineal gland of the rat. And just by measuring serotonin we found that in the dark serotonin was very low and in the light it was very high. The reason for the low serotonin and high melatonin in the dark was, that in the dark serotonin was acetylated and methylated, so it was just the opposite of melatonin. We thought that would be a measure of melatonin synthesis. Then Bob Moore came to my laboratory to work on this project. He brilliantly identified that the biological clock responsible for the formation of melatonin from serotonin at nights was in the suprachiasmatic nucleus and the pineal gland, that did a lot of other things as well, was just an arm of that clock.

LH: Did you ever think melatonin would become such a big thing as it is now?

JA: Well, I think it's a lot of hype. It may have something to do with sleep, I think.

LH: I think so.

JA: Yes, but cancer and aging and all of that, it's a lot of baloney, I think.

LH: It makes some sense that it may be related to sleep and perhaps the fragmentation of sleep in older people.

JA: Oh, sure. I know Dick Wurtman actually uses melatonin for all kinds of indications. I think they sell it over the counter now because it's a natural compound. It's a big seller.

LH: Well, I didn't think there were many things that would put me sound asleep until I tried melatonin. But melatonin sure could put me to sleep.

JA: Yeah, I tried it. It didn't help me. Well, anyway, that's the short history of melatonin. We also found that it stimulated the  $\beta$ -adrenergic receptor that in turn stimulated the enzyme acetyl transferase. It was acetylation as David Klein had shown that drove the biological clock.

LH: The cycling of melatonin.

JA: We missed that one. Let's see, where am I now?

LH: Well, you must be somewhere close to about 1970.

JA: Well, then I worked on methylation reactions, on histamine methyl transferase, which is the major enzyme for the inactivation of histamine. Then we found a curious enzyme that methylated tryptamine in the lung and the brain. It became a big thing. Some people thought it might be one of the compounds that would cause...

LH: Endogenous psychosis.

JA: But, I didn't buy that. It was too simple an explanation. Our brain was not that simple. But it was fun working on it, and it gave other people something to work on. You remember the pink spot and the Ackerfeld test?

LH: Oh, yes. Once Ackerfeld and I were on a panel together, and he was reporting on his negative results.

JA: Well, he wrote a very influential article for Science about the kind of sloppy work done. You know they found that the reason why schizophrenics reacted differently from normals on the Ackerfeld test was that they didn't drink orange juice.

LH: Well, there was a wonderful article published way back in the 1950s. A biochemist from Illinois wrote something called "Fact and Artifact in the Biology of Schizophrenia," and it should be on everybody's wall.

JA: Of course. I remember one story that happened at the Mental Health Institute. They were doing studies on paper chromatography in the '50s and found that schizophrenics always had two spots, which the controls didn't. Kety was very skeptical about the finding. He said something must be wrong. And when the findings were scrutinized it turned out that the controls were Mennonites who didn't drink coffee. So, you know, you have to be very critical about this sort of thing.

LH: Well, you didn't rest on your laurels after 1970, but have done a hell of a lot of things since then.

JA: Well, yes. I worked on the transduction of arachidonic acid. I retired officially in 1984. I wasn't even called emeritus, but a guest worker, a guest researcher. I was interested in transduction reactions, and one transduction reaction we were especially interested in was the receptor-mediated activation of phospholipase A2. We found that it formed arachidonic acid, a very active carcinoid substance.

LH: So you began to get in the 3rd messenger field.

JA: 2nd messenger. I didn't get to the 3rd messenger. It got too complicated. But I was involved in research with Carol Gelsma on G proteins that became very important in signal transduction.

LH: Oh, yes.

JA: Actually, the Nobel Prize was given to Marty Rodbell and Al Gilman for that discovery. These G proteins were heterotrimers. You know, it was thought that the alpha subunit activates phospholipase C or A, or whatever, when the first messenger, a transmitter or a hormone, recognizes a receptor. But, later it was shown that it was the  $\beta,\gamma$ -subunit that activates phospholipase A2. We sent that paper to Nature. They rejected it. And just four months later another paper came out saying that the  $\beta,\gamma$  - subunit activates one of the potassium channels. The  $\beta,\gamma$  - subunit became a big thing. Of course, we didn't get much credit for it. If Nature would have accepted our paper, we would have gotten more recognition. But it was fun working in this area of research. One problem I'm working on now should have importance in neuropharmacology. It is cannabis.

LH: Yes, the cannabinoid receptor.

JA: Right. It was cloned in my laboratory by Lisa Matsuda and Mike Brownstein.

LH: You know Raphael Meshulam?

JA: Sure, of course. Once the cannabinoid receptor was identified we knew that there had to be a natural ligand for it. And Bill Devane, who worked in Meshulam's laboratory at Hebrew University, actually isolated the natural ligand. It is arachidonylethanolamide, which they named anandamide. Bill Devane came to my lab and we found one of the enzymes that make it. It's one of the enzymes that make anandamide. I think it's an important enzyme because its receptor is distributed in very interesting places: the hippocampus, the striatum, the cortex, and the cerebellum. It must be doing important things. I think it has a great future.

LH: This raises an interesting philosophical question. Why in the world would the body have receptors, as you mentioned before, for drugs it never heard of?

JA: Well, these receptors were there for the normal ligand. Evidently, they lack specificity but they have survival value. I have a feeling that the anandamide receptor is not there to give you a high. It's there for other reasons. It must be for very important reasons because of its distribution.

LH: Yes. What we need is a theory very similar to what the Japanese fellow did with the antibodies.

JA: Oh, sure. Well, I think like the antibodies, we can recognize and detoxify any compound that the chemists can synthesize. But anyway, we are at it for an hour and a half.

LH: No problem.

JA: You should have gotten by now a general idea of what I have been doing.

LH: Well, I think it has just been a remarkable career. You have had more influence in psychopharmacology than any person I can think of, largely because of the eminence of your graduate students and fellows.

JA: Well, thank you. You're very kind. But, you know, these post-docs were so bright to begin with. And when they came to my lab, I realized that most of them were much smarter than I am. You know, I could never have gone to Harvard Medical School or Hopkins or wherever they went. They picked up things fast. They developed things. But I think the interaction between their good brains and my ability to see connections made a good combination. I tried to pick a problem that we're both interested in, and got them enthusiastic enough to succeed initially, so that they could go off on their own, as most of them did.

LH: Now it goes into the second generation. There is this wonderful book, called Apprentice to Genius, in which you figure very prominently.

JA: Yes, well, I came out very well in that.

LH: And now you tell me you are going to be 85. But, it's so true, you know. You and Brodie had a tremendous influence.

JA: Yes, Brodie had a tremendous influence. I think I mentioned it in the book that the greatest thing that happened to me in research was working with Brodie. The second greatest thing was leaving Brodie. It's been beyond my wildest dreams to think that I would last so long and will do the things I did. It was very satisfying.

LH: Well, it must be a very satisfying career to look at, and I think the whole story of your life is inspirational.

JA: Yeah, well, you know, I wasn't a brilliant student. I was a good student. I will be 85 years old next month, on May 30.

LH: And you still have a laboratory.

JA: Yes, actually, I have a new post-doc now. I can't tell you much about what we are doing because it is still in the process of development, but if it does develop it's going to be an interesting thing.

LH: I see you are still publishing.

JA: Oh, yes, I publish, but not like I used to. I used to publish 15 to 20 papers a year. It is good if I publish one or two a year now. I've been lucky. You know, doing research wasn't always a very happy experience. There are lots of disappointments. Most of the experiments don't work out. I had very high expectations, and when experiments didn't work I felt pretty depressed. But once an experiment works, there is nothing like it.

LH: Well, you certainly have been an inspiration, and I want to thank you so much for taking time out and coming down here.

JA: Well, it's a pleasure. I don't know whether you want to ask me any more questions.

LH: I just wish you could be around for the next 50 years.

JA: Well, I'll be happy to hang around until the year 2000.

LH: And see all the great developments in the future.

JA: Well, things are happening so fast. You know, just in the last five years the reuptake molecule has been cloned. We call it a transporter.

LH: It's an exciting period.

JA: Yes, I know. I think neuropharmacology has a great future.

LH: Thank you so much. It has been a great pleasure.

JA: Well, thank you.

#### 4. FRANK J. AYD, JR.

LH: Frank\*, you are one of the older hands in the field of psychopharmacology. I think you were one of the faces on the historic photograph taken at the Woodner Hotel a number of years back where the founding fathers met together. How did you get into the field?

FA: Well, Leo, I got into psychopharmacology because I had some experience before I graduated from medical school with the impact of electroconvulsive therapy (ECT) on my father, who happened to be a manic-depressive. I saw the dramatic effect of ECT on my dad. He made a fairly prompt recovery and didn't require hospitalization again. At the time we didn't have succinyl chloride, intravenous barbiturates, or the machinery that we have today. So it was a rather crude thing. Still, it worked. But it did produce a lot of memory impairment.

LH: That got you into the biological side of it.

FA: I had started a residency in pediatrics but got called to active duty by the Navy. In the incomprehensible way the Navy does things I was assigned to surgery at Bethesda Naval Hospital with no manual dexterity whatsoever and no interest in surgery.

LH: You actually went to surgery from pediatrics.

FA: That's right. Quite a change! At any rate, Admiral Hogan was commanding officer at the Naval Hospital at Bethesda, and I knew him. He happened to be Roman Catholic and we had been at a couple of retreats together at the Jesuit retreat house at the Naval Academy. So I had no hesitancy in saying to him: "hey, Ben, somebody's made a terrible mistake." He looked at my credentials and said: "well, we need psychiatrists. I'm going to send you to Bainbridge and they'll loan you to the VA hospital at Perry Point." So I went into that program. I thought it was a fate worse than death, because I had no real interest in psychiatry. But I was determined that I could take care of the physical aspects of things. It didn't take me very long, Leo, to realize that chronic schizophrenics are a different breed from the rest of us; they have altered temperature and pain

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\*Frank J. Ayd, Jr. was born in Baltimore, Maryland in 1920 and graduated in 1945 from the University of Maryland School of Medicine. From 1955 he was chief of psychiatry at Franklin Square Hospital in Baltimore. He was also director of education at Taylor Manor Hospital in Ellicott City, Maryland, and president of Ayd's Communications. He died in 2008. He was interviewed in San Juan, Puerto Rico on December 13, 1994.

sets. The only physical treatments at that time were insulin coma and ECT and since I had seen what ECT did for my father I volunteered to do the ECT. While at Perry Point, I was approached in my third year by Squibb. They had mephenesin, a muscle relaxant.

LH: That was sort of a meprobamate-like drug?

FA: That's correct. It preceded meprobamate. Anyhow, they were interested in somebody doing a study to see whether it had any value as a sedative drug. I did a small study in a number of chronic schizophrenics, and it did absolutely nothing. But it got me identified as an individual who might be interested in doing research with pharmaceuticals in psychiatric illnesses. As a consequence, when I left Perry Point and went into private practice, I received a phone call from a psychiatrist by the name of Bill Long. Bill was with Smith, Kline and French (SK&F). He knew me because his brother had taught me. And he said: "I hear you've got some interest in testing drugs." And I said: "I do." And he said: "Well, we've got one from Rhône-Poulenc, and we're looking for people who will take a look at it." I agreed that I would take a look at it. That was in December 1952.

LH: Needless to say that the drug was chlorpromazine.

FA: It was chlorpromazine. I tested initially the 10–25 mg dose. Within a year, I had enough data to prepare a paper. I presented the paper at the Southern Medical Association meeting in St. Louis. Titus Harris and Doug Goldman were the discussants. The paper was well received and CIBA had somebody at the meeting. I don't remember his name.

LH: Dick Roberts?

FA: No, it was somebody that I didn't know. But somebody from CIBA approached me after I had given my paper and wanted to know if I would be interested in taking a look at reserpine. I said, "Well, I'll try it." So I did. And the following year I gave a paper on both chlorpromazine and reserpine at the American Psychiatric Association (APA) meeting in Atlantic City. And from there on it's just been plucking at one drug after another, trying to determine not only whether they work, but also how do they work, and at what price.

LH: I take it that your initial experiences with chlorpromazine and reserpine impressed you pretty much about their efficacy.

FA: That's correct. Mainly, the experience with chlorpromazine. Reserpine worked, but the price was too much in the way of side effects. I was never convinced that reserpine was a depressogenic agent. It certainly produced enough, not dangerous, but uncomfortable side effects. I

considered it really wrong to persuade a patient to take this stuff for a long time because the benefits were not that apparent as they were with chlorpromazine.

LH: So you got launched in the field after working with those two drugs, and you say you've studied God knows how many. How many drugs did you study?

FA: Well, I really don't know the exact number, but practically speaking, every neuroleptic that ever got on the market in this country except for Clozaril (clozapine) and Risperdal (risperidone). I've looked at both after they were marketed. I don't do any more research prior to marketing. It's impossible to do that now.

LH: Why?

FA: Well, first of all, managed care is having its impact on your capacity to do research. I'm in private practice and if you are not approved with a particular insurance carrier, then you lose the patient unless they can pay out of their own pocket. The number of my new referrals decreased because I have not become a Health Maintenance Organization (HMO) or preferred provider doctor. And I don't want to be. I want to maintain my autonomy and independence. That's the first problem. The second problem is, you know as well as I, Leo, the Food and Drug Administration (FDA) criteria for baseline data has increased tremendously. A lot of people just don't want to do electrocardiograms (EKG's), electroencephalograms (EEG's), and maybe even ophthalmological examinations, often at their own expense, to get a medication and a general physical free. So research with outpatients is declining. At any rate, I looked at not only the antipsychotics, but also the antidepressants. Nate Kline and I were good friends up until the day he died. But Nate got very angry with me because I published a paper on Marsilid (iproniazid) in the American Journal of Psychiatry. It was just a brief report, but he felt that I did it to steal his thunder, which was not the case.

LH: Oh.

FA: Nate was the man who got the credit for the discovery that monoamine oxidase (MAO) inhibitors were psychic energizers. As you know, it was disputed whether it was him who deserved the credit. In fact, I ended up with Henry Brill testifying along with Jack Howard in a court case.

LH: In Saunders' suit?

FA: Saunders' suit against Nate. Saunders didn't sue the first time when Nate got the Lasker Award for reserpine. But when he got the second one, he said I should have gotten that.

LH: Well, I don't think Lawrence Saunders was very active in Nate's work with reserpine, but he was probably intimately involved in the work with Marsilid.

FA: I'm sure he was. He left CIBA to join Nate at Rockland State. But, as you know it did end up in the courtroom. It was finally settled, and Nate got the credit.

LH: Well, that's not the first time that a major prize has been disputed.

FA: No.

LH: I think somebody disputed Waksman's Nobel Prize for streptomycin.

FA: Yes, I know that only too well.

LH: I can't tell you anything you don't know.

FA: He went to Israel when the Waksman Institute was dedicated. On his way back he stopped to have an audience with the Pope, and I interviewed him for the Vatican radio. At the luncheon after the interview, we got talking about different things, and he mentioned that he had been almost sued, so to speak.

LH: You indicated that early on you did a whole lot of clinical studies, but it is difficult to do these studies now in private practice.

FA: Oh, yes. Number one, it was easier to do clinical studies then. Number two, there was no competition. I was a pioneer. There weren't many people around doing clinical studies with drugs. It's no secret, Leo, in my hometown of Baltimore I was looked upon as an oddball, the guy who instead of thinking about the id and ego was interested in what's going on in the brain of people who have different psychiatric disabilities, and trying to treat them with chemical restraints, as they called it in those days.

LH: Oh, really?

FA: Oh, yes. I was different. There were very few psychiatrists either at the University of Maryland or at Hopkins working with drugs.

LH: I can't think of anybody from Baltimore in the early days. How about this fellow Winkelman in Philadelphia? How did he get on to work with chlorpromazine?

FA: Well, Bill worked in Philadelphia. He's an analyst working in private practice, but he always had some interest in physical methods of therapy.

LH: I thought he was a prominent neuropsychiatrist and neuropathologist.

FA: That's correct. Bill was serving as a consultant to SK&F. He and Bill Long. Long was an eclectic psychiatrist. That's how Winkelman got chlorpromazine.

LH: Were you aware of his work at that time?

FA: When I first went to meet Dr. Long he told me about Bill. In fact, it was just about that time that Bill's article appeared in the JAMA (Journal of the American Medical Association). So he was really the first in the United States to do enough patients to get a paper together.

LH: Now, of course, you knew Heinz Lehmann as well.

FA: Oh, yes. I met Heinz very early. He was the first in North America, not just in Canada. I also met, of course, John Kinross-Wright. In 1953, Bill Winkelman, Frank Jay and John Kinross-Wright were the three people who did the early work with chlorpromazine in the United States.

LH: I guess reserpine was only Nate.

FA: Nate Kline was the principal man with reserpine. I did some work with reserpine, but I didn't go on beyond the first 50 or so patients, I then stopped.

LH: I don't know whether that chap, out in Augusta State Hospital who also got that Lasker Award for reserpine was working about the same time as Nate. I can't remember his name.

FA: I can't think of his name either. I guess that shows where we are.

LH: So much for glory. While we are talking about studies here, what was the drug that impressed you most?

FA: Well, obviously, chlorpromazine was tremendously impressive; mainly because of its immediate impact on agitation and anxiety. You could take a pretty disturbed individual and in a matter of hours you could see a change. They were still hallucinating and they were still deluded, but by God they were changed. In the antidepressant field it was impressive to see patients respond to imipramine almost as well as some responded to ECT. They were not the psychotically depressed patients, but what you would call in those days endogenous depressed patients; those patients, who come in with a history of recent weight loss, have early onset of their disease and late insomnia. You know, they're melancholic; they have a lot of vegetative symptoms and so forth. With an adequate dose of imipramine in a matter of four to six weeks you saw a lot of dramatic improvement in these patients.

LH: When you go from nothing to something that works, that's a huge jump. But then after that, the jumps become incremental.

FA: That's very true. But you see, they opened a whole new field. I mean it was the first really good option in the treatment of depression beside ECT. The monoamine oxidase inhibitors (MAOIs) had also a place in the treatment of depression. They still have a very valuable place.

But you had the problems of the side effects of Marsilid (iproniazid) which were not necessarily dangerous, but troublesome. Then you had the problem of jaundice.

LH: I got that on the third patient I used Marsilid on.

FA: A couple of patients died, and that really hurt. For a while it looked like the end of the MAOI and would have been the end if SK&F had not already started looking at tranylcypromine.

LH: Well, the peculiar thing is that Marsilid was first for tuberculosis. It was used in tubercular patients when the famous picture was published in which patients at the Public Health Service hospital in Staten Island were dancing.

FA: Dancing on the ward.

LH: Yes, but because of the problems with iproniazid, it was replaced by isoniazid.

FA: Right.

LH: And a number of studies done with isoniazid were negative.

FA: Right.

LH: The reason for this was that isoniazid was unlike iproniazid. It did not block MAO.

FA: Well, be that as it may, as you know, the MAOIs came close to death themselves.

LH: Well, I think, it was Zeller first to point out the fact that there was a difference between iproniazid and isoniazid. If they had gone on with isoniazid and found nothing going, this group of drugs would have dropped dead right there.

FA: Right. Well, it didn't take long to realize that MAOIs interacted with foods. We now know it was tyramine and sympathomimetics that created the trouble.

LH: That was a big deterrent for a long while, but lately people don't seem to be as much concerned about it as they used to be.

FA: Well, I think partly because they warn patients, and they give them a list of dietary substances that should be avoided. They warn them about taking over-the-counter preparations that contain sympathomimetics. And I think that in actual fact phenelzine is safer, and probably even tranylcypromine is probably a little bit safer, than Marsilid, although I don't know of any direct comparison studies.

LH: No, I don't know any studies either.

FA: But the MAO inhibitors definitely have a place in treatment. We owe a lot to people like Fred Quitkin here and Will Sargant and his group in England because they stuck with them. And I've stuck with them even to this day. I prescribe more, I'm sure, than most people in my

geographic area because I'm convinced of their value in certain types of patients. When you think about it, you've got an alternative to MAO inhibitors and you have an alternative to ECT with imipramine. That really opened the gate for developments.

LH: Well, some of the earlier comparisons, I think one that Milton Greenblatt was part of, seem to indicate that the tricyclics were not a whole lot better than placebo; that ECT was better than tricyclics. Do you think that was because they were looking at very severely ill patients?

FA: Well, I think that may be part of the answer. I think the other part was dosage. Greenblatt's study also included phenelzine, if you recall, and the patients only got 30 mg of phenelzine a day when most patients with a moderate to severe depression require 90 mg. So it was a question of too low a dosage for too short a period of time. It was a methodologically flawed study.

LH: It almost did him in, too, didn't it?

FA: Yes, it almost did him in. Because Milton was a very fine man and very prestigious, and here he is at Harvard and working at the Mass Mental Health Center.

LH: Well, it's amazing how the drugs survive. You weren't at the Paris meeting in 1954 on chlorpromazine, were you?

FA: No. My wife was there, and she gave my paper for me.

LH: I had occasion to review the proceedings of that, and I didn't remember your name. What was the first big meeting you recall on these drugs in the US?

FA: Well, I guess the first really big one was the one on Thorazine (chlorpromazine) that SK&F sponsored, in Philadelphia.

LH: But that was a private session, wasn't it?

FA: Yes, it was private, but there were several hundred people there. And they published a little monograph of the papers that were presented, and they did the same thing later when they launched trifluoperazine, Stelazine. I guess the APA meeting in 1956 probably was the first big meeting where there were a number of papers not only on chlorpromazine but also on other drugs, such as my paper on reserpine. It was also the meeting where meprobamate was first mentioned. That gave cause for thinking about which way the wind was blowing. It certainly was blowing in the area of biological psychiatry.

LH: Yes, I think the pendulum still is on the side of biological psychiatry. Some people are arguing that perhaps it is too far over on the biological side. What do you think about that?

FA: Oh, I don't think so. I think that you can't lose sight of the fact that you are not just treating an illness but a human being who has the illness. You have to be aware of the physical status of that individual, and also of the fact that he is the one who has the illness and is going to react to the illness differently than somebody else who has the same illness. You can't treat just with drugs alone. There's got to be some psychoeducation, or whatever you want to call it, and some type of psychotherapy. I can't conceive of an internist treating a diabetic without at least giving the diabetic something besides diet and insulin in the way of counseling.

LH: Foot care, and other things.

FA: That's right. You have to do this. You are not just dispensing pills if you are practicing rational psychopharmacotherapy.

LH: You mentioned before a few people who were using chlorpromazine early. One of the people I think everybody often forgets is Mark Altschule.

FA: Mark was a very interesting person. He was a very intelligent man.

LH: A real scholar.

FA: No question about that. His wife had schizophrenia. She was in McLean Hospital. Mark really believed in the marriage contract. He stayed with her until she died, and he always looked for something that might help her. Yes, he definitely became very well informed about chlorpromazine at an early time.

LH: He was an internist, more interested, I think, in cardiology than in psychiatry, but he was one of the first people involved with the drug.

FA: Yes. One man we haven't mentioned so far is Fritz Freyhan. Fritz was involved very early with chlorpromazine. He was at Delaware State Hospital. Like everybody else working in a state institution or a Veterans Administration (VA) hospital, he had hundreds of patients and no drugs. So he could really test drugs on a large number of patients very quickly. Fritz was a very astute clinician, I thought.

LH: Yes.

FA: Well trained in a German school. He was a very good observer. I learned a lot from him. I had more contact with him than I did with Heinz Lehmann in the beginning because Heinz was in Canada, and Fritz was in Wilmington, 60 miles away from where I was. He did a lot of studies for SK&F. We worked together on chlorpromazine. We looked also at prochlorperazine. He and I did two studies on prochlorperazine for SK&F, and we looked at trifluoperazine. Fritz also got

interested in fluphenazine. Then we both looked at Temaril (trimeprazine), an antipyretic phenothiazine.

LH: Yes, but it has a different kind of pharmacology. It makes it more of an antihistamine.

FA: That's right. We tested it as a potential antipsychotic, and it just didn't work.

LH: Do you know Pacatal (mepazine)?

FA: Pacatal was the most anticholinergic antipsychotic, if it was an antipsychotic. It really was a very strong anticholinergic substance.

LH: Yes, it never went very far.

FA: No.

LH: And do you know Sparine (promazine)?

FA: Promazine, the Wyeth product. Again, there were some patients who improved, but only because it was sedative. As far as I'm concerned, it never had any true antipsychotic properties.

LH: Well, if you give patients enough promazine they get seizures.

FA: Oh, yes. But that's true for practically every psychoactive drug. If you give a high enough dose, you can produce a seizure.

LH: Well, not to the same extent as with promazine, I think.

FA: That's true.

LH: Fifty% seizures once you got up to about 1,200 mg.

FA: Yes, that's true.

LH: In a way it is interesting that truth won out. Some drugs fell by the wayside, like Pacatal and promazine, whereas others were more acceptable and efficacious and lasted. Well, I guess the early people in the field were pretty astute.

FA: Right. Anybody who has success with psychopharmaceuticals today owes a debt of gratitude to the people who pioneered these drugs.

LH: It is remarkable also that most of the people we have mentioned were outside of the academic community.

FA: That's true.

LH: Why do you think that was the case? Was it simply the fact that the academics were all psychoanalysts?

FA: Basically that's the truth. The medical schools in my area were dominated by psychoanalysts as they were practically everywhere else in the US, and there was no encouragement to think in terms of anything beyond the psyche, so to speak. I don't know of a medical school, in the beginning, that got into psychopharmacotherapy.

LH: Yes, it's hard to think of any. I guess; you know, Kinross-Wright was at Baylor.

FA: Well, he actually was in Carolina first and then went to Baylor.

LH: Then, of course, Mark Altschule was in the department of medicine at Harvard.

FA: And Paul Hoch who was at Columbia, at the New York State Psychiatric Institute.

LH: Did Paul do much with antipsychotics?

FA: He did a little, but not a great deal.

LH: He was more interested in hallucinogens.

FA: That's correct. But my point is that it was not easy to do what Henry Brill, Nate Kline and myself were doing in those early days. Everybody was suspicious. But at the APA meeting in Atlantic City in 1956 that I mentioned before, the executive director of the National Mental Health Association was present. He got Henry, Nate and I agree to go to Washington and testify before the senate and Mr. Hill's committee, and to tell them what was happening in our field with the hope to get the federal government involved in funding research in psychopharmacology. And so Henry Brill, Nate and I went to Washington. We each gave a presentation and suggested the formation within the National Institute of Mental Health (NIMH) a division devoted solely to psychopharmacology. Senator Hill was very impressed and, as a matter of fact, he supported it. That accounted for another meeting in Washington. Lou Lasagna was there, so it was more than just psychiatry. We got pharmacologists involved. Ralph Gerard from Michigan came. He was the man responsible for Jon Cole becoming the first director of the Psychopharmacology Service Center (PSC).

LH: Gerard was the author of that famous line: "Behind every twisted thought lies a twisted molecule," that I guess for a long while was kind of the moral of biological psychiatry.

FA: Yes, that's true. When you get to that point you begin to attract more attention. Before that, we were called medicine men. We were compared to the guys from the old wild-west going around selling snake oil. Reputable medical journals were not interested in publishing articles on the various psychopharmaceuticals. I gave a paper at the New York Academy of Sciences, Leo, one of the first papers I ever gave. The discussant was Nolan Lewis. You remember Nolan? He was

president of the APA at one time. And the closing comment of his discussion of my paper was: "fellows, we ought to prescribe this stuff while it still works." Well, that's not a very good endorsement, is it?

LH: Well, I think that was the prevailing attitude in psychiatry in those days. Drugs couldn't work because they had been tried before and didn't. There had been over the years a lot of attempts to use drugs. Well, what do you think was the biggest accomplishment that you've made? I know that's a tough question because you've made a lot of them.

FA: Well, I think aside from looking at the drugs and being persistent, I was sort of a St. John the Baptist in the wilderness preaching the gospel of the psychopharmaceuticals and their potential value for people. But as you know, some people called me for a while Dr. Side Effect, because I was very interested in adverse effects. I felt that I should tell a balanced story that for every blessing there can be smite; you can help and you can smite people with these drugs. That was the first thing. The other one was that I started talking very early about the potential advantages and disadvantages for long-term therapy. I gave a paper at the Third World Congress of Psychiatry in Montreal on one-year continuous treatment with imipramine; then I published a paper in the New England Journal of Medicine on a year's clinical and toxicological experience with perphenazine. I've been interested in long-term therapy. In addition of testifying before Congress I was very much involved in getting the American College of Neuropsychopharmacology (ACNP) started. I also went to Milan for the initial meeting of what was to become the Collegium Internationale Neuro-Psychopharmacologicum (CINP.) I played a role in the formation of the British College of Neuropsychopharmacology. I went over there at the request of David Wheatley, Tony Horden and Max Hamilton and met with them for a couple days, told them how we started the ACNP. I've tried to extol the virtues as well as the liabilities of the drugs, because they are the only things that have really changed psychiatry. There is nothing new in the psychotherapy field. Well, you have cognitive therapy and so forth. But the concepts haven't changed.

LH: I think it's become a little less dogmatic.

FA: Yes, I would say that.

LH: Psychotherapeutics now embraces a whole variety of techniques.

FA: Right. Well, the challenge of the drugs, Leo, is that you give a pill and over a period of days or weeks, there is a change in the individual. Bernie Brodie and I became friends because my

interest was in what happens. I would ask "what happens when you run a current from both temples through the midbrain, what did you do that suddenly changed a psychotic individual into a perfectly normal person?" And, in the early days, we didn't know how much of the drug was absorbed. We didn't know where it was going, how it got there. And so I was very interested from the beginning in what we call today pharmacokinetics and pharmacodynamics.

LH: Well, I think Bernie Brodie was probably the father of biochemical pharmacology, trying to explain drug action in biochemical terms.

FA: Right. I regretted that he wasn't around that I could have had him on the program of the symposium on Discoveries in Biological Psychiatry, because all we know today stems from his pioneering work. One of my benefits from starting the College was that I got to know him quite well. He, Jon Cole and I were on a committee, and we met frequently because Jon was still in Washington, he was in Washington and I was in Baltimore. I had ample opportunity to get to know him as a man.

LH: You mentioned earlier your testimony before Lister Hill's Committee. We were talking about political pressures in the early days. How about Mary Lasker's and Mike Gorman's work on the political front?

FA: Mike was the executive director of the National Mental Health Association. He was a very dynamic fellow. I don't know if you knew him personally?

LH: No.

FA: He really was a crusader for mental health. He believed in it and used his contacts in Washington. He played a major role actually in putting pressure behind the scenes on the other members of the committee who may not have been as convinced as Senator Hill was. Right from the beginning, every one of us had a feeling that he listened attentively and seemed to believe that there was something to what we were saying. You know how a Congressional Committee is. They sit. They look.

LH: In those days it was easier to persuade a senator than your own colleagues.

FA: Oh, absolutely. That's very definitely the truth. Well, anyway, Mike played a major role in publicizing psychopharmaceuticals. He saw that it was the only concrete thing that really made a difference. And, of course, he had his connections everywhere. He had connections both in Washington and in New York with Mary Lasker. I strongly suspect that Mike played a role in Heinz Lehmann, Pierre Deniker, and Nate Kline getting the Lasker Award.

LH: Do you think the reason that Hill became such an advocate of health was that his first name was Lister?

FA: I really don't know. But he definitely had an interest in this field. There's no question about that.

LH: You were almost a pediatrician and reluctantly, a surgeon.

FA: That was very short-lived. Three weeks.

LH: Sort of accidentally you became a psychiatrist. Do you have any regrets about the way things have turned out?

FA: No, none whatsoever. You know, when I was in medical school, psychiatry was not high on the list. Your exposure consisted of a few lectures, mostly on psychodynamics, and then a trip out to the state hospital. You were sort of taken on a guided tour: that's schizophrenia, this one's manic, this is mental retardation.

LH: Like a zoo, wasn't it?

FA: That's right. And, you know, there was nothing appealing about it whatsoever. But a few weeks after I got to Perry Point, I was assigned to what was euphemistically called continuous treatment service.

LH: That meant for people who were there for years.

FA: Well, there were 800 patients in the ward that I was assigned to, Leo. Most of those people were still under 60 years of age, but they had been in that hospital, most of them, 20–30 years.

LH: Many since World War I.

FA: That's it. Well, I even had one from the Spanish-American War, an old geriatric guy. But, actually, you learned one thing: schizophrenia was chronic and devastating. And it would be true if you put over the portal "abandon hope all ye who enter here", because your chances of leaving, outside of a pine box, were pretty slim.

LH: Well, it has been sort of gratifying, hasn't it, to see the changes that have occurred.

FA: Yes.

LH: Do you think we've gone too far in de-institutionalizing people?

FA: Well, I think so.

LH: Is there still room for an asylum?

FA: Yes. And that's one of the things the New York Psychiatric Association and the ACNP ought to be taking a very strong stand on. Look, there are people who can be controlled with these

medications in a structured environment, but they cannot be relied on to comply with a pharmaceutical program on their own out in the community, and they deteriorate. So, as you know, then tragic things happen. We had a woman in one of those so-called halfway houses in Baltimore some time back who was found dead in bed with a ruptured appendix when they did the autopsy. She was a deteriorated schizophrenic. She was put out of state hospital. She wasn't bothering anybody. She was too deteriorated to bother anybody.

LH: Schizophrenics seem to be so indifferent to pain.

FA: That's very true. When I got to Perry Point, the ward I had was approximately 3/4 of a mile to the dining hall, and three times a day the patients walked over to the dining hall. The attendants had to fight these guys in cold weather to put a coat on. And I remember one night, Leo, I was the officer of the day, and an attendant called and said a patient had gotten out from the shower and they couldn't find him. And, in my naivety, I said to him: "Oh, it's so cold now. He can't be gone long. He'll be back." This attendant was a farmer who worked part time at Perry Point. He said, "Doc, you don't know schizophrenics. If we don't find this man, he's going to be dead." And so he impressed me and we organized a search party. When we found this fellow he was hypothermic. We were lucky we saved his life. I didn't intend to become a psychiatrist when I went there but made a resolution that I could take care of their physical needs. But I saw patients collapsing from ruptured ulcer who never complained. We had a couple of patients who developed nausea, vomiting, clear meningitis, who must have had horrible headaches, but never complained. I remember one night a fellow stuffed himself with newspaper and ignited it. And when I got there he was pretty badly burned, but he was still sitting there, hallucinating and answering to voices. We never gave him any morphine. He didn't need it. You're right. Their pain and their temperature sense are quite different.

LH: It could be that Harry Beecher's old idea that pain is processed up here in our head, could explain this indifference to pain that psychotic people seem to have. Well, would you do it again?

FA: Yes, I would. In fact, when I look back, and I do that fairly often, I wish I had done more.

But that's in retrospect. I couldn't have done it if I had wanted to. We didn't have what we have now. The excitement today is still as intense as it was back in 1953, '54, and in the 1960s, with the neuroimaging and all these other things that are happening.

LH: Yes, science is changing so rapidly, and even the vocabulary constantly changes.

FA: That's why I wrote my Lexicon.

LH: You have to know now what LOD scores are and all kinds of things that you have never thought of before. Well, I think you can look back on a very interesting and illustrious career. You have already put some of your thoughts about this subject in writing and published them. I think this interview helped bring out a few more personal things than you would have put in your writings.

FA: That's true. I want to say one thing before we end, Leo. The credit for what I've accomplished should be given to my admiration of other people. You know, when I got involved with drugs, there weren't many people around I could turn to. ECT was not done at the medical schools, either at Maryland or at Hopkins. There was one fellow doing ECT, Lothar Kalinowsky, who was sort of looked upon as a renegade. So I wrote a letter to him and said, "I would like to come and spend some time with you." He graciously agreed to have me. I went up for a week, stayed at a hotel, and spent one week with this man. He was one of my tutors. I did the same thing with Howard Fabing who was in Cincinnati. I called Doug Goldman, and I spent time with Doug Goldman. I went up to Canada and spent time with Heinz Lehmann. They were my mentors. These were the people who taught me. So did Titus Harris. He was not a biological psychiatrist. Still, he was a champion of physical methods of treatment, and developed one of the first departments of biological psychiatry in the US. There were a lot of people like that who played a major role. Well, even you. Look how much you've shared with me and taught me. That's been a lot.

LH: It's always mutual.

FA: No man accomplishes anything by himself.

LH: Well, thank you, Frank, for a rather interesting discussion and anytime you want to say more...

FA: Well, that's up to you.

LH: God, you're easy to interview.

FA: Thank you.

## 5. THOMAS A. BAN

LH: It's Monday, December 9, 1996, and we're at the annual meeting of the American College of Neuropsychopharmacology in San Juan. I am Leo Hollister and today I am going to be interviewing an old hand in this field, Tom Ban.\* Tom, welcome to San Juan for the umpteenth time and we have the great pleasure to talk with you. You and Tom Detre, I think, are the ACNP's biggest beneficiaries from Hungary.

TB: Thank you, Leo.

LH: After the uprising or whatever it was, in 1957, you both immigrated and both wound up in the ACNP. Were you a full pledged psychiatrist when you left Hungary or were you just in medical school?

TB: I graduated from medical school in 1954 and had two years of psychiatry before I left.

LH: Oh, you'd had some psychiatric training?

TB: Yes. We didn't have a formal residency training program in Hungary at the time but I was working as a junior physician at the National Institute for Nervous and Mental Diseases in Budapest. LH: I see.

TB: I even had my first exposure, in Hungary to some of the new psychotropic drugs, like chlorpromazine (CPZ), reserpine, etc.

LH: Now, I suppose there were quite a few who left Hungary at that time? They didn't like to live under a communist regime. At least, Hungary is in better shape today than it was then. Now, you came to join Heinz Lehmann in Montreal. Had that been arranged before you arrived to Canada?

TB: No.

LH: Well, then, what made you go to Montreal, of all the places in North America that you could have gone?

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\*Thomas A Ban was born in Budapest, Hungary in 1929. He was initially trained in psychiatry at the National Institute for Nervous and Mental Diseases in Budapest. When he left Hungary in 1956, he obtained a fellowship at the Montreal Neurological Institute, followed by further psychiatric training at McGill University. During his time at McGill, he conducted research in psychopharmacology and conditioning in psychiatry. In 1976, he moved to Vanderbilt University to direct the clinical division of the Tennessee Neuropsychiatric Institute. He was interviewed in San Juan, Puerto Rico on December 9, 1996.

TB: After I left Hungary I was working for about two months at the psychiatric clinic of the University of Vienna in the EEG laboratory primarily. I was also involved with some of the patients at the clinic, mainly as an interpreter. While trying to find a place in the world where to go, I wrote to Wilder Penfield, and in my letter I mentioned that as a medical student I had won an award in a competition with my dissertation on post-traumatic epilepsy. It was a real surprise that he answered and an even greater surprise that he generously offered a fellowship in his Institute.

LH: Penfield was a giant. The Montreal Neurological Institute at that time was world class.

TB: It was a fantastic place.

LH: So, that's how you got to Montreal and then it was just sort of accidental that you got to work with Heinz Lehmann?

TB: It was not completely accidental. After my arrival to Canada in January 1957 I spent six months at the Montreal Neurological Institute (MNI). My assignment was in neuroanatomy but I also participated in the activities of Herbert Jasper's neurophysiology division and attended the epilepsy and multiple sclerosis clinics.

LH: Did you have any contact with Penfield?

TB: I had some contact with Penfield but it was Francis McNaughton who took me under his wings. Then, I did a rotating internship at the Victoria General Hospital of Dalhousie University in Halifax. I spent two months from that year at St. Joseph's Hospital in Glace Bay, Cape Breton Island delivering babies, before returning to Montreal.

LH: How did this happen?

TB: During my internship I applied to the residency-training program in psychiatry at McGill.

LH: So that is how you got to work with Heinz.

TB: Yes. I marked on the applications form that my preferential first rotation would be the Verdun Protestant Hospital, one of their training facilities, because I knew that Dr. Lehmann was the clinical director of that hospital. I didn't know him, but I had read one of his papers while still in Hungary, and heard people talking about him while I was at the MNI and also at Dalhousie. I became interested in psychopharmacology very soon after I started at the National Institute.

LH: By using chlorpromazine?

TB: After using chlorpromazine for a couple of months in a limited number of patients I became so enthusiastic about its advantages over the old treatments that I persuaded Dr. Sandor, our service

chief, that we start in the Institute a quarterly publication on new developments in neuropsychiatry and especially in pharmacological treatment. So, I was familiar with Lehmann's name already in Hungary from reviewing the literature for our publication

LH: Sure. Well, you made a lucky contact. Actually, you got a mentor right at the top.

TB: Yes, I was very lucky. I met Dr. Lehmann for the first time at the Verdun Protestant Hospital on the 1st of July 1958. It was the first day of my residency.

LH: I guess, by that time, Heinz was pretty heavily into research, wasn't he?

TB: Yes, he was. He already got his Lasker award for his contributions to the clinical development of CPZ, about a year before that. And, I think he had just published his paper, the first paper in North America on imipramine.

LH: I think so.

TB: Heinz was very much involved in psychopharmacology and in all kinds of other research in psychiatry in those days and within a month I was working with him on several of his projects. In fact, I started to work with him on the second day of my residency. He was interested in the effects of drugs on biological systems of low complexity at the time and we were studying the effects of prototype drugs like dextroamphetamine, secobarbital, chlorpromazine, prochlorperazine, imipramine, lysergic acid on enzymological, growth and reactivity systems. I worked with urease, firefly lantern extracts, proteus bacteria, oat seedlings, the feeding reflex of hydra, and dandelion sleep movements. We were also trying to make mute patients speak by inducing fever, giving ECT and administering them amobarbital, dextroamphetamine, chlorpromazine, LSD, etc.

LH: Now, how long were you in Montreal?

TB: About nineteen years.

LH: Nineteen years. Of course, during that time, you become more and more an independent investigator.

TB: Yes, but all those years Heinz and I worked very closely together. The first independent line of research I conducted was in conditioning. It was supported from a grant I received from the Medical Research Council of Canada. But, actually, I got involved even in that area of research on Heinz's initiative. At the time to get our diploma in psychiatry at McGill we had to write a thesis and I got involved in research in conditioning because the hospital had a conditioning laboratory and Jim Prescott, the psychologist who set up that laboratory was leaving.

LH: So, it was the laboratory that dictated your career.

TB: Yes and essentially that Heinz was looking for someone who might be interested to do research with him in the conditioning laboratory.

LH: He had done a lot of such work before he got into chlorpromazine.

TB: That's right. He had done a lot of research with psychometric performance tests, and also, some research in psychophysiology. For my thesis I had to review the literature on classical conditioning and had to do also some laboratory research in conditioning in human.

LH: When did you finish your training?

TB: I received my diploma in psychiatry from McGill in 1960. My thesis, Conditioning and Psychiatry, was published with some minor modifications as a monograph, first in 1964 by Aldine in Chicago, then in 1966 by Unwin in London. The foreword to the book was written by Horsley Gantt, at the time one of the last living disciples of Pavlov. During the 1960s my research in conditioning and in psychopharmacology was closely linked.

LH: So, this is how you got involved in conditioning research.

TB: My objective was to develop a common language for mental pathology and psychotropic drug action, using conditioned reflex variables. To bridge the gap between pharmacodynamics and psychopathology, we developed a conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects. I perceived conditioned reflex variables as functioning patterns of the central nervous system and described mental pathology and the action of psychotropic drugs in terms of the presence or absence of these variables, such as the startle response, extinction of the orienting reflex, acquisition and extinction of the conditional reflex, delayed and trace reflex formation, and so on. One of our papers on the development and use of the battery won the Canadian Psychiatric Association's McNeil Award in 1969

LH: So, your first line of inquiry was in classical conditioning.

TB: Yes, but I combined some of our research in conditioning and psychopharmacology. We had some interesting findings in those studies.

LH: For example?

TB: For example, findings in one of our studies indicated that changes in orienting reflex behavior was more closely linked to a favorable response to neuroleptics in schizophrenia than the appearance of fine tremor in the hands.

LH: Well, I know you've been one of the few people in our world, who has tried to develop new tests based on classical conditioning for identifying biologically homogenous diagnostic

populations in psychiatry. Are you very happy with the present state of affairs in psychiatric diagnosis?

TB: Well, I think, at least in the past 15 years or so we are trying to develop a common language for diagnosing patients.

LH: At least, we are defining our terms.

TB: We have at least diagnostic categories that can be reliably identified. Consensus based diagnoses undoubtedly are an important step forward in the provision of psychiatric service. They might also be useful in epidemiological research. The problem is that they are detrimental for progress in nosological research. They cover up their component diagnoses that might be selectively affected by psychotropic drugs. It seems the use of consensus-based diagnoses has not provided the necessary feedback for developing clinically more selective and thereby more effective psychotropic drugs.

LH: Well, I think it is a step forward to have this common language and that we all have definitions for diagnoses, but I sometimes wonder whether it might not get in our way because it lumps all kinds of people together and labeled for example as schizophrenic.

TB: The diagnostic concept of dementia praecox or schizophrenia, as you know, was created by Kraepelin by pooling together three major diagnostic categories of illness, hebephrenia, catatonia and dementia paranoïdes on the basis of their course and outcome. From the time of its inception the diagnostic concept of schizophrenia has been challenged. Karl Kleist in the 1920s divided schizophrenia into two classes of disease, and his disciple Karl Leonhard divided it into two classes with three forms and several sub-forms in each. In the 1980s I had a grant from NIMH at Vanderbilt, to study chronic schizophrenia. And in this study we showed that each form and sub-form of the two classes of disease Leonhard described exist. In fact there were no major changes in the distribution of the different forms and sub-forms of disease in Christian Astrup's patient cohort in the 1950s in Oslo, from Leonhard's patient cohort in the 1930s in Berlin, and in our patient cohort in the 1980s in Nashville.

LH: That's telling evidence that there must be something real about them. How about the stability of the diagnoses?

TB: We developed two diagnostic instruments and with both we could reliably identify each form and sub-form of disease in Leonhard's classification, but we didn't study the stability of the diagnoses. Clinically, patients who are diagnosed with one or another of the sub-forms of the

continuous forms of the disease, referred to as systematic schizophrenias, seem to display constantly the same syndrome whereas patients diagnosed with one or another sub-form of the episodic forms of the disease, referred to as unsystematic or non-systematic schizophrenias are more difficult to diagnose when in partial remission. But in relapse they seem to display the same syndrome as in their prior episodes. The same applies to unipolar depression, a class of disease in Leonhard classification that is also divided into two categories of disease, pure melancholia and pure depressions. These are episodic diseases and arguably patients are symptom free, between episodes. But it seems that in repeated episodes patients are diagnosed with the same subform.

LH: Well, that's true in individuals. Well, how about the concept of spectrum disorders, like depressive spectrum or schizophrenia spectrum diseases?

TB: The concept of spectrum disease implies a relationship between diseases. It is a broadening of a pharmacologically and genetically already broad, heterogeneous category of disease. We need narrower, biologically more homogenous populations for neuropsychopharmacological research.

LH: What do you think about diagnoses like dysthymia? They surely are depressed but they don't meet the criteria of a full-blown major depression. Does that make any sense to you to have these kinds of diagnoses?

TB: Patients diagnosed with dysthymia have depressive personalities displayed by all kinds of depressive symptoms. They don't have a depressive disease in which the mood transforms their experiences.

LH: Let me ask you a question. How much of what we see in these diseases is organic, biological, and how much is functional, the result of interaction with the environment?

TB: In spite of my research in conditioning and my interest in learning theory I look at the different forms and sub-forms of schizophrenia as natural forms of disease in which the interaction with environment plays little role. But, then if you look at the disorders in the DSM- IV, many of those disorders are probably the result of an interaction between nature and nurture.

LH: Well, I think everybody will agree on that it's not just all in our genes. Let me throw another curve at you. How about this issue of co-morbidity? Not only do we have a problem with spectrums, but, we now have an increasing problem of co-morbidity. When you speak of depression, you are often speaking of two or three other things, as well, aren't you?

TB: If you want to get a psychotropic drug prescribed to the widest possible population in which patients have a better chance to respond than to an inactive placebo, the concept of co-morbidity is very useful. For neuropsychopharmacological research, in which progress depends on the identification of treatment responsive forms of illness both concepts are counterproductive.

LH: Since we are talking about psychopharmacology and diagnosis, what do you think of Don Klein's idea that you can establish new entities based on the reaction of patients to a particular drug or drugs.

TB: Well, obviously a diagnostic system based on responsiveness to drugs is desirable. A good starting point would be the identification of treatment responsive forms of illness within the currently used diagnoses. Research in this area must be based on an understanding that responsiveness to the same drug depends to a great extent from the underlying condition.

LH: Your career then in Montreal was in neurophysiology and drugs?

TB: I would say I was primarily doing research in psychopharmacology and conditioning in this order. My primary job was directing the activities of our Early Clinical Drug Evaluation program as Dr. Lehmann's co-principal investigator of a grant from the NIMH.

LH: That's right. You were part of the ECDEU network.

TB: Yes, we were one of the first grantees and we were there from the very beginning. After the completion of my thesis I had a research grant as I mentioned before, from the Medical Research Council of Canada to pursue my research in conditioning. But, most of my research in conditioning was closely linked to my research in psychopharmacology.

LH: I see. So, your primary activity was directing the ECDEU.

TB: I spent part of my time for a few years on Ewen Cameron's team, who was the chairman of the department in the late 1950s and early '60s. I was responsible for recording psychophysiological measures after the administration of psychotomimetics, like LSD or psilocybin to our patients. Actually, I got on Cameron's team because he needed someone with some experience in conditioning and with psychotomimetics. My first research project in psychopharmacology, and this was back in 1958, was with phencyclidine, a substance originally developed for general anesthesia, that turned out to be a psychotomimetic.

LH: So, you worked with Heinz Lehmann and also with Ewen Cameron while at McGill. Did you work with anyone else while there?

TB: I also worked with V.A. Kral in a NIMH funded psychogeriatric program in which we studied the effects of psychotropic drugs in the aged.

LH: Now, in your work with the ECDEU I suppose you looked at the same drugs as the others in the network.

TB: I think we worked with all the psychotropic drugs during the 1960s and early '70s in Canada and the United States which were available for clinical investigations. Bill Guy, who at the time was with the Biometric Laboratory at George Washington University told me that they processed more studies from our unit than from several of the other units together. We were among the first in North America to study several of the thioxanthene and butyrophenone preparations. And, with drugs that showed clinical promise, we conducted a series of investigations. We also discussed the findings of these studies at symposia organized by the Quebec Psychopharmacological Research Association. We were especially interested in the differential therapeutic profile of drugs. So in one of our studies we compared chlorpromazine, chlorprothixene and haloperidol in the treatment of acute schizophrenia.

LH: That's an interesting comparison. In the company brochure, chlorprothixene was supposed to be good for everything, but it turned out not to be good for very much.

TB: In our study it was comparable to chlorpromazine in acute schizophrenia.

LH: Well, I don't doubt that chlorprothixene was an active drug, but it never went anywhere, you know, never caught on.

TB: We also worked with drugs that didn't catch on in the United States. One of them was methotrimeprazine, Nozinan, and another one was prochlorperazine, Stemetil. They were marketed as antipsychotics in Canada but not in the USA.

LH: I think that decision, though, was probably commercial. At the time SKF had trifluoperazine and they didn't want another piperazine-phenothiazine to compete with it. So, they developed prochlorperazine as an antiemetic rather than as an antipsychotic, but it's a perfectly good antipsychotic.

TB: Then, we also worked with drugs like trimipramine that was marketed in Canada in the early 1960s and in the United States in the late 1970s.

LH: I think the drug that most of us ignored or didn't pay much attention to at the time which ultimately, became very important was lithium.

TB: Yes. It happened that I used it first in Hungary in 1955 or '56 at the National Institute and I remember we had to get lithium prepared by the pharmacist of the Institute.

LH: The pharmacist had to make it.

TB: Yes. It was not available commercially. We had a couple of patients on it.

LH: It's surprising that you were able to work with lithium so early in Hungary when lithium was discovered in an English speaking country. You would have thought that it would have more impact in Britain or the U.S. rather than it had in Hungary?

TB: Dr. Sandor, my service chief and mentor, was fluent in many languages and he probably read the papers of Schou or Trautner. And he was interested in trying in his patients everything he learned about. We even managed to monitor blood levels. We tried every possible new treatment he ever read about and we were able to put our hands on.

LH: Those were the good old days when you didn't have to go through six committees and have a waiting time of eight months before you could do a study.

TB: We actually did not conduct clinical studies with any drug; we just used them on the ward trying to help patients. I started to work at the Institute just a few months before chlorpromazine became available. So, I'm probably one of the few survivors who saw how things were before the introduction of the new psychotropic drugs. We didn't have chlorpromazine readily accessible for several months even after we saw how well it worked. We used it first only in some privileged patients who were able to get it sent by their relatives living outside the Iron Curtain. I remember using Largactil from France in one patient, Megaphen from Switzerland in another, and Hibernal from Sweden in a third. I also remember the first patient I treated with chlorpromazine. He was an involutional melancholic. He was agitated, depressed, delusional and theatrical as most patients with involutional melancholia were in the old days when admitted to hospital. Our plan was to treat him with ECT when his family got Largactil from one of their relatives in France. He responded promptly to the drug. We were impressed. My second patient was a negativistic catatonic schizophrenic whom I had to tube feed and catheterize daily for several months. It was a kind of miracle to see him revived, walking and talking and taking care of himself. In both of these patients we used very small doses compared with current standards, about 25 mg intramuscularly three or four times a day. We knew that we must be prepared for blood pressure drop, orthostatic hypotension. So, after the injection I stayed with these patients and took their blood pressure every half an hour or so.

LH: In our original studies, we also gave relatively small doses. I am curious what would happen if we would go back to those small doses.

TB: It would be interesting to see. I also had some experience on Dr. Sandor's service, with reserpine in schizophrenics and with Hydergine in elderly patients with memory problems. Both these drugs were available in Hungary for clinical use in hypertension in those days. Reserpine, was also frequently prescribed as Serpasil for neurotic patients, probably most often for patients with neurotic depression.

LH: Well, I think the whole history of the early development of psychopharmacology has been full with serendipity. Somebody would make a clinical observation that a substance is good for a particular condition and this was sufficient to try to use it in others with the same or similar conditions.

TB: I agree that serendipity played a major role in the discovery of most of our psychotropic drugs, but after a few month of the publication of my Psychopharmacology in which I attributed the discovery of chlorpromazine to serendipity, I received from Henri Laborit a copy of a book he just published at the time with a dozen or so drugs listed on the blank page of the book in the front with the question below: "All these by serendipity?"

LH: Well, you had nineteen pretty good years in Montreal. Why did you leave?

TB: I accomplished the task of organizing a division of psychopharmacology. It was the first division of psychopharmacology in any psychiatry department in the world. But then, I ran into difficulties in implementing a structural reorganization of the psychiatric service in our hospital in a manner that would use optimally what psychopharmacology could offer. I was also interested in extending the scope of my activities

LH: Was Cameron the chairman of the department all through your stay?

TB: No. Cameron resigned in 1966.

LH: And, then who succeeded?

TB: Bob Cleghorn. It was during his tenure that I was appointed director of the Division of Psychopharmacology. It was also during his tenure that we became the Canadian National Reference Center for Psychotropic Drugs, part of an International Reference Center Network organized by the Division of Mental Health of the World Health Organization in collaboration with the Psychopharmacology Division of the National Institute of Mental Health of the USA. Then, in 1970, the activities of our Reference Center were extended to education, and we became

WHO's first training center for teachers in psychopharmacology and biological psychiatry in developing countries. We introduced our fellows into the methodology of clinical investigations. During their six to 12 months stay they became familiar with the assessment instruments and rating scales included in Bill Guy's ECDEU Assessment Manual. Most of them participated in at least one of our clinical trials in which the collected data were sent to the Biometric Laboratory Information Processing System that was set up at George Washington University to analyze the data of ECDEU investigators. It was during this period that I began with the translation and adaptation of the AMDP and AGP manuals used in the documentation of changes in treatment in adult and geropsychiatric patients in German speaking countries. In the mid 1970s, Heinz Lehmann succeeded Bob Cleghorn as chairman of the department of psychiatry at McGill. During his tenure the activities of the division were extended to all six hospitals affiliated with the Department. In 1976, at age 65, Heinz retired from the chairmanship. And, in the same year I accepted an offer from Vanderbilt and moved from Montreal to Nashville.

LH: So, you went to Vanderbilt?

TB: I went to Vanderbilt.

LH: Vanderbilt has always been very strong in clinical pharmacology.

TB: Yes. Now, clinical pharmacology was a division of internal medicine at Vanderbilt that was directed by John Oates. We did our research in clinical psychopharmacology at the Tennessee Neuropsychiatric Institute, part of the department of psychiatry, located on the premises of Central State Hospital. TNI was established from a center grant of NIMH and supported by the Department of Psychiatry and the Division of Mental Health of the State of Tennessee. The late Earl Usdin, Dan Efron and Morrie Lipton played a major role in getting the center grant for establishing the TNI.

LH: Now, who was the chairman of the Department of Psychiatry when you went to Vanderbilt?

TB: Marc Hollender.

LH: He was rather supportive of psychopharmacology, wasn't he?

TB: He was very supportive of my activities but I don't know how supportive he was of my predecessor. Marc was a psychoanalyst, a very well organized, honest man, dedicated to teaching. After my arrival he referred to me for consultation some of his long-term patients in analytic psychotherapy and we became friends after one of his patients with a phobic-anxiety-depersonalization syndrome promptly responded to phenelzine, a monoamine oxidase inhibitor he

prescribed on my recommendation. A few months later when the patient developed delayed and retrograde ejaculation we wrote it up and published it. A couple of years after my arrival the director of the outpatient clinic died. It took about a year to find a replacement and during this time I spent three half days a week at the clinic supervising residents, and answering their questions related to the use of psychotropic drugs. The questions the residents asked and my answers to their questions were recorded, and Marc decided to edit and organize the material in a logical sequence. Then we complemented the material by a few additional questions and answers. It became a book with the title of Psychopharmacology in Everyday Practice, published by Karger in 1980. Marc and I were very pleased when we learned that our book was translated from the original English into Japanese and Dutch.

LH: I think that having you two on the same book was quite an achievement.

TB: And he really worked on that book. He kept on editing my answers until they were crystal clear.

LH: So, it wasn't primarily a tag along authorship.

TB: It would have been a very different book if he had not done his part.

LH: What do you think of writing books? I always thought you make more money digging ditches.

TB: You are probably right but I never looked at it like that.

LH: Well, it's not only the money; that's probably the least of it. It's the fact that you hope it will have some influence but even then, you're always dubious about it.

TB: Writing a book forces me to conceptualize the findings in our research and integrate it with the information in the literature. And, that, in itself, I find a rewarding experience. Now, I should add that it takes me a long time to write a book or a review because I keep on conceptualizing and re-conceptualizing my findings until I find the way to express what I would like and be able to communicate it.

LH: That's one of the beauties of writing a book. You can philosophize or tell anecdotes or things that are more personal. And, I find it rather discouraging that many of the new books are lacking this personal touch. All you've got is a lot of information. It does not make any sense to write a book if the author's personal touch is not there.

TB: I think not only books but also reviews should have the identity, the conceptualization of the reviewer. A good review should be more than a summary of all the papers.

LH: Now, when you went to Vanderbilt there was the beginning of a budding institute there, wasn't there?

TB: The Institute, the Tennessee Neuropsychiatric Institute was founded about ten years before my arrival.

LH: That was when Fridolin Sulser went there?

TB: Yes, Fridolin went there about that time. I think he got to the Institute just a little bit after Jim Dingell.

LH: Now, didn't John Davis spend some time there?

TB: That's correct. John Davis was the first clinical director of TNI. But I think John Davis and Dave Janowsky his close associate arrived considerably later than Dingell and Sulser. And, when John left for Chicago, Dave Janowsky, Eddy Fann and other members of John's team left as well. There was no one there on the clinical side for two or three years before I came.

LH: Did you take John Davis' place?

TB: Yes, I was John's successor. But there was a period of time between John's departure and my arrival during which all the funds of the Institute were used by the preclinical division. The Institute also had a Center grant which just expired around the time of my arrival. At the time John arrived the Institute was prosperous whereas at the time of my arrival virtually all the money the Institute had was used by the pre-clinical division. There was not enough money there to operate a clinical research service safely.

LH: So, you came there when they ran out of money.

TB: The Center grant expired and it was up for renewal. To be able to present an acceptable research grant proposal I had to organize a clinical unit first.

LH: Could you transfer your ECDEU grant there?

TB: Our ECDEU grant with Dr. Lehmann was terminated few years before I left McGill. In fact just about the time I moved to Nashville, ECDEU's Biometric Laboratory was closed, and some of the professional staff of the Laboratory, Bill Guy and David Schaffer joined me at Vanderbilt.

LH: Did the funding for the continuous operation of TNI come from the state or private sources?

TB: It came from three sources: the State of Tennessee, Vanderbilt University and the National Institute of Mental Health.

LH: You were at Vanderbilt when Earl Sutherland was there, weren't you?

TB: He died before I arrived.

LH: So, you never had a chance to know him.

TB: No, I just knew that he got the Nobel Prize.

LH: Now, what was your primary thrust at Vanderbilt in psychopharmacology? Were you continuing to test new drugs?

TB: I continued with clinical investigations and we tested several new drugs but the primary thrust of my research was in developing a methodology that would identify the treatment responsive forms of illness, or sub-populations within the diagnostic categories to psychotropic drugs. Development of a pharmacologically valid psychiatric nosology was central to my research during the past 40 years Since pharmacokinetic factors did not seem to explain why one patient in the same diagnostic category responds whereas the other remains refractory to the same psychotropic drug given in the same dose, as early as in 1969 in the concluding remarks of my Psychopharmacology I noted that the “introduction of therapeutically effective psychotropic drugs focused attention on the pharmacological heterogeneity within the diagnostic categories of mental illness.” For some time I believed that biological measures would identify pharmacologically homogenous groups within the diagnostic categories of mental illness but by the mid 1980s it became evident to me that this was not the case and that biological measures were state dependent epiphenomena of mental illness. I published a paper on this with the title, “Prolegomenon to the Clinical Prerequisite: Psychopharmacology and the Classification of Mental Illness.”

LH: It's in an interesting title.

TB: The paper was an extension of my presentation on Psychopharmacology and the Classification of Mental Illness at a symposium on the 15th CINP Congress that was held in San Juan in 1986, in the same hotel we are now. After my presentation I went to the beach with Corneille Radouco-Thomas, who was at the time the editor-in-chief of Progress in Neuropsychopharmacology and Biological Psychiatry, and in the course of our conversation he told me that he would be interested to publish my presentation in his journal. He even suggested Prolegomenon to the Clinical Prerequisite as a possible title. I thought it was a good suggestion and the paper was published in his journal in 1987. In Prolegomenon, I argue that it's not only unrealistic to expect that biological measures would provide pharmacologically meaningful clinical categories of mental illness in the foreseeable future, but I argue also that we need clinical end-points to render findings with biological measures clinically interpretable.

LH: Now, as someone who has been interested in methodology of studying drugs, are you happy with the way things are today? You know that most of the companies now have in-house help that is able to develop a protocol and also have the statistical help to analyze the results. They usually vend out the writing of the paper to some professional writing group and all the investigators do today is gather data. It seems to me like a very dull way to do business.

TB: This is correct and very unfortunate. But I wouldn't blame the companies for doing that. They are business organizations responsible to their shareholders to generate maximum profit. It is the task of the profession that the new psychotropic drugs are optimally used in individual patients. To meet regulatory requirements companies must demonstrate that their drug is not toxic and is efficacious in treatment in at least one of the consensus-based diagnostic groups of mental illness. By the accepted standards a drug is proven efficacious if it is statistically significantly superior to placebo in two clinical studies in that population. We have been aware for some time that our consensus-based diagnoses are pharmacologically heterogeneous, so, it would have been the task of academic psychiatry to extend clinical drug development with clinical psychopharmacological research to identify the treatment responsive subpopulation to psychotropic drugs. I have been rather frustrated for some time that this is not done at the universities, and, I just formed a small company with some of my former associates and a few other interested psychiatrists to fill in this gap in clinical drug development. It was just formed. I retired from my professorship from Vanderbilt to be able to dedicate my time in developing the company.

LH: What's the thrust of the new company?

TB: The development of psychotropic drugs in a manner that they can be used selectively. We intended to achieve our objective by developing a methodology for the identification of treatment responsive forms of illness, employ the new methodology in multi-center clinical investigations, and delineate the differential therapeutic profile and indications of psychotropic drugs. We hoped to be able to generate the necessary support from industry, government and foundations to achieve our objectives.

LH: Do you think our clinical tools are sensitive enough to pick up minor differences in the pharmacological profile of psychotropic drugs.

TB: I don't think that the current methodology of clinical investigations with behavioral rating scales focused on the detection and demonstration of efficacy has the necessary sensitivity. But there are some findings that indicate that the "Diagnostic Criteria of Research Budapest-

Nashville," we developed at Vanderbilt in collaboration with Bertalan Pethö's group at Semmelweis University, has the necessary sensitivity. The DCR is based in part on Leonhard's classification of endogenous psychoses. As you might know, some 40 years ago Frank Fish had shown that one subpopulation of unsystematic schizophrenia in that classification, affect-laden paraphrenia, responds selectively to phenothiazine neuroleptics. There are also some indications that the Composite Diagnostic Evaluation or CODE System provides the necessary sensitivity for the detection of differences in the pharmacology of psychotropic drugs.

LH: That's an interesting and ambitious undertaking. Let me go on to another facet of your multi-faceted career. I remember I recently picked up a copy of Thirty years of CINP, a book you and Hanns Hippius edited some years back. More recently, of course, I've been going through your History of the CINP that you and Oakley edited together. You've been interested in history for a long while, haven't you?

TB: All through my professional career I have been interested in the conceptual development of disciplines like psychiatry and neuropsychopharmacology. I also enjoy figuring out or reviewing developments that lead to our current state of affairs. It is difficult for me to see how research could contribute to the development of a field if it is not done in a historical context.

LH: It would help to have the historical context to put things in. I'm generating a letter, currently, to the Journal of Psychiatry because they had a letter saying neuroleptic drugs are unpleasant to take. I thought that was common knowledge thirty years ago. And, the problem, it seems to me, is that the indexing systems now that are giving this search of the literature so easily and complete, go back only to about fifteen years. And, it's like there's no history beyond fifteen years ago.

TB: It is very disappointing that we have the capability to review historical development properly with the help of computers and we don't use this capability fully.

LH: Now, you and Oakley, are undertaking a similar task with the ACNP history, is that right?

TB: This is, more or less, the case. It would be more correct to say that we are ready to undertake the task.

LH: Well, I think these kinds of interviews are very good, historically, but I'm still a print man. This project with all the visuals is important but I still would like to see something written in print.

TB: I'm very glad to hear that, because we would like to see these interviews transcribed and in print as well.

LH: You know, David Healy has been doing something similar to what you are doing but, actually, he is writing up these interviews rather than filming them. And, I found the first volume of his interviews very interesting. But, there are of course several different approaches to presenting a coherent historical account.

TB: We seem to have the necessary information in these interviews to present in print a coherent account on the history of the field. Do you think it would be a worthwhile undertaking?

LH: I think it's a worthwhile undertaking, yes.

TB: We are ready to do it. That's all I can say.

LH: You see the problem is that many organizations start off with no concept that they are going to want, someday, to know what their history was, and so they ignore it for the first decade or two. And, then, all of a sudden, someone says, "Gee whiz, we've got a history!"

TB: As you know we have already put in print the history of the CINP. I think it will be much easier to reconstruct the history of the ACNP because ACNP's record keeping has been much tidier from the beginning. And I have a feeling that probably in the "Oakley era" that began with his election as Secretary/Treasurer in 1979 we will be able to find all the records we need.

LH: You know, there's a depository of information that they're setting up with Vanderbilt now. It's fine, but really I don't have any old notes. I, periodically, cleaned out my files and pitched them. I guess some people are compulsive about keeping things.

TB: I think it is very fortunate that finally we have an archive. It was Oakley who got the necessary funds to start it.

LH: Well, Tom, you've not only been a historical figure but now you're a major historian of both of the large organizations connected with the world of psychopharmacology. And, I certainly wish you well in your venture to put it in a coherent, logical and written form. I think a lot of what comes out of these interviews are personal things, the people you've met along the way and people who have influenced you and so on.

TB: I remember Leo when we first met.

LH: You do?

TB: Yes, I do.

LH: Your memory is better than mine. I've got a few years on you though.

TB: You were already well known in the field. It was in 1960 or '61 at the first ECDEU investigators meeting in Washington, DC. At the time the group was small, we could still sit around a table.

LH: Well, one of the great things from my point of view, of being in this field has been the wonderful people, the right people that you meet along the way, some of whom who become very good friends and others you cherish who follow you. And, I think we live in a wonderful era and we're lucky to be in the field we're in.

TB: Yes, we are very lucky.

LH: Well, there's been a great deal of progress since you and I began and I hope we will be able to see some of the bright future that seems be in the making.

TB: I hope so.

LH: OK, Tom.

TB: Thank you, Leo.

## 6. FRANK M. BERGER

LH: I am privileged this morning to interview Dr. Frank Berger.\* I am Leo Hollister. Frank and I have known each other for almost 40 years. It is quite a pleasure to welcome him at the annual meeting of the ACNP for this interview. I think Frank's name will always be associated with the drug meprobamate, the first tranquilizer developed, I guess, in history. Tell me, Frank, how did you begin? What was your training, and what led you to do drug research?

FB: I was born in Czechoslovakia and got my MD in 1937. I worked first as a microbiologist at the Czechoslovak National Institute of Health and studied various typhoids and paratyphoids. When Hitler occupied Czechoslovakia in March 1939, I got married, left the country, managed to get into England, and spent the next year or two as a general physician in a refugee camp. In 1941, my medical degree from Prague was recognized and I got a position in a hospital for infectious diseases in Manchester. It was a lovely job. I learned English while I looked after patients.

LH: So, you were a practicing physician in those days.

FB: Oh, yes. I was taking care I think of about 800 patients. It was a most interesting period of my life. There was a highly toxic diphtheria in the community with something like 15 admissions a day. They were mostly babies and quite a few of them died.

LH: That was a sort of tragedy because diphtheria antitoxin had been developed earlier.

FB: Apparently it was not prepared or used properly. It was a strenuous job because one felt that the survival of the baby was dependent on one's ability of administering diphtheria antitoxin intravenously. This was a major undertaking in a one-year-old baby in shock.

LH: How did you do it? Did you have to go through the skull?

FB: I did it as I could. I had also patients with polio, meningitis and all kinds of other diseases.

LH: When you talk about diphtheria and polio and all those diseases, it reminds me how much progress has been made. We no longer need to bother about any of them.

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\* Frank Berger was born in Pilsen, West Bohemia, in what is now the Czech Republic, in 1913. He graduated in medicine from the University of Prague in 1937. He conducted experiments in basic pharmacology as a student; and in 1939 fled Hitler's troops and moved to England, where he worked for a time in a refugee camp, before continuing his investigations at a British drug firm. He moved to the United States in 1947, taking a job at the University of Rochester, before moving in 1949 to Wallace Laboratories, a subsidiary of Carter Products, in New Jersey. He is noted for developing the first antianxiety agent, meprobamate, in the 1950s. He died on March 16, 2008 in New York City, New York. He was interviewed in San Juan, Puerto Rico on December 14, 1995.

FB: Yes. Few physicians of your generation have ever seen acute, bull-neck diphtheria.

LH: It had to be frightening.

FB: Oh, it was. And so was polio. We had about nine iron lungs going at all times to keep them alive. That is another disease eradicated now.

LH: Except in the developing countries. I guess we still have a way to go there. But, theoretically, it could be eradicated just as smallpox was.

FB: Then, in 1942, I got a job in a bacteriology laboratory in Wakefield. It was shortly after that Florey and his collaborators purified penicillin and the effectiveness of penicillin was shown in experimentally induced infections in mice and patients suffering from staphylococcal and other infections. To extract penicillin, they acidified it and in the course of this process lost 90% of the precious substance.

LH: Well, now, what was your better job?

FB: It was with the British Drug Houses, a company that was supposed to produce penicillin on a large scale. Of course, I was delighted to have my salary double and promptly moved to London. In those years penicillin was supplied in solution and the antibacterial effect of penicillin solution was lost because of penicillinase-producing bacteria that everything is contaminated with. My assignment was to find a non-toxic substance that could be added to penicillin solutions for selectively inhibiting penicillinase-producing bacteria. There was one such product, but it could inhibit the bacteria only a little bit. It was phenoxytol, a phenyl ether of glycol.

LH: How did you come across that one?

FB: It was known that phenoxytol has that effect. So, my boss, Bill Bradley, told me that we have to find a non-toxic agent that is like phenoxytol but thousand times more potent in inhibiting penicillinase-producing bacteria. We prepared all kinds of glycerol, erythritol and other ethers and substituted phenols in our search. I supervised the testing of these substances against penicillinase producing bacteria. There was one substance I particularly liked because it very nicely inhibited the growth of bacteria while it preserved penicillin in the solutions. It was called mephenesin.

LH: Was mephenesin at the time on the market for clinical use?

FB: No, it was a new product of Bradley.

LH: Now is this the same Bradley whom I associate with electrophysiology?

FB: No. My Bradley was a chemist, pure and simple.

LH: He must have been.

FB: An excellent chemist. To test the toxicity of mephenesin I injected it into mice and other animals. It was not toxic. But while studying its toxicity I also found that in large doses it produced tranquilization and muscle relaxation limited to voluntary muscles. It did not affect respiration or the heart. About that time somebody in Philadelphia discovered much better ways to preserve the activity of penicillin and interest at British Drug Houses in mephenesin was lost. I was told to forget about it.

LH: So that was the first use of mephenesin.

FB: Yes. But I could not forget the unique behavioral effects of the drug in animals. No other compound I knew about produced a state of paralysis in animals in which consciousness was maintained. The animals looked at you, could not move, but continued to breath. Since no autonomic disturbance seemed to be associated with the paralysis of voluntary muscles, I thought that mephenesin would be wonderful in operations and asked permission to develop the drug for human use. I published my findings on mephenesin in 1946 in the British Journal of Pharmacology and in my article I pointed out that the compound has a tranquillizing action.

LH: Did you use the term tranquilizer?

FB: Yes, in the first paragraph.

LH: That must be one of the first uses of the term.

FB: I was particularly struck by its effect on guinea pigs, which are nervous animals that are not easy to catch but after a small dose of mephenesin became tranquil. I also collaborated with several physicians on the clinical development of mephenesin. More than 10,000 surgical patients in England received the substance for relaxation during operations. But I had to stop with my research in England because we received our visas to the United States and my late wife persuaded me to move to the States. So in October 1947 we moved to the States. At the time it was not permissible to enter the United States with a prearranged job. I know that this sounds unbelievable now. There was also a British regulation that did not permit us to take more than about 100 pounds, that is about \$150.00 out from the country.

LH: So instead of landing on these shores with just a dime, you arrived with 100 pounds and no job.

FB: But I had a typewriter and knew a few people who were interested in my publication on mephenesin. I went to see them, offered my services and was very fortunate in getting several job

offers. The one I accepted, on the recommendation of my good friend George Brecher, head of hematology at NIH, was at the University of Rochester Medical School. It was an assistant professorship in pediatrics of all things.

LH: My goodness! From infectious diseases to pediatrics.

FB: Since infectious diseases are usually caught by children they thought they need somebody on their staff who knows a little bit about them. So that was the job. I got it after six weeks of our arrival. It did not pay well.

LH: You made up for it. Don't worry.

FB: I remember they paid me \$5,400, which at the time was much more than it is now, but by getting a license to practice I was able to supplement my income very nicely by taking night calls. I was fortunate because I got all kinds of grants and was able to start clinical trials with oral mephenesin.

LH: For what did you use it in children?

FB: I used it in everything.

LH: Just exploring?

FB: Right. Although I was assistant professor of pediatrics, I had access to patients with parkinsonism, stroke, multiple sclerosis, and cerebral palsy.

LH: Anything where there may be muscle spasticity?

FB: Muscle spasticity and involuntary movements. We found it quite effective in cerebral palsy and in some post-stroke paralyses. We also found that spasticity that results from the disturbance of reciprocal innervation between contraction and relaxation could be corrected by the drug. I published a paper on mephenesin in 1948 in the Journal of the American Medical Association that helped Squibb to get the substance on the market. By the end of 1948 Tolserol was one of the best-selling Squibb products.

LH: That is something.

FB: I also presented some evidence in my paper that mephenesin has a very short duration of action. Using the diazo-reagent I found breakdown products already 10 to 15 minutes after taking the medication.

LH: So it is very rapidly metabolized.

FB: That is right. And I said that we need to produce a drug that would be many times as active and longer acting than mephenesin.

LH: So that got you to other glycerol derivatives.

FB: That is right. Shortly after the publication of my paper I had several offers from pharmaceutical firms. I was anxious to find a better paying job because my wife was expecting a baby. That was in 1949. The baby is now a big boy. I believe you know Frank.

LH: Oh, yes. You have two sons, don't you?

FB: Yes. So I had various offers, and I accepted the offer from Carter Products, that shocked everybody at Rochester.

LH: Because they were only known for liver pills.

FB: "You must be insane, you should join a more reputable firm, like Lederle or Squibb," people told me. I was warned that Carter had a minuscule pharmaceutical business which at the time perhaps yielded about \$80,000 a year. But they offered me more than most of the others. I remember the salary they paid me was \$12,000 a year. I really felt I was a rich man.

LH: In the late 1940s that was not bad pay.

FB: But there was one other reason to be honest with you why I joined them. I said: "If I develop a better drug than mephenesin, I want to get a little bit from the sales. If I make a firm out of you, I want to get royalties." And the only firm that was prepared to pay me royalties was Carter. Then we addressed the issue why mephenesin is so rapidly metabolized. I didn't know any chemistry, but Carter-Wallace, or Carter as it was called at the time, had a fine chemist, Bernie Ludwig, and we found out that mephenesin's rapid deactivation by oxidation of its terminal hydroxy groups could best be blocked by carbamates. It was also necessary to make several other structural changes in the molecule.

LH: So you ended up with a carbamate.

FB: That is exactly right. So when that happened we synthesized a few hundred carbamates. Meprobamate seemed to be the best of them all around. It was patented in the fall of 1949. So I had a lot of fun developing it. And I will never forget the help you have given. You conducted one of the first clinical trials with meprobamate.

LH: That was trivial.

FB: That was not trivial. That was an act of great courage.

LH: Tell me, how did you get the name Milltown?

FB: We had about six or seven products and we named them after the various villages around New Brunswick where our laboratories were. One of the villages near New Brunswick was Milltown. Another one, and this would have been a much better name, was Hopewell.

LH: Oh, boy. What a name for a tranquilizer.

FB: One of the investigators rushed into publication and used the name Milltown in the paper he submitted to the JAMA. When the paper appeared, the compound was named. It was not a good idea to stick with that name at all. Carter-Wallace did not have enough people and money to promote the drug. It had to license it to other companies. One of the licensees was Wyeth Laboratories who gave it the name Equanil. That was much more acceptable to physicians who, as a result, prescribed three or four times as much Equanil than Milltown.

LH: So that was the beginning. When was meprobamate introduced for clinical use?

FB: In the spring of 1955 and I would like to say it again that you played a very important role in it. Soon after the drug went on the market, either late in 1955 or early in 1956, I organized a big conference at the New York Academy of Sciences. Do you remember that?

LH: Oh, yes.

FB: You got Aldous Huxley to attend. He was very interested in drugs and especially in those that affect consciousness. He came and gave the introductory address. And you gave a paper too in which you reviewed all the publications on the drug. You discussed how difficult it was to decide what a psychotropic drug should be used for.

LH: It still is.

FB: You examined the whole spectrum of possible indications for meprobamate.

LH: So from 1955 until around 1960 when Librium came along, Milltown had the whole field.

FB: That is right.

LH: And it became the most widely prescribed drug.

FB: Yes, it was widely prescribed, and it certainly made Wallace Laboratories. When I joined them, as I mentioned before, the sales were \$85,000 a year. By 1960, they were something like \$200 million a year.

LH: And guess who had a royalty?

FB: I had big problems with my royalty and spent a good part of my time fighting for my rights.

LH: While you were talking I was thinking of George Renshell who, as a graduate student, developed what ultimately became known as Benadryl. He had a similar arrangement with Parke-Davis and became one of the richest men around.

FB: But I was new in America. I signed a document that I did not understand. And once you sign something, it is very difficult to modify it. So that is how I failed to become the richest man in America. Since I failed to become the richest, I tried to become the happiest.

LH: Of course, Milltown was an astounding commercial success. Then Wyeth put it together with promazine.

FB: Yes.

LH: But you didn't have anything to do with that, did you?

FB: Not really. I was never enthusiastic about combinations. But regardless, our sales went up to \$200 million a year. I was everything at the company including sales manager and advertising manager. There was no other executive there and the firm was largely privately owned.

LH: By the Hoyts?

FB: Yes. And they hired a business advisor who told them that "this fellow Berger, who does not even know how to read a financial statement, is running a business of more than 200 million a year." He also told them that I run it differently from others in that I would not employ detail men. So they decided to get people experienced in the pharmaceutical business to run the business, and I did not like that.

LH: Well, you know, even running a \$200 million a year business, without having anything to do with development, you should have been paid pretty well.

FB: After the patent expired, I had no more royalties.

LH: Now, as I recall, Wallace put out a combination product with benactyzine.

FB: Yes, Deprol. It was one of the first products, I thought, that was effective in depression. And I remember that you did some clinical research with Deprol.

LH: Well, I guess so. I cannot remember. But, I remember that we were having dinner together in New York around 1957 or '58, and you were saying that you thought the next big development in the field will be the introduction of antidepressants.

FB: Yes. I cannot remember now exactly when Deprol was introduced. It was in the late 1950s and at the time it was found effective in some depressed patients. But when the true antidepressants came along, Deprol faded out.

LH: Yes. Now, let us see. I remember that both Carter-Wallace and Wyeth put out meprobamate for slow release by delaying absorption.

FB: Yes.

LH: And I studied both of them and came out with equal results. It turned out that both came out from the same mill. They were different only in colors. That was sort of gratifying that I could not find a bit of difference. Well, let us see, that gets us up to the late 1950s. What do you do for an encore after having something-like Milltown?

FB: Well, back in the 1960s I reverted to my first love that was bacteriology and immunology and started a collaboration with people at the Pasteur Institute in Paris on the development of adjuvants, substances that increased immunogenicity.

LH: I guess the only one at the time was Saponin.

FB: That is right and Saponin is not suitable for use in humans because it produces swelling and is potentially carcinogenic. So, jointly with the late Werner Braun at Rutgers and Louis Chedid in Paris, we developed a chemically well-defined substance from the wall of acid-resistant bacteria, which had a potent adjuvant action. And my other interest was the development of a substance that would increase nonspecific immunity. My interest in developing such a substance was triggered by the well-known fact that not everybody who is exposed to an infectious agent catches the disease. Not everybody who is exposed to a carcinogen gets cancer. What is it that makes the difference? And I prepared an agent from bacterial sources that increased nonspecific resistance in animals. I called the substance protodyne and published on it since 1968 extensively. If you shut down the immune system of mice, nonpathogenic bacteria will kill the animal. And this x factor of mine, protodyne, will protect the animal. This is what I have been working on for the past 10-15 years. It seems to work beautifully in vitro. I prepared a patent application for protodyne and offered it to every pharmaceutical firm in the world, but none of them got interested.

LH: That was, of course, before AIDS.

FB: Yes. But I don't really blame anybody. I was 82 this year. Most firms are not too anxious to start a research project with an 82-year-old man.

LH: Well, there is something about aging that takes the zip out of you, doesn't it. I remember talking to Paul Janssen about levamisole. They had no idea that it has adjuvant properties. But there was a Frenchman who tried the substance and it worked. Now levamisole found its place in the treatment of colon cancer.

FB: Yes. I think it is still used for that purpose. And a lot of work is being done to develop this area of research further.

LH: Well, from muscle relaxants to immunological boosters, you have traveled a long way. The last time I saw you, I think it was down in Louisville. John Schwab, who was then chairman of the department of psychiatry there, had the good sense to have you and Joel Elkes as visiting professors. What was your role there?

FB: Well, I think I had an opportunity to learn some psychiatry. I had the opportunity to see some psychiatric outpatients, and I found it most interesting. My feeling was that most people we saw had really no psychiatric disorders. They were people, in my opinion, with problems of living, people who did not get along with their spouses, did not get along with their children, did not get along with their boss, and had not been taught, had not been educated, had not been prepared to handle all these crises of life. So they got stressed, broke down, and had to see a doctor, and the doctor did not know what to do. So he put one of the psychiatric names on them.

LH: That's right. You are absolutely right. So much of the general practice of medicine consists of people who have problems in getting along, and there is no easy cure for that. You should have started 30 years earlier.

FB: And, as you know, we don't get enough education how to handle problems of living. And I don't know what should be or could be done about it.

LH: I guess when religion had more influence people developed more of an ethical and moral sense than they do today. I am appalled of these young kids who think nothing of killing somebody for some trivial reason.

FB: Yes.

LH: They have no idea about the worth of human life. It is a kind of amoral society that we are engendering and we are paying the price for it. Well, that was an interesting career you had from microbiology to infectious disease, chemistry and back to the clinic, then more chemistry, running a drug company and becoming rich, and then, going back to immunology. What a checkered career. Would you do it over again?

FB: Yes. Oh, yes. I am not ready to die. I am ready to continue. Whether I liked it? Yes, I did, it was outstanding.

LH: Yes, I would say so.

FB: It was very interesting.

LH: It kept you busy and interested all your life.

FB: Yes and still does. I have been very fortunate.

LH: I think all of us who have the opportunity to have a job that we like are blessed. You know, there are so many people who belong to the Thank-God-it's Friday club. I always say I belong to the My-God-it's-Friday club.

FB: Do we still have time?

LH: Sure. You want to say something more?

FB: Yes. I thought you were going to ask me what is it you would have liked to achieve or what do you think the contribution of those tranquilizers was to medicine?

LH: Good question. I am glad you asked it.

FB: I can tell you only what I think. I am sad, at times, that I have not been able to convey to more people my opinion about anxiety, meprobamate and all the new antianxiety drugs. And I find it hard to understand that there are so few psychiatrists who believe what I do about anxiety. Namely, that anxiety is a disease state. It is an inappropriate emotion that should be differentiated from fear. As you know, anxiety is apprehension of something you don't know.

LH: But fear you know.

FB: Fear is appropriate. Now Freud implied that anxiety is one of the great motivational forces in life. John Locke, before him, believed that we do things because we are anxious, we are afraid. That anxiety pushes us along. I think they were wrong.

LH: It hinders rather than helps.

FB: Exactly. And this is now well authenticated. You know Cattell, a leading psychologist at the University of Chicago. He did an extensive study on anxiety using factor analysis and found that anxiety is not good for you. It decreases your productivity, your ability to perform, and everything else. Yet, there are so many psychiatrists who say: "Yes, too much anxiety is wrong, but a little anxiety is necessary." I don't think that is so. I think the people who perform best are the people who are not scared, people who don't have this undefined feeling.

LH: Well, when you are always apprehensive about what is coming next I think it interferes with your thinking process and obviously decreases performance. I think in recent years there are more people beginning to subscribe to your notion that anxiety is pathologic and needs to be treated. But in so many people's mind anxiety is a kind of minor emotional disorder, akin to the problems

of living that you don't need to bother too much about. So a lot of doctors are reluctant to prescribe any medicine for it.

FB: Right. On the other hand, you see, tranquilizers are over-prescribed. For instance, a patient has a heart attack. He is brought to the hospital. The first thing he gets there is a tranquilizer. I think that is a mistake. A person with a heart attack is not anxious. He is afraid. You know, there are some fine studies showing that anti-anxiety agents are effective only in true anxiety. They don't affect fear. Even if you load up somebody with antianxiety drugs and a car or a tiger is running towards him he will jump. So I think a patient brought to the hospital with a heart attack should not get Milltown or Librium or whatever. He should get morphine. He is in pain.

LH: Yes, but there was a very provocative study published a few years ago in which it was shown that during the stress of a heart attack catecholamines go way up and diazepam blunted that response. And since the circulating catecholamines may play a very significant role in fatal cardiac arrhythmia, diazepam might be just as effective as lidocaine in preventing it. It is unfortunate that nobody followed up that report because it might have given some justification for giving antianxiety drugs for patients with heart attacks. But, of course, we are talking about a very temporary use. People are increasingly recognizing that anxiety is pervasive in all disorders. We found in our depressed patients that anxiety was just as common a symptom as depression. And there is also a fair amount of anxiety seen in schizophrenic patients.

FB: What is called anxiety in schizophrenia might be fear. The schizophrenic is afraid of the content of his hallucinations.

LH: That's true. If some voices are telling you what a bad person you are that awakes fear.

FB: Perhaps the "anxiety" of schizophrenics disappears if you do something about their hallucinations.

LH: Oh, there is no question about that. Well, what you are saying in effect then is that we need not be ashamed to treat anxiety. That we should recognize it as a disabling disorder and consider it just as important as treating other illnesses.

FB: I think when we both were young physicians, psychiatry had a taint and we should try to remove that taint by conveying to people that there is really no difference between the diseases of the mind and the diseases of the body.

LH: Yeah. The old idea was that if you had stronger moral fibers you could pull yourself together and beat it.

FB: That is all nonsense.

LH: Well, of course, you know that Freud was a very dominant influence on psychiatric thinking when you and I were young. I think every department of psychiatry in the United States was headed by a chairman who was psychodynamically oriented. Now the pendulum has swung almost 180 degrees and almost every chairman is biologically oriented. Maybe it swung too far. Maybe, as one of my colleagues said, we are now talking about a mindless brain.

FB: Yes.

LH: So maybe we have gone a little bit too far. But the old influence that has tended to lessen the importance of anxiety and made anxiety a kind of normal phenomenon is still hard to shake. FB: Perhaps, but both you and I contributed one thing. We made psychiatry a part of medicine. LH: Yes, I guess the drugs did that. I recently had an occasion to introduce Joe Coyle and I said, as far as I knew, he was the only chairman of a department of psychiatry who also had been president of the Society for Neuroscience. And that sort of an overlap is increasingly apparent now, even at this meeting. So, I guess, by learning a lot about the brain we might be able to help patients better, which I think your discovery certainly played a role in. It has been a pleasure after all these years to have this conversation with you. I learned something about your career that I had never heard before.

FB: Thank you very much, Leo.

## 7. JACK BLAINE

LH: Good morning. This is April 14, 1997, and we are in Washington, DC, doing another interview in the series of the history of psychopharmacology. Our guest this morning is Dr. Jack Blaine,\* who has been a long-time fixture here in Washington. It seems to me that over the last 30 years, in one guise or another, we have run into each other. Jack, welcome to the history project.

JB: Thank you, Leo.

LH: Could you begin by telling us something about what got you into medicine? You are an M.D., aren't you?

JB: Yes, I'm a psychiatrist.

LH: And what led you into psychiatry and what led you into government service, all in one.

JB: That's a broad question. Well, with medicine, I was always interested in science, and when I went to college I considered some of the careers that were available for people interested in science, and medicine, is an interesting thing to do, and is a helping profession. I went to medical school at Albert Einstein College of Medicine in New York.

LH: When did you graduate?

JB: I graduated in 1968. Actually, I got interested in psychopharmacology back then, although I'm not sure I knew it at the time. In my second year, we had a pharmacology course, and Dr. Jerry Jaffe taught part of that course when he was at Einstein, briefly. He taught a section on the opiate drugs and drug abuse, and I got interested in it at that time and then took a seminar from him separately later in the year. In my senior year of medical school, I did a traveling fellowship to London, where I had the opportunity to work with Griffith Edwards and Philip Connell at the Maudsley Hospital on drug abuse.

LH: Phil was the father of amphetamine psychosis, wasn't he?

JB: Right. That was a wonderful experience and it increased my interest in the field. I did a general medical internship at UCLA affiliated hospitals. These were the years of the Vietnam era,

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\* Jack Blaine was born in New Brunswick, New Jersey in 1943. He graduated from the Albert Einstein College of Medicine of Yeshiva University in 1968. He completed his residency in psychiatry at the University of California at San Diego in 1975. He spent his career in various leadership positions in the National Institute on Drug Abuse and National Institute of Mental Health. He was interviewed in Washington, DC on April 14, 1997.

and I at that time, hadn't really thought about a residency or what I was going to go into. So I went back to work for what was then the Center for Study of Narcotics and Drug Abuse at the National Institute of Mental Health. That was the precursor of NIDA, actually. And that's where I met you, I guess, for the first time. That was the experience that really solidified my interest in psychopharmacology, and especially in the psychopharmacology of drugs of abuse.

LH: So, you started working in the precursor of NIDA and you're still in the same place.

JB: Yes, it seems like I can't get away.

LH: But, I believe you have had some peregrinations along the way, haven't you?

JB: Yes, I have.

LH: After you started off in the field of substance abuse, did you continue on in that field all the way?

JB: I spent two years with that precursor of NIDA, and after that I spent one year at the National Commission on Marijuana and Drug Abuse as the Assistant Director for Medical Sciences. After, I went back for my psychiatric residency. I decided to go into psychiatry and psychopharmacology, in particular. I went out to the University of California-San Diego for three years. Following that, I came back to what became NIDA, in 1975. I worked from '75 - '80 at NIDA. Then I went over to the National Institute of Mental Health where I was in the Psychopharmacology Research Branch from '80 - '86.

LH: That was John Cole's operation.

JB: John Cole had started it, and Jerry Levine was, at that time, the branch chief, and Nina Schooler, Bob Prien, Al Raskin, and Ron Lipman were there. So I worked there for six years, from '80 - '86, and then I returned to NIDA in '86. I became chief of the Treatment Research Branch at NIDA, and I've been there since '86.

LH: Well, that's more or less the way I remember it in our various meetings. You were on the National Marijuana Commission.

JB: I was a staff member on the National Commission.

LH: Traveled around the country and the world?

JB: A little bit around the world; mostly around the country. I did get down to Jamaica. That was an interesting experience.

LH: We'll probably have to have another one. Marijuana is always so controversial.

JB: It seems to be coming back.

LH: What do you recall from your work on the commission? What did the commission finally decide?

JB: The Commission on Marijuana ended up recommending a decriminalization of marijuana, a recommendation that was not very well accepted by then President Nixon.

LH: Nor, I guess, by the present crew either.

JB: Or by anybody. But it was an interesting experience.

LH: What I told them is, "Don't make it legal; make it less illegal."

JB: It looks like we took your advice, but nobody listens.

LH: That's still a hot issue, isn't it?

JB: Yes, it is.

LH: Then in San Diego, who was running psychopharmacology when you were there?

JB: It was a combination. Dr. Arnie Mandel was the chairman of the department, and Lou Judd was the deputy chair at the time, and they were just about running the department together. I probably did more things with Lou than with Arnie at the time. I was real fortunate to work with Dr. David Janowsky who had come to San Diego when I was a resident, and we did some work together on marijuana. That was a very good experience.

LH: Arnie was a colorful character, wasn't he?

JB: He certainly was.

LH: He later became a professor of mathematics at some foreign university. He used to send me his stuff, and finally I wrote him and said, Arnie, I can't understand what you're talking about. Don't waste the postage. But, he was, always a few steps ahead of us. Didn't he win one of those very prestigious MacArthur Fellowships that they give to young geniuses?

JB: I suspect he did. I think he was, at least at that time, the youngest chairman of any department of psychiatry. I don't know if he still holds that record or not. But it was a very forward-looking department. There was a very, very strong psychopharmacology program.

LH: Yes, when you've got people like Mandel and Judd and Janowsky around, all of whom became chairmen later on. Well, you had some pretty good exposure to famous people.

JB: I was very lucky!

LH: Then following that was when you went to NIDA for the first time.

JB: Yes, I came back to NIDA in July of '75.

LH: Who was running it then?

JB: At that time, Bob DuPont was the director of the institute, and Bill Pollin was the Director of the Division of Research, and I was in what was called the clinical behavioral branch, led by Pierre Renault.

LH: Whatever happened to Pierre?

JB: Unfortunately, Pierre died several years ago.

LH: Oh, I'm sorry to hear that.

JB: It was a horrible tragedy. He had Hodgkin's, and then he actually did well with the treatment for Hodgkin's, and then he developed leukemia in response to the treatment.

LH: That is unfortunate. He had a secondary malignancy.

JB: Yes, he had a secondary malignancy.

LH: Yes, I remember Bill Pollin was so concerned about one of the people in our field who developed Hodgkin's. He came to me and was almost in tears, and I said send him out to Stanford, they'll cure him, because at that time the cure rate was about 90% for five years. It's amazing how the whole prospect of that disease has changed. Well, Pierre was unfortunate then, wasn't he?

JB: He certainly was. It was a real loss for the field. He was a wonderful person.

LH: So, in your job in that division, which I guess was under Bill Pollin's overall direction, did you have to supervise grants?

JB: I supervised grants and contracts. I think one of the main things I did at the time and where I certainly learned a lot about psychopharmacology, was the development of LAAM. We were working on LAAM and naltrexone in '75.

LH: It's incredible.

JB: Which we finally got on the market.

LH: You were working on LAAM in the 1970s and it wasn't until two or three years ago it was approved!

JB: That's right. I was in charge of the first phase III study of LAAM.

LH: It was so straightforward a drug. I don't know why all the problems with it.

JB: It ran into a political mess, actually.

LH: You want to expand on that?

JB: I don't think you want that. Well, it was actually a very complicated deal where the government had all the right intentions. Jerry Jaffe was the one who started the interest in LAAM when he was at The Special Action Office for Drug Abuse Prevention (SAODAP) and Jerry

thought it would be an easy thing for the government to get a drug on the market. They would just get some people together, and it would happen. Unfortunately, it didn't work that way. Since the FDA requires that the government also follow the same rules and meet the same requirements that are necessary for pharmaceutical companies to get a drug approved, the government embarked on a series of studies first sponsored by Jerry Jaffe and the Special Action Office of Drug Abuse Prevention (SAODAP), what we call phase II studies of LAAM. There had been a number of small clinical trials with LAAM that showed that it was an effective drug compared to methadone. SAODAP, the VA, and NIDA sponsored the early two strong phase II clinical trials of LAAM. One was the VA study, the other was the VA-SAODAP study, and those two were completed just about when I came back to NIDA. Based on the positive results in those studies, NIDA and a variety of advisors decided that the government should go forward to try to get an NDA for LAAM, and it tried very hard to interest drug companies, major drug companies, or any drug company, in the project, but they didn't want to touch it with a 10-foot pole. Jerry Jaffe and others like Avram Goldstein, I think, tried very, very hard to interest the companies. I think at that time Eli Lilly had methadone, and that was the drug that was on the market, and naltrexone hadn't been approved either. Endo had naltrexone. But I don't think either drug made a great deal of money. Methadone had all the negative associations of being a drug for heroin addicts, so really nobody was interested in LAAM.

LH: At that time, I think methadone was being made largely by Monsanto, wasn't it?

JB: Maybe.

LH: As a chemical company rather than as a pharmaceutical company.

JB: You're probably right, but I thought Lilly was marketing it, but I honestly am not sure, Leo. So the government, in an attempt to get a drug company interested, advertised the contract to do the phase III study of LAAM and produce it, you know, write the NDA, submit it to FDA, and put it through. Unfortunately, the government underestimated the task. I think the initial contract was a two-year contract for \$2 or \$3 million, a very small amount even at that time. Bob DuPont was very, very supportive of getting LAAM on the market. He really wanted it done. He also wanted LAAM to be used by many, many people across the country, so the phase III study that was developed was a combination of doing a phase III study and getting LAAM well known. The smaller part of the study was a comparison, a random assignment to methadone and LAAM, and the larger part of the study was an open trial in lots of clinics across the country.

LH: Just exposing a lot of people to it.

JB: Right. I think, in part, what happened was exposing a lot of people took a lot of effort and pulled back from the amount of time that could be spent on the clinical trial and getting people into it. So, it took longer than one would have hoped, and probably two years was overly optimistic to start with. We intended to put women on LAAM, and early on there was some question about the mutagenicity laboratory study in some, I don't remember exactly which preparation. It wasn't an animal. It was some kind of test. That kept women from going in the study and cut our sample size dramatically. So the study took longer than it had to. Although I think we got six or seven thousand people in that study, the contract needed to be reissued, and that became a political nightmare because we were trying to sole-source the contract back to John Whysner, who had a small consulting firm in Washington that coordinated the original contract.

LH: Who was that again?

JB: John Whysner. He was just a young man who had a degree in internal medicine and had actually worked briefly at SAODAP and put together a group of people, an advisory board, who could do the contract, who could do the study, and set up heroin treatment clinics across the country to do it. So the contract was re-advertised, and the initial contract was a cost-sharing contract where he didn't get any profit, and for his giving up profit he got the rights to the data for LAAM, because LAAM was not under patent any more, as you well know. The question always was how whoever got the NDA would keep it exclusive. The scheme that the lawyers came up with was that whoever got the contract would be given the exclusive rights to the data, the government's data basically, since it was a government contract. The government would give him for his cost-share, the rights to the data. When the contract was going to be reissued again, he didn't have enough money, really, to continue his operation and continue to give up his cost-share, or his company would have gone out of business. The government was in an untenable position, where it felt like they had to continue this cost-share, and the contract fell apart.

LH: What a laborious issue this drug was!

JB: The complicating factor was that he had the data. In other words, he had the government's data, and so the government couldn't proceed without that data and he couldn't proceed without a contract from the government. So the data had been gathered and was sitting in his computers, in his files, but had not been analyzed or put together in an NDA. Years later, the government

actually negotiated to buy that data from him and, more recently, it proceeded to do another phase III study of LAAM and put the NDA through.

LH: Now the last hurdle was put up by the FDA, wasn't it? Didn't they want long-term studies?

JB: You mean recently?

LH: Yes, within say the last 10 years.

JB: I think what happened was that when in the late '80s, early '90s, NIDA formed its medication development division and got together the expertise to actually do an NDA, it had the data. The people in the medication development division went to the FDA and said, you know, we'd like to use this data, and what do we need now to get LAAM on the market. They said, oh, my God, you're talking about data from 1977 to 1980. That's the most recent data you have on LAAM. And here we are in 1990! They felt that there had to be a study done with addicts, current addicts who were using other drugs, especially cocaine, that wasn't in very prominent use back then.

LH: A more naturalistic situation.

JB: The study we did was a naturalistic study, but it was done in 1977 to 1980. This new study was done in the early 90s.

LH: Who did that? Walter Ling?

JB: Walter Ling was certainly a prime person. Walter has been involved in all the LAAM studies. He was the head of the first VA study and the VA-SAODAP study. He was also very prominent in the Whysner phase III study. Jerry Jaffe has also been very involved in all these studies.

LH: A chap lives over in Arlington, and his last name escapes me, Alex...

JB: Bradford.

LH: Bradford. How did he get into this picture?

JB: He got into this picture because he actually bid on the contract. When the government had another proposal for a contract, I guess in the early '90s or late '80s, we put out another request for a contract, to take the data and put it into an NDA and negotiate with FDA to see what was needed to get the NDA. Alex Bradford who was a statistician and vice-president or president of the Biometric Research Institute (BRI) was awarded the contract to do the last phase III study of the NDA. So he was actually the one who put together the group and worked with FDA and then NIDA's medication development division and was successfully awarded the NDA for LAAM finally after all these years.

LH: That is an interesting history of a 20-year odyssey, of a rather straightforward compound, that was a technological improvement on methadone.

JB: I'm sure you remember, since you mentioned Alex, he and BRI were the people who got the NDA for naltrexone as well—this small, little company, a consulting firm, actually.

LH: They may be selling more naltrexone now for alcoholics than they are for heroin.

JB: I think they are.

LH: I'm actually not sure if naltrexone is working as well in clinical practice as it did in the studies. Have you got an opinion about that? You probably know more about the data than I do.

JB: The experimental data looks very good. I think that what has happened with naltrexone, truthfully, is that the studies that were done to get the approval were done in very controlled clinical trial programs, at the University of Pennsylvania by Joe Volpicelli and Chuck O'Brien and at Yale, by Stephanie O'Malley, and both of those centers do a fair amount of psychosocial behavioral interventions with the treatments. I think naltrexone was done in the context of a fair amount of psychotherapy, not psychotherapy in the sense of classical psychotherapy. But, you know, talking interventions, behavioral interventions, it seemed to work very well in that context. I think what's happening now is that it is being prescribed mostly by general practitioners and internists in offices with very little talking involved, and because of that, my guess is that it is not being taken as prescribed. I believe that even if the drug works pharmacologically, just don't hand somebody a drug and expect that they are going to take it the way they're supposed to take it and that it works. You need at least clinical management, maybe even some psychological intervention, counseling intervention.

LH: The rationale with all of these seems to me to be somewhat questionable. Virginia Davis, many years ago, came up with the idea that alcohol could be changed in the body to tetrahedral and isoquinoline and something that had morphine-like qualities, but never really nailed that down. I know Mo Sievers was absolutely appalled by the idea. So why should a mu receptor antagonist be effective?

JB: I certainly don't know the answer to that question, and I'm not sure anybody does, but I believe they think it's because the opiate receptors and the serotonin receptors all interact and modulate each other, and that causes the modulation of the opiate receptor or the serotonin receptor, or possibly, the dopamine receptor. Naltrexone, of course, theoretically, should have been the perfect drug for opiate dependence.

JB: Oh, it is the perfect drug for opiate dependence, except we have the trouble that . . .

LH: Nobody will take it.

JB: Nobody will take it, right. Well, we're working on that.

LH: It's a wonderful drug, but we can't give it away.

JB: You know, it's interesting, you mentioned Pierre Renault earlier. When he was at NIDA and I was at NIDA and involved with naltrexone, he felt, back then, that it wasn't the drug for all opiate addicts. It was for a subpopulation of opiate addicts who were highly motivated or early stages of their addiction.

LH: Like O'Brien's study.

JB: Like O'Brien's people. People who, such as physicians or other professionals, who have something to lose and have a lot of strengths and psychosocial support. For people who might be on parole or probation where if they become dirty they have something to lose. They're motivated. A population that Pierre used to mention that I think really hasn't been studied yet, is the adolescent population. Think of people in the experimental stage, early on in their opiate careers. Naltrexone might be a good drug for them. Nobody has actually studied it. And in the population of people who are sort of chippers but wanted to stop. Not hardcore addicts yet. I think it would have some promise. The population it has been used on mostly are people who have been on methadone and who have done well on methadone, and you're trying to get them off and switch them from methadone to buprenorphine, or some kind of detox, and then to naltrexone. That group is a very difficult population to work with at best. Naltrexone works while they take it. But then they lose the motivation to take it.

LH: One of the reasons people might not like naltrexone is that it has somewhat aversive qualities. I think Lou Judd did a study with naloxone, and we later did one with naltrexone, that showed if you give it to normal people in the way you give it to addicts, at the same dosage schedule, they don't feel good. They don't like it. And if you think the endorphin system has anything at all to do physiologically, it...

JB: It must be there for some reason.

LH: It makes sense that if you blocked it, people might not feel as happy as they normally do.

JB: Some addicts report mild dysphoria. That certainly isn't something that is prominent on naltrexone. Whether that is some kind of withdrawal still or . . .

LH: Or protracted abstinence.

JB: Or protracted abstinence is unclear. But it hasn't been successful. We are now doing some work with it in combination with more behavioral therapies. Bruce Rounsville and Kathy Carroll at New Haven are using naltrexone together with contingency management voucher incentives.

LH: That's for heroin.

JB: For heroin addicts. And meeting with some success. They are basically reinforced with some vouchers of monetary value. They don't actually get money, but they get to spend them on socially reinforcing items.

LH: Like M&Ms.

JB: Like movie tickets.

LH: How do you motivate kids without M&Ms?

JB: Right. Movie tickets or money for gas or rent or things like that. I mean, they're supposed to be spent on positive things that help with their rehabilitation, and although it's too early to tell, they're just in the process of this study, that seems to be helping to get people to take naltrexone. It adds a little bit more motivation, the monetary value of continuing to take it. The other side of "you know, if you're dirty you go back to jail." If you stay clean, you get these monetary positive rewards.

LH: That's a highly motivating circumstance. You've been close at hand on the development of what would now be the two major approaches of treating heroin dependence. How about cocaine?

JB: That's how I've been involved with cocaine. Unfortunately, I can't say that we or anyone else has been too successful with cocaine at this point, but the Division of Medication Development is still certainly trying hard, looking for a medicine to treat cocaine and crack cocaine. I guess since at least the mid-'80s, we have been testing anything that might possibly work for cocaine, and we are continuing to look for a drug that will be useful. I think the Division of Medication Development has built a system in place at NIDA to work with industry and the universities to screen chemicals, to look for hopeful chemicals. They have put together a system of investigators who can now test promising drugs to come up with the right drug. I think we will be able to do it.

LH: Is the first order a cocaine substitute or a cocaine blocker?

JB: I think we are looking for anything that would work, to tell you the truth, Leo. I think, at this point, that there hasn't been a focus on the substitute, although I think we are beginning to look at agonistic-like drugs that may be like a methadone for cocaine. Obviously, there has been some thought about an antagonist, a cocaine antagonist. As you well know, the trouble is that cocaine

works at the dopamine receptor, and you probably need dopamine around. So I don't know that an antagonist for dopamine would work all-that well. It may work for cocaine, but it would be bad for the person. There has been some recent work to show that dopamine and cocaine work at a slightly different site on the reuptake pump. Possibly, if you could block the cocaine site, but not block the dopamine reuptake inhibitor, maybe that would work. We are looking for drugs that might do that. Some years back I ran into one of the pharmacology letters in Life Sciences that indicated that bupropion bound to the dopamine transporter, and it occurred to me that this might be an approach. But our study floundered because we had so much trouble getting the cocaine people to take the drug. The results were essentially negative.

JH: I guess Tom Kosten has come up with a similar result.

JB: Well, Tom Kosten tried bupropion in New Haven, and I think it was a small open study. There were positive effects. And this was in a population of opiate addicts who were on methadone, and he gave them bupropion in that context. Based on that small study, NIDA supported a three-site collaborative study. I know Walter Ling was one of the sites. I think maybe Chuck O'Brien was the other site, and Tom Kosten. And, again, in methadone- maintained opiate addicts who abused cocaine, bupropion didn't work in that context. I was recently told by someone, and I don't remember who right now, that they were trying bupropion in cocaine addicts who were just cocaine addicts and weren't on methadone or opiate addicts. An open study saw some positive results and they were moving toward a double-blind study with bupropion again.

LH: That was the group we studied. They were pure cocaine users. But the attrition was so great that you couldn't really draw any conclusions. It still might be worth considering that approach at least, and that makes some sense.

JB: Yes, attrition is a real problem in the studies with cocaine addicts.

LH: Because that's the only true way to go, isn't it? You either find a substitute or you find something that blocks a drug.

JB: I think the other direction that the people in the medication development division are looking at also is finding a drug for the craving, whatever that is.

LH: That's hard to define.

JB: To prevent the compulsive use, which might be different from, an agonist or antagonist, maybe you would call it a relapse prevention drug. We are able to get cocaine addicts clean for a short period of time. They are able to stop taking the drug, whether that's for weeks or sometimes even

months. But there certainly is a strong tendency to relapse back to cocaine. And it's unclear what the physiological role or function is that's causing that, the neurobiological underpinnings of craving and compulsive desire for the drug, and an agent that might aim at that might be different than an agonist or an antagonist.

LH: No, but it would have to be something fairly specific to the action of the drug. I always remember Mo Sievers who, of course, was the dean of the whole field, saying that he tried cocaine once, but he wouldn't dare try it again.

JB: That's right. I remember that story too.

LH: I think that more pithily describes the tremendous amount of attraction that cocaine has for people. Similarly, in the animal self-administration studies, they work harder for cocaine than anything. So it's a tough drug to deal with. When covering your career in drug abuse, how about the stint you did with the Psychopharmacology Research Branch, NIMH?

JB: When I was there, I was working primarily with Bob Prien in the affective disorders section.

LH: Was that the lithium study?

JB: I think he had completed the first lithium study at that point, and he was doing the next study with David Kupfer on lithium, together with an antidepressant for recurrent unipolar and bipolar depression. It was a big multi-center collaborative study. I wasn't really involved with that, but Bob Prien was the primary person in that study with David Kupfer. I was also working with him on electroconvulsive therapy, which was the area that I was pretty much in charge of when I was at NIMH.

LH: This was ECT for mania?

JB: For depression and mania. I think we even supported a study at the time with schizophrenia, but mostly depression with an occasional study with mania.

LH: What was that, a comparison between ECT and bipolar depression versus unipolar depression?

JB: Most of the studies that we supported at the time were studies of different wavelengths or different waveforms or electrode placements or energy levels of electroconvulsive therapy versus other ones. There had already been a few sham ECT studies done in Europe, showing the advantage of ECT over sham ECT. So it wasn't felt it was ethical in the United States to give somebody an anesthetic without giving actual treatment. We supported grantees to do studies

using low currents or sine wave versus brief pulses with different intensities, different placements, to look at cutting down the side effects.

LH: Unilateral versus...

JB: Unilateral versus bilateral electrode placement, to see if you could maintain the effectiveness of ECT and decrease the memory and confusion side effects, the cognitive side effects.

LH: Yes, that's a big problem.

JB: It certainly is.

LH: I had a lab technician who had ECT and after that he had to write everything down on a pad.

JB: Was it bilateral?

LH: It worked beautifully on him, but for a long time he had a significant memory problem that he dealt with by simply making a written record. The government has played a huge role, then, in drug development, especially in drugs for treating mental illness as well as drugs of abuse. What do you see in the future? Let me give you a real tough one. Do you think the war on drugs is worth continuing?

JB: Certainly, I think the war on drugs is worth continuing, in the scientific sense at least. Having had a lot of experience working with people with drug addiction, whether that be cocaine or heroin, or even to some extent marijuana dependence, I think the drugs do have devastating effects on many people's lives, so that it is important that as clinicians and scientists, we work on finding treatments for the people who come to us for treatment, and try to encourage people to come in for treatment so that they can have more functional lives. Many of the people who are addicted to these substances, their daily function is very dramatically affected negatively, so that I think that we have to continue to try to come up with medications as well as behavioral therapies, including counseling, to help them extricate themselves from the addiction, and then allow themselves to be rehabilitated to more functional lives.

LH: I see you come down firmly on the treatment side.

JB: Right.

LH: But much of the war is fought on the idea of interdiction, and that seems to be totally disastrous, you know. It hasn't been working.

JB: I would agree with that. It seems that the supply side is a very difficult side of the war to win, and I would obviously be in favor of some shift in emphasis toward the demand side, prevention and treatment. I suspect you still need some emphasis on the supply side as well, to keep the flow

of drugs out of the country as well as the inventive chemists in the country from making up new abusable and possibly more addictive compounds.

LH: These are very complicated questions that get into many different areas. I suppose one of the things we are going to have to do is learn to live with drugs.

JB: At some level.

LH: The idea of a purely drug-free society doesn't seem to be very feasible. I've often said I can imagine the situation after a meal where somebody is drinking a brandy and smoking a cigar and having a cup of coffee, all three national drugs at once. It has become so much a part of our society!

JB: That's true. Many people can use those drugs and others do abuse and become addicted to them. You said cigar instead of cigarette. I think people are less addicted to cigars than they are to cigarettes.

LH: Probably, I guess if nothing more than the cost of them.

JB: Maybe.

LH: I remember when you could get a good cigar or a reasonable cigar, at least, for five cents. Now you have to pay about four bucks. JB: That's outrageous.

LH: I suspect it's just a current fad. But, there is no question that nicotine, is very addicting, and you can get nicotine, of course, from cigars, can't you?

JB: Oh, yes. But that's an interesting example. Nicotine addiction and cigarette addiction is actually, in part, in NIDA's purview, as well as the National Cancer Institute, and the Institutes of Heart, Lung, and Blood. So it's sort of split. Interestingly, I think that the physical harm from tobacco is very clear with heart disease, emphysema and cancer, and yet many, many people still become addicted to it and stay addicted to it because of the drug nicotine, the psychoactive component of tobacco.

LH: It's not the drug, per se, it's the way you administer it.

JB: That's right.

LH: You have to separate out the drug addiction from the smoking addiction.

JB: With that drug, I guess, people are more bothered by the physical harm that the tobacco causes than the addiction to the substance, nicotine.

LH: What thoughts do you have about marijuana, which is currently a drug of controversy?

JB: I still think that, in some ways, in this country, there is a de facto decriminalization because there isn't very much penalty or arrest and prosecution for possession of marijuana.

LH: I used to believe that too, but by God, the figures these days show that a sizable number of people in federal penitentiaries are there because they either possessed or were selling marijuana.

JB: I'm less aware of those statistics, and you are probably right. I would suspect that is more sale than possession.

LH: This came to light a few years ago when a journalist who was writing an article for The Atlantic Monthly called me up and wanted my opinion about some aspect of it. But when I read his article, there were these horror stories of people with relatively small amounts of marijuana winding up doing hard time in federal pens for 15 or 20 years. It was incredible.

JB: I'm surprised.

LH: I used to think the district attorneys and the police had the sense to ignore a lot of this, but they seem to be going gung-ho at it now because it's an easy arrest and it's an easy conviction. It makes their record look good.

JB: That would be unfortunate if that were true. I was not aware of it.

LH: There is going to be a lot of debate, I think, or continuing debate about which way we should go with this problem, and I would think that if I had NIDA to run and I escaped that many years ago, I would have probably set up some sort of permanent group of scientists and sociologists and all the disciplines involved, thinking of ways to deal with the problem on a larger basis than purely the scientific or medical model, because we don't seem to be making a whole lot of headway. You know, the impact of naltrexone on opiate dependence has been very, very small.

JB: Right.

LH: And methadone, of course, was a major step forward, but that started, when was that, in 1960?

JB: Late '60s.

LH: So we haven't come a long way since.

JB: I think it was marketed in the late 1960s.

LH: You have had an interesting career, Jack, shepherding all these things through the twirls of the government bureaucracy.

JB: It's been a very interesting career, yes.

LH: There aren't too many people, I guess, who have been connected with the field as long as you have been . . .

JB: That's not true.

LH: And still enjoy a high level of regard, you know.

JB: Thank you.

LH: It's a thankless effort. I want to thank you for coming this morning.

JB: Thanks very much. It was a pleasure.

## 8. JOSEPH V. BRADY

LH: Joe,\* it's really an unusual pleasure for me to be assigned to be your interviewer here, for many reasons, first, for our long standing friendship and, particularly, all of your contributions. Of everyone I know in the field of neuropsychopharmacology, you represent a person who has contributions over a very wide range of areas and you and the work you've done with your colleagues, has had an enormous impact in terms of 3 to 4 decades that have followed. Now, I thought we'd perhaps chat a little bit, first of all, about your personal background, in terms of your schooling and let's start pretty much at college. I think you went to Fordham.

JB: Yes, I was trained by the Jesuits.

LH: Did anything happen during college, perhaps, that steered you in the direction in your career?

JB: Well, obviously, the main event was the war. You remember the war, the period from 1942 to 1945?

LH: Yes, I was there.

JB: It was in all the papers. I had no choice but to take ROTC (Reserve Officers Training Corps) training and was inducted into the Army even before I finished my degree. That sort of launched me on a career starting in the infantry. I ended up in Germany at the end of the war, and for reasons that only the United States Army could fathom I was picked up bodily and sent to the Neuropsychiatric Center of the European Command. That was in 1945, I guess, right at the end of the war. I spent two and a half years as the Chief Clinical Psychologist of the European Command, with absolutely no training, whatsoever to do that.

LH: That clearly got you oriented in this area.

JB: I began to learn a little bit about what went on. And perhaps, the single most important event was that I got to the Neuropsychiatric Center of the European Command. We did not have all the fancy and effective psychopharmacological approaches. People were plugged into the light European Command, you received a set of electrodes and electroconvulsive shock, a major therapeutic intervention. And we also had the tubs. All those good things were in effect circuit in

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\* Joseph V. Brady was born in New York City, New York in 1922; in 1951 he earned a PhD in Psychology from the University of Chicago. He worked for a number of years at Walter Reed Army Institute of Research, before joining the faculty of Johns Hopkins University in 1967 as director of the Behavioral Biology Research Center. He died in Baltimore in July 29, 2011. He was interviewed in San Juan, Puerto Rico on December 13, 1994.

those days. Along with your slippers and your bathrobe, in the psychiatric center of the.

LH: In regard to your impact in neuropsychopharmacology, I know that you go way back, to Walter Reed. What people or events steered you in regard to your activities relevant to ACNP and neuropsychopharmacology?

JB: Well, I was picked up from Germany and sent to the University of Chicago in the late 1940s. I took my degree there with Howard Hunt. I capitalized a bit on what had gone on in Germany and I did an experiment with electroconvulsive shock. We had some methodologies that we developed, conditioned emotional responses in animals, and that was really the beginning of my interest in this area. After finding that the electroconvulsive shock effects were clearly demonstrable experimentally, we began to look at what kinds of pharmacologic agents would produce these attenuating effects on conditioned emotional behavior. There wasn't a helluva lot available in those days.

LH: Why don't you just talk about your paper on reserpine?

JB: That was just one paper, right?

LH: Yes.

JB: That was done after I had left Chicago and came to Walter Reed in Washington. Reserpine was the first of the tranquilizers. The major tranquilizers appeared on the market and we tried the effects of reserpine on this conditioned emotional response. Our paper was published in *Science* in the mid '50s, and really it provided the basis for those things we have been able to develop for screening some compounds, using behavioral procedures to determine the ones that had an effect on chronic psychiatric illness.

LH: So, you're saying that experience was somewhat pivotal in getting you in that field?

JB: Oh, no question about that.

LH: Were there any people, individuals that had a significant effect in regard to your career at that time?

JB: Well, obviously, Howard Hunt at the University of Chicago was a major influence in getting me into this sort of animal model type of research, but the people I interacted with at Walter Reed, of course, were also largely influential. And also people from other disciplines had an influence: Dave Rioch, Murray Sidman from Columbia, Bob Galambos, a neurophysiologist, John Mason, an endocrinologist, and, of course, Walle Nauta, a neuroanatomist. We did a lot of work together on lesions of the central nervous system and it was an easy transition to begin to look at the effects

of drugs. Reserpine turned out not to be the panacea, needless to say, and we gave it to a lot of animals who never recovered.

LH: What were some of the problems that you had to face at the time that you had to deal with? What was going on in terms of drug interaction with behavior? What were the early concepts that you had at that time that may or may not have changed, regarding the interaction of drugs and behavior? What were the issues?

JB: Well, obviously, I have written and spoken before about what I think progress in this area has been. It's an interaction between conceptual changes and methodological developments, essentially. It was the methodological developments which were sort of the drivers at the beginning. We had a technique for measuring effects on emotional behavior; we looked upon it that way. We looked how lesions, electroconvulsive shock, drugs were acting upon the organism and that was the major conceptual thing. Needless to say, this has changed dramatically.

LH: In what way?

JB: The development of the tranquilizers, both the minor and the major, and the monoamine oxidase (MAO) inhibitors opened up a whole new field with respect to areas that we hadn't expected, that is, drug abuse and drug dependence. And it was there that the notion of an interactive effect between drugs and behavior became really crystallized. When, for example, it was demonstrated that animals would self-administer drugs through indwelling catheters, this had a dramatic effect upon looking at drugs having the same kind of stimulus functions that all other events in the environment could have, both internal and external, so that not only did they function as reinforcers, as consequences, which control behavior, but they functioned as signals, for example, and this was where the whole drug discrimination area has come from. So these are the results of a conceptual shift, which then produced methodological changes and then conceptual changes over the past 30 or 40 years.

LH: During your very successful career, in which you've had impact in so many areas, what were some of the problems that you faced in carrying on this very important research? Was it easy as pie? What did you have to do?

JB: I don't remember any great problems. I, obviously, was involved in a number of different areas, not only the neurobehavioral and psychopharmacological, but one of the great satisfactions of my life is that the domain I selected, or was driven into, the study of behavior, is every man's dependent variable. No matter what new fad comes along, whether it's microwaves, whether it's

electroshock, whether it's drugs, whether it's space, everybody wants to know what the effect is upon behavior, so I've been sitting pretty for 50 years. No matter what anybody had, they always wanted to know was about behavioral things.

LH: I would be remiss during this interview, if I didn't ask you how about the executive monkey?

JB: Quite serendipitous finding, needless to say. We were, of course, interested in the physiological changes that occurred in animals who were doing avoidance performances, an extremely stable performance over extended periods of time. We were, in fact, measuring hormones with John Mason at the time, 17-hydroxycortisol, steroids, all those sorts of things. We had a young pathologist working with us by the name of Bill Porter, who had done post-mortems in a number of the animals that had died, and he came in one morning with a handful of guts, essentially, showing me the stomach of one of the monkeys and saying that he had a very serious ulcer, duodenal ulcer. And I said, "Well, that's too bad, we'll have to do something to see if we can prevent that." And, as he repeated this on several occasions, it became obvious that, maybe something we were doing actually produced that. So we launched a systematic series of experiments, and when we did control and experimental animals it was pretty clear that there was a difference between them in this regard.

LH: I'm always impressed by the wide range of impact you have in so many significant events, even training a monkey for space.

JB: That's part of the business I'm telling you. No matter what, anything that comes along, everybody wants to know what the behavioral effects are. That was again a consequence of being in the right place at the right time. While we were doing the monkey experiments, which of course got a lot of wide exposure in the press and elsewhere, we had a visit at Walter Reed from Werner von Braun, who was, at that time, working for the Army on the Ballistic Missiles Agency, and this was even before NASA (the National Aeronautics and Space Administration) had come into existence. And, he wanted to know if I'd be interested in putting one of my livestock in the nose-cone of one of his rockets. I had not much idea of what he was talking about at the time, but we ended up with very small rhesus monkeys, two of them, I believe, put in a plaster cast, because you get knocked around a lot in those cones, with one finger left out, and my job was to train that finger so that the animal would make some response during this period of orbiting. Well, the initial flights were ballistic flights. You just went up 300 miles at 10,000 miles per hour and came back down. And there were no physiological or pharmacological measures at the time for the integrity

of the organism. This is another reason why behavior is every man's dependent variable. It's the best indicator of the integrity of the organism, but with this behavior you know he's alive and well.

LH: Let me jump ahead. We'll come back again to the continuation of your career at that time but let me jump ahead with this point. I personally find, as you probably do, a real shift in regard to research attitudes, using gross-criteria behaviors as opposed to molecular biological approaches. I think there's been some moving away from heavy research in the whole animal and using these behavioral measures where people who are not behaviorists or molecular biologists may have a somewhat different attitude than you or I in terms of its relevance in regard to research. What thoughts do you have, in terms of the role of behavior in the future, how it's going to sustain itself, in view of all of these breakthroughs at the molecular biological level?

JB: Well, I also have an appointment in the Neuroscience Department at Johns Hopkins with Sol Snyder. I regard my job there as to keep these guys honest, and the way you keep them honest is to having them recognize that the objective of why they are interested in the nervous system is because it has something to do with the way organisms interact with their environment, and that's really the major objective. Furthermore, the illusion that your mind accounts for that process, that very complex interaction process, by identifying the receptor sites seems to me to be a little far-fetched.

LH: Do you think that we're going to continue to impress people about the importance of behavior as it is now headed?

JB: Well, I don't think there's any question about this because that's where they end up eventually, anyway. As I've said to Sol on numerous occasions, understanding the nervous system is a piece of cake, compared to understanding the complexities of the way organisms interact with their environment, and you don't have to agree with that.

LH: Let's go back again, now. I know you had a very heavy influence in regard to your consultantships with various drug houses, and they incorporated a number of test procedures you had worked out at Walter Reed.

JB: I think that influence was more in the direction of the people that ultimately went to work for the pharmaceutical industry. And, to go back to where we left this earlier, it was that 1950s paper on reserpine that caught the attention of a number of people in the industry and sort of flagged the notion that maybe every pharmaceutical company in the country had hundreds of compounds on the shelf that could potentially be useful without any good way of telling their behavioral effects.

In other words, the behavioral effects were the ones they wanted. That's what caught the attention of people, and, as you know the pharmaceutical industry better than I do, too, once one of them gets into something that begins to look promising, everybody's going to have some. It was largely the fact that we had a reservoir of people at Walter Reed.

LH: Who were they?

JB: Guys like Dick Herrnstein, Murray Sidman for example, and Tom Verhav, Larry Stein, and John Boren, and people who were provided to us by General Hershey, as a matter of fact. These were the days when the draft was going wide. So these people were assembled there, because they were putting in their couple of years' service.

LH: What about Irv Geller during the '50s and '60s. Wasn't he down there?

JB: Irv Geller, absolutely, he was there. He was my first research assistant, as a matter of fact.

LH: So, we both saw that during the 1950s and 60s the phenothiazines and the benzodiazepines, the meprobamate series were primarily identified with behavioral tests.

JB: It was a behavioral endpoint that was of interest then.

LH: The behavioral endpoint was what decided, let's invest our 30 or 40 million dollars and develop this drug. As people go on, again, to the future, they're not using, today, as many of these criteria to identify drugs. Where do you see drugs in the future? How are they going to be discovered?

JB: Well, it could well be that the molecular biologists will provide fertile leads in this regard and, you know, receptor dynamics is clearly a most efficient way to proceed in some areas, but the ultimate test is going to have to be some measure of changes in that interaction between organism and environment.

LH: You were a very good seer of the future. You've been a good seer. If someone said, okay, we've had the antipsychotics and we've had the anxiolytics and we've had the antidepressants and we're beginning to see drugs that may modulate cognitive processes.

JB: And, enhancers, clearly. Incidentally, that is not a new idea, as you know.

LH: So, we have these classes of drugs and I'm sure that we're both going to see in the next decade drugs appear that will be therapeutically effective in modulating neural processes.

JB: Yes, I think the memory area is clearly one.

LH: Where do you think psychopharmacology is going to go 20 to 30 years from now? Do you have any thoughts about that?

JB: Well, obviously, we're going to be creating drugs according to a model that is not even available to us now. But, in terms of the kinds of measures that we're taking, it seems to me the major methodological advances will have to come from the behavioral site of events. We've seen it and, as I say, in the drug abuse field, the notion of measuring a subjective response, that was a real breakthrough and that was a behavioral measure that we couldn't now ask animals to discriminate between contact measures. That was a great advance and I think we'll see similar kinds of advances occurring.

LH: I know that, now, among the many things you're doing, drug abuse is something you're spending a lot of your time on and attending to. How does it fit into your continuing concept? What are some of the things you're doing in drug abuse?

JB: Well, one of the things I've seen developing over the past 10 or 12 years is a broadening of the arena for behavioral pharmacology in this area. As I say, the dramatic effect occurred, and the thing that everyone looks at, of course, is the drug self-administration, then, the drug discrimination, of course, came along to tell us that, so to make you use animals to tell us something about whether the drug made the animal discriminate, but there's a third area that has not received much attention and it's classical behavioral pharmacology, and what I think of as behavioral toxicology. That is, the effects of a drug, there is the abuse liability of the drug, the thing that makes it is determined, not only, by whether it is self-administered and whether you can discriminate it, but the effect it has upon the organism and the price the organism pays and the price the community pays for that. And, this was a dimension of the whole drug abuse field that we have started to develop pretty well now at Hopkins. We see this as a sort of three-pronged approach, the abuse liability being defined, largely by, dependent upon, self-administration and drug discrimination, but we now have a whole battery of auditory measure thresholds, for example that we can now measure very carefully with drugs in animals.

LH: Drug abuse continues to be a problem. If you had your druthers and you were kingpin, making the decisions as to how to really address the drug abuse problem and you could remove yourself from what you're doing, how would you direct the national posture to the problem of drug abuse?

JB: There would have to be a substantial shift from the supply side to the demand side, eventually. The notion that we can win the drug abuse problem by, essentially, sealing the borders was crazy. On the other hand, we can do something about controlling the demand and there are some rather substantial contributions that have been met. In my view, there are some clearly convincing

experiments of nature that have been done, the Lee Robbins work, for example, that's respected returning veterans who had very heavy drug habits. Once they got here, they were all right. The effects, being able to control drugs at the work place by setting up certain contingencies, I think this would be a major way that we could use to control drug abuse.

LH: I have been asking you questions to give the audience some perspective and windows into Joe Brady. What are the things that I haven't touched upon that you feel have been very significant in your career?

JB: Well, one of the things about that early 1950's experiment that is frequently overlooked is the nature of the conditions under which that reserpine effect was demonstrated. Most of us look at drug effects in very acute ways. We say, now, we've got this animal trained and we give him the drug and he'll be way out of change. Very few people have paid much attention to the details of that experiment, namely that the drug was given, first, after the animal ran each day, not before. So, the animal ran every day for like an hour or two hours and, then, we administered the drugs.

LH: So, you were testing the residual effect 24 hours later?

JB: Exactly, and nothing happened for a week. Only after two weeks of running with it, all of a sudden the continuation appeared. At that time, who would have ever thought that that's the way to do screening, but, now, what we're looking at, as you say, the antidepressant effect. That's exactly the kind of dimension that is critical.

LH: You just touched on something that I feel very strongly about and that's the residual effect of the drug behavior interaction.

JB: Right, and you can produce change, for example, in behavior very frequently, and this is one of the nice things we discovered early on, too, that the organism changes and, then, you can take away, for example, the drug and that effect.

LH: Yes, plus, that he was different yesterday.

JB: Exactly. I think that's very important, but it's one that people don't look very closely upon.

LH: No, because they look upon, how did the drug affect behavior rather than what is the residual effect of the drug behavior interaction to what your paper really was on.

JB: I guess the other point that seems to me to be worth making is that all of the kinds of methodologies and conceptual changes that we find of value in a given area like behavioral pharmacology don't necessarily come from our intents and offerings there. The experiments, which we have done over the past couple of years in the programmed environment, where the

people lived for periods of 2 to 3 weeks at the time, now, the measures are not acute measures but continuous measures. That didn't come from our interest. In fact, that came from NASA. The necessity of developing methodologies that would make it possible for people who are going to be in NASA, talking about sending people in these little boxes off for two years and, under those circumstances, it was necessary to develop a behavioral technology, essentially, that would maintain performance under isolation and confinement conditions over extended periods of time, a technology that was at least as powerful as the engineering technology that makes that possible. After we spent a few years working in this, we realized that, hey, that's a great place to study the addiction cycle. I want to look at the effects of drugs and we did marijuana studies where it's been virtually impossible to demonstrate anything related to this, i.e. the "motivational" effects of marijuana. But in a setting like that, we had a fighting chance and we were able to demonstrate a lot of interesting changes that occur with repeated use when you're looking at everything and a process, not simply a given magnet in terms of X-ray.

LH : Over the 40 years we've known each other and dealt with each other, I've always noticed that you always enjoyed what you were doing?

JB: Well, shall we say, put in more technical language that I'm in a reinforcing field. Every time you do something and you got reinforced for it, this is a career evidence that is something.

LH: You've had fun though.

JB: Absolutely. Now, the latest things I'm involved in, of course, have been pretty heavy duty and I'm not sure this is, I've been running a mobile drug abuse program on the streets of beautiful downtown Baltimore.

LH: Tell me about it.

JB: Well, that, if you're interested in a research career in behavioral pharmacology, this is not the way to go. Once you get into a field of this sort, the notion that you have control of what's going on is really the difficult part. So, it hasn't been a rich research area, but it has had the effect of opening up, we run, essentially, a full service drug abuse program without a fixed site. So by just going out to various areas and making treatment accessible to people who would not normally have it, I guess the most striking effect is retention.

LH: One of the aspects of the last 40 years is that you and I and others like us started with a blank check, a blank piece of paper, as the field emerged and there was nothing for us to read to help us. There were no books for us to read.

JB: But, we had a repertoire. I mean you were a pharmacologist. You still are a pharmacologist, so you knew that area and I was in the behavior analysis area, and what we did, essentially, was built upon that repertoire by expanding it, but not with dramatic big changes, but a little bit.

LH: Essential steps.

JB: That's right. Let's see what would happen if we did experiments, right? That's the way progress is made.

LH: Because, I want to follow that with a point. What we're doing right now with this videotape, since it provides for the generations that follow, separately. Who is Joe Brady? What did he look like? What were his thoughts? Now, it's an opportunity for you and others to kind of look at the next generation, or, perhaps, the one after that, in terms of any advice guidance principles that you may relate to them. I don't mean for them to be the great seer, but there must be thoughts that you have projected for the future. Is there anything you would like say, on a serious note, in regard to the research that you see today and where the future is going? Any comments you would like to make to the young people that are going to see this video, perhaps, 10 to 20 years from now?

JB: Well, my best advice is to keep making responses. The important thing is to, at least, make sure you have your field down cold and you know what you're doing. Another important thing is the idea of trying new things. I've always thought of myself as leading an experimental life, and if something doesn't work, you try something else, and essentially that's the way both you and I have progressed. Everything you do doesn't always work, but if you have enough foundation that you can return to so that you've got to have some domain which you care about, it seems to me. You can't be all things to all people, but if you have some area of confidence, some discipline, if you develop a high degree of confidence, then you can move from that, but you always have that to build on that foundation.

LH: We enjoyed something at that time, which was enormous freedom. We had the resources during the Golden Era to do almost anything we thought that was worthwhile to do. Today, and I'm concerned about the future, the resources may not be there to allow the scientist to follow his nose. He doesn't know if he's going to be dictated to. His research is going to be highly programmed, overseen by different committees and that type of thing. What is your concern?

JB: I don't have that pessimistic view.

LH: You don't?

JB: No, and simply because having been around for the past 40 or 50 years, I've seen us go through cycles like this before, as well. I was at the Walter Reed in the days when one of our Secretary's of Defense, Charles Wilson, under the Eisenhower administration, when asked about the kind of research that we were doing and supported by our defense department, said that we don't really care why the grass is greener. In other words, there was no interest in basic research and, therefore, that should not be funded. Well, you know, that, too, will pass and I think that's the only way to look at this. The era we're in at the moment always seems to be the one that's, God, this is unique. There's never been anything like this before. It's going to be a disaster.

LH: So, you're optimistic about the research?

JB: Absolutely, no question about it. Just keep making responses and everything will turn out all right.

LH: What is it that you'd like to say that we haven't touched on?

JB: Well, I don't know. Seems to me we've touched on just about everything. I wasn't sure I was delighted about doing this in the first place. Yeah, you'd take anybody here. But, I'm quite content. I think we've done very well covering my life.

LH: Well, I could tell you, Joe, that you've always been a fan.

JB: The only thing we haven't touched on is that meeting in Rome we went to.

LH: Do you really want to talk about that?

JB: Maybe that's, what was the year of that?

LH: 1958.

JB: My Lord. Well, about 40 years ago.

LH: And, we enjoyed Rome.

JB: And, we enjoyed Rome and that was the beginning of the International College of Neuropsychopharmacology, as I recall.

LH: Right. That's when I gave my first paper on chlorpromazine there. I don't know if you joined us when we went to visit the Pope.

JB: Of course, I had Rosary beads blessed.

LH: So did I. I gave them out to all my neighbors.

JB: Well, they told me "you've got to take them out of your pocket." I said, "Well, what kind of blessing can it be if it doesn't go through my pants?"

LH: Joe, it's been an absolute pleasure to know you, in all sincerity, over these years and I just hope that the scientists of the future have the drive, the intelligence and the perspective of research you have.

JB: And have as much fun.

LH: Okay, thank you.

JB: Thank you.

## 9. BERNARD J. CARROLL

LH: Today is December 17, 1998. We're in Los Croabas, Puerto Rico for the annual meeting of the American College of Neuropsychopharmacology. Today, we're interviewing Barney Carroll,\* who has been part of this organization and part of the history of psychopharmacology ever since he arrived from Australia in the United States. Barney, welcome to Puerto Rico and the ACNP.

BC: Thank you, Leo. Thank you, Tom.

LH: I'm Leo Hollister and this is Tom Ban; we are going to jointly interview Barney. I guess around 1973, I was refereeing a paper for the Journal of Clinical Pharmacology and Therapeutics, a review on monoamine precursors in psychiatry and it was a very good paper, but I had never heard of the author. He was some strange Australian named Carroll, and just to check things out, I called up Dave Hamburg, who was then our chairman of psychiatry, and I knew that David had just been in Australia and made an extensive tour and I said, "Who is this fellow, Carroll?" Dave's reply, without hesitation, was "Topnotch," and so, without any further hesitation, I enthusiastically felt that the paper should be published. But it was only later that I really got to know Barney Carroll. Tell us, Barney, how did you decide to go into medicine?

BC: It's all one of those accidents of being some place at the right time for things to happen. Leaving high school, I thought at first I would be a lawyer and, then, I switched to thinking about medical school. The system in Australia is that right out of high school, you go into professional school. You don't have to do four years of college first. So, medical school there was a six year deal and I knew that if I enrolled for medical school and didn't like it, I could switch to a science degree later and that would be no problem. And, the person really responsible for getting me into psychiatry, however, and pharmacology is Sam Gershon, because in 1959 and 1960 when I was a second and third year medical student, Sam was our lecturer in psychopharmacology and he

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\* Bernard J. Carroll was born in Sydney, Australia in 1940. Dr. Carroll has served on the faculties of the University of Pennsylvania (1971 to 1973), the University of Michigan, Ann Arbor (1973 to 1983), and Duke University (1983 to 1998) where he was the Chair of the Department of Psychiatry from 1983 to 1990. From 1991 to 1998, Dr. Carroll was Director of the Duke University Mental Health Clinical Research Center for Depression in Late Life. He was interviewed by Leo E. Hollister & Thomas A. Ban in Las Croabas, Puerto Rico on December 17, 1998.

impressed me so well that I took a year out of the regular curriculum in 1961 to work full time in his lab. And, we published our first paper from that work. Parenthetically, one of the drugs that we had in the lab and that I used in 1961 is a drug that has lately, like Phoenix, been resurrected, namely tacrine.

LH: Tetrahydroaminoacridine. I see the anesthesiologists used that to wake people up, didn't they?

BC: Well, I'm not sure that they used it as an analeptic, but they certainly used it as a cholinesterase inhibitor. The interest in Australia at that time was because the farmers were getting themselves poisoned with cholinesterase inhibitor insecticides, so there was a lot of interest in cholinergic pharmacology. And, that was actually my first research project with Sam Gershon. It was funded by the US Army and the CIA.

LH: That was part of the behavioral program?

BC: It was to develop antidotes to anticholinergic hallucinogens. In the Cold War, the feeling was that the Russians would come and spray the American troops with anticholinergic hallucinogen drugs. Ditran was the drug we used and my job, as a research student, was to give Ditran, JB 329 of Lakeside Laboratories to dogs, watch the behavioral syndrome, and develop a rating scale for that behavioral syndrome in dogs. It was about a two hour period of what, today, we would call anticholinergic delirium and, then, to give putative antidotes to this anticholinergic agent. Tacrine was the main drug that we worked with to reverse it. So, we ended up recommending to the US Armed Forces that Tacrine would be a very good drug to use if the Russians came. And, then, twenty odd years later, it resurfaced as a new old drug to treat Alzheimer's disease. I had a good laugh when I saw that happen, believe me.

LH: I guess, it coincided with the notion of cholinergic deficit in Alzheimer's.

BC: Yes.

LH: But, do you know what the JB stood for?

BC: I sure do. It stood for John Biel, who was one of the early chemists in the psychopharmacology business.

LH: That's right and I thought we should at least mention it, because he's no longer here to mention it, himself.

BC: That's right.

LH: You know he did a whole series of these compounds, 318.

BC: 329.

LH: 329 and a whole series of them. I guess a couple of them made the market of therapeutic agents for irritable colon and things like that.

BC: Yes, as spasmolytics, right.

LH: Well, I never knew you had a Gershon connection. Sam was also using another drug, yohimbine. Did you have anything to do with yohimbine?

BC: I didn't work directly with yohimbine, but that work was going on in the lab while I was there. I can well remember those dogs standing up in the lab in their harnesses after being injected with yohimbine and going into, what I guess, was a panic attack.

LH: Fear as extrapolated in the dog.

BC: That's right.

LH: So, that was a defining experience, then?

BC: Well that was. And the next main step for me was at the end of that twelve month period in Sam's lab when I went to spend the summer in John Eccles' laboratory at the Australian National University in Canberra. I got a three month summer studentship to go up there. Eccles had, not very long before that, been awarded the Nobel Prize for, basically, discovering or nailing down chemical neurotransmission within the central nervous system. And, so, I was very fortunate to get a chance to go up there and spend three months before returning to medical school. And, when I arrived in Canberra, after having met Eccles some months earlier and setting this up, when I got there Eccles had completely forgotten who I was or why I was there, and he sort of abruptly said, "Well, alright, you're here now. You go down the hall and you work with David Curtis." Now, David Curtis and Jeff Watkins, at that very moment, were defining the excitatory neurotransmitter role of glutamate and aspartate, so I was in their lab for three months, pulling multibarrel microelectrode pipettes, putting in glutamate, GABA, strychnine and so on. All of that early excitatory amino acid pharmacology was being worked out right there. I had a great introduction to very fundamental neuropharmacology through that experience. And, I remember at the end of all of that, I was due to go back and complete three more years of medical school and, then, residency or whatever, and I remember telling Sam that I was kind of worried about going back and wasting all that time on medical school, because so many really great new drugs had just come along. This is 1961 we're talking about. Amitriptyline, imipramine, chlorpromazine, were just really new agents, and, of course, we had lithium from John Cade right there in Melbourne. And,

I said to Sam Gershon, “Maybe, I should just go directly into a psychopharmacology career and bypass finishing medical school”, because, I said, in the way young people do, “By the time I get through three more years of medical school and residency, all the major questions will already be solved.”

LH: That’s the optimism of youth.

BC: And, Sam, in his wisdom, said, “Nah, go on back. There’ll be plenty to work on by the time you get done.” And, of course, he was right.

LH: Well, that really was a flying start in neuropsychopharmacology. I guess you were one of the few people who really began before actually going to medical school.

BC: I did, yes.

LH: Most people, I suppose, began after medical school.

BC: That’s true; that’s true. In fact, after I completed medical school, Sam, by then, had moved to the US. I actually signed up for a residency in Internal Medicine, not in Psychiatry, and I did two years of Internal Medicine, thinking that I would then have a career as a Clinical Pharmacologist, a General Pharmacologist, not specifically in Psychopharmacology. And it was during the second year of my medicine residency that I had back to back rotations in Endocrinology and Psychiatry, and I put together, then, the idea of using Pharmacology and Endocrinology to test the theories about antidepressant drug action. In other words, I kind of articulated the neuroendocrine strategy of using neuroendocrine dependent variables to test ideas about neurotransmitters in psychiatric drug action and by extension in the pathophysiology of psychiatric illness. So, that was how I got into psychiatry. So, I left the medicine residency at that point and signed up for a psychiatry residency and did three more years of psychiatric residency. I had a very, very good Chairman, Brian Davies, an Englishman who had come out, having trained at the Maudsley, so he had a very sensible approach to psychiatry.

LH: He was a long time Chairman there, wasn’t he?

BC: He was, and I like to say that one of my benefits in training was that my mind was never particularly corrupted by psychoanalytic psychiatry.

LH: That wasn’t too popular in those days in Australia.

BC: No, it wasn’t.

LH: Of course, another thing is that psychoanalysis was riding pretty high in the US.

BC: Oh, it was dominant in the US. So, Brian arranged that I could continue being affiliated with his research program while I completed my residency in psychiatry. And, out of that came the first of my clinical studies, done in collaboration with Brian Davies and with a very good endocrinologist, Skip Martin, in Melbourne. We began a systematic survey of hypothalamic pituitary function tests in psychiatric patients and the idea was to get the baseline measures, then give the drugs and, through the changes, we would see then what the drugs were doing. That all took a right turn, because when we were getting the baseline measures, one of the procedures we used was a low dose dexamethasone suppression test, because already there were ideas that cortisol was elevated in depression.

LH: You were doing the clinical test that was used for Cushing's disease. Is that right?

BC: That's correct, yes. We were using the low dose DST with a single early morning blood sample, with a single overnight administration. I well remember; I was the guy running the protocol. I was the guy drawing the blood. I was the guy processing the blood samples and I was the guy running those cortisol assays through the spectrophotofluorimeter in the hospital biochemistry department.

LH: You were a general factotum.

BC: And, we had these post dexamethasone cortisol levels coming back from the depressed patients that were sky high, so, it finally dawned on us that we had something important here and we pursued that in its various ramifications for many years afterwards.

LH: Why, with those high cortisol levels, did patients not show any of the signs of hypercortisolism?

BC: That's true. That was something...

LH: Was there some kind of receptor bad?

BC: That's exactly on target, Leo. Even back then, we said to ourselves, they should look Cushingoid, but they don't, and maybe there's a receptor deficit. And, that has been another fairly extensive line of research. It's so far, inconclusive in the endocrinology of depression.

LH: Well, that opened a whole new approach. For long, people thought that the endocrine system would be a window to the nervous system, and especially to some of our illnesses.

BC: Right. I think I should say that, you know, like a lot of things, this was a changing experimental strategy or an innovation in experimental design that was waiting to happen and we were not the only people to kind of stumble into this new approach. Gerald Besser in London was

doing it at the same time, unknown to us. At NIMH, in David Hamburg's old unit, they were doing it there. Jan Fawcett and other people in NIMH were also running dexamethasone procedures then. And, Peter Stokes in New York was also doing it at the same time.

LH: How about the chap at Columbia that died early in his career? I can't remember his name.

BC: Ed Sachar at Columbia was doing intensive studies of baseline cortisol secretion, but Ed had not taken it to the point of challenge procedures, interventional probes. Ed was doing very detailed blood sampling across the day and night cycle of cortisol secretion in, not just depression, but psychotic patients, schizophrenia patients.

LH: He was more interested in the daily cycle secretion.

BC: Yes, and Ed, at that time, was very focused on correlating the endocrine elevations, with, what he called in his psychoanalytic orientation, indices of ego disintegration. So, he had this elaborate rating scale for ego disintegration in psychotic patients and his primary theme for a long time was that elevated cortisol results from ego fragmentation and the attending anxiety that induces in the psychotic patient. And, it was not until he got his nighttime cortisol values back and looked hard and long at them that he finally said to himself, OK, this is something else, because, even while these people are asleep, in fact, while they are asleep, the cortisol values are elevated.

LH: And, they're presumably not active.

BC: So, it was at that point, when Ed Sachar began to shift away from the psychoanalytic interpretation of psychoendocrine data.

LH: Well, insight comes to everybody.

BC: Right.

LH: Well, I noticed that your second publication was on Lack of Sensitivity to Dexamethasone Challenge. Is that one of the citation classics?

BC: Yes, that's a citation classic.

LH: I should imagine so.

BC: Yes that certainly is, yes.

LH: Now, another one that I reviewed on the Precursors of Monoamines, tell us how that got started, because I gather that's another citation classic.

BC: A lot of people knew me for DST research, but not everybody knows that I have worked in quite a few other areas of our field, as well, and some of those studies have really had a major

impact. The study you just mentioned, Leo, was one. This was a review of monoamine precursors as antidepressant agents. That came about, because in the late 1960's, Alec Coppen in England published an article using, essentially, retrospective data in which he claimed that L-tryptophan was as good as ECT in the treatment of depression. On the face of it, that seemed like an astounding claim to us.

LH: Certainly, if you were trying to verify it.

BC: So, we designed a study; Brian Davies, who I've already mentioned, Bob Mowbray, who was our Reader in Clinical Psychology and main statistician in Melbourne, and myself set up this study. Bob designed a very elegant sequential trial design where individual patients were matched to have, either L-tryptophan or ECT and, you know, the way these are set up, you track the winner in each pair and when the cumulative line crosses the predetermined boundary set by the statistic power, then you have your answer.

LH: Essential to sequential analysis.

BC: Right. So, in a very economical way, we were able to demonstrate a clear superiority of ECT over L-tryptophan in treatment of depression, and that was in 1970, '71, we did that. And, in the course of running the clinical trial, I had immersed myself in the clinical pharmacology of tryptophan, L-dopa, dihydroxyphenylserine, all of the potential monoamine precursors and, based on that then, was this review article which has been very highly cited ever since.

LH: That's a pretty good batting average, then, two citation classics within a few years of each other and in a completely different field. After you went to medical school, did you feel the need to go into psychiatry, say, neurology or endocrinology?

BC: Well, you know, I was tempted first to go into clinical pharmacology and that's why I went into a general medicine residency, but I kind of put this neuroendocrine idea together in the course of my medicine training and that was when I switched then to psychiatry and I've been very happy with that choice ever since.

LH: You should be. Well, now we're up to 1973. When did you come to this country, first?

BC: I completed all of my medical and psychiatric training and my PhD in clinical psychobiology in Melbourne. Then, on my thirty first birthday in 1971, with my wife and two young children we flew to the United States on what was to be a two year Research Fellowship and, now, twenty seven years later, we're still here.

LH: Did you never go back?

BC: I never went back to work, no. The deal was that the Medical Research Council in Australia had kind of obliquely hinted that they would be setting up funding for a psychiatric clinical research unit in Australia and when I came back, with the benefit of some Fellowship training in Philadelphia, that I would, then, run that unit. And, as the two years came to a close in Philadelphia, I was in contact with the Medical Research Council and, you know how funding priorities and political things change, the bottom line was, they said, well, we're not going to do that; we've decided against it. And, I said, well, I'm trying to think about what I should do. They said, come on back, we'll extend your Fellowship for one year and, then, you're on your own. And, meanwhile, by then, several people, John Davis in Chicago and Al Silverman at Michigan, were asking me to join their faculties, so with this news from Australia, I, basically, said, well, at least for now, I'm not going back there and I went in 1973 to Ann Arbor. I stayed at Ann Arbor for ten years, went there as an associate professor. That was my first real job. I had, essentially, nine years of Fellowship and residency, between graduating MD and my first real job.

LH: You must have been getting tired of living on Fellowship stipends.

BC: Well, it was great. I mean, it was really great and when I talk with young people now, I make a point of telling them this and telling them they have to pay their dues.

LH: Well, that's a long time to pay.

BC: It was two years of medicine residency, three years of psychiatry residency, two years of Fellowship, then, to complete my PhD in Melbourne and, then, two more years of Fellowship clinical research training in Philadelphia. So, that adds up to nine years, yeah.

LH: I'm surprised that at thirty-one, you did pretty well with all that training behind you. Now, how did you get to Duke? Was that when Keith Brodie was Chairman and quitting?

BC: I spent ten years at Michigan and we should come back to talk about that, because that was a great period, but, then, in 1982, Michigan was looking for a new Chair; Duke was looking for a new Chair, and I interviewed for both positions, ended up going to Duke and that was right at the time when Keith Brodie had been Chairman at Duke from '73 to '82, and, then, he was moving into being Chancellor, at that time, of Duke University.

LH: And, ultimately, President.

BC: And, ultimately, President, so I came in as the next Chair of Psychiatry at Duke in '83.

LH: Was the Mental Health Institute at Ann Arbor founded while you were there, or was that in operation?

BC: No, but I owe a great deal to the Mental Health Research Institute at the University of Michigan. It was founded around, I want to say, '62, I think in embryonic form about 1958. Jim Miller, the general systems theory person, and Ralph Gerard founded Mental Health Research Institute at Michigan and, then, Gardner Quarton from Mass General came as its director around 1968 or 1970. Al Silverman came in as Chair of Psychiatry around 1970, '71 and I came in 1973, and I owe a great deal to Al and Gardner Quarton for, basically, making it possible to function as a junior faculty investigator within the resources and infrastructure of that Mental Health Research Institute.

LH: You mean, they allowed you enough free time from teaching?

BC: They sure did and they gave me some seed money to get going, so that I could get grant support. When I look at what young people now have to cope with to get started on a research career and I say to myself, you know, you were very fortunate to be starting your career in that era and not in this era.

LH: Yeah, other than getting trained at NIH, which has sort of unlimited resources, it's very hard for somebody to come up through the ranks in most schools because they can't provide any of the free time or the seed money.

BC: Right. But, I had a unique position at Michigan. I like to joke that I was brought in there as the obligatory biological psychiatrist. It was a heavily psychoanalytical department. Al Silverman's mandate, which he succeeded in, was to change that and I was one of the frontrunners to effect that change and, within the Mental Health Research Institute, I was also a pioneer. The Mental Health Research Institute was occupied mainly by full time research scientists, either in basic laboratory studies, people like Bernie Agranoff and Norman Radin or social scientists: Anatol Rapoport was there, the game theory person, and a group of psychologists. But, they had never, in the fifteen year history of Mental Health Research Institute, had a practicing clinician as one of the Institute's research scientists, and when I was brought in and given that Institute appointment, the level of paranoia was unbelievable.

LH: You were a threat.

BC: I was a threat and my given role was to be an agent of communication between this very powerful, but very isolated pure research group and clinical problems in psychiatry. And, one of the ways that I did that was to establish, within an annex of the building, the first lithium clinic in

Ann Arbor so, suddenly, these people saw patients coming in and out and that increased their paranoia even more.

LH: On the other hand, it sounds like ideal training for Chairmanship because a good chairman has to be sort of a symphony conductor.

BC: Absolutely, yes, right. I think I learned a lot watching Al Silverman as Chairman. He went through a number of, you know, kind of expected crises of chairmanship and administration within Michigan and I paid a lot of attention to what happened, what the faculty did, how he handled it, and how the administration responded. When I finally left the Chair in 1990; there were similar political and administrative pressures there. I was really glad, actually, by the end of my time as Chairman at Duke, to be stepping out of the Chair. In the beginning, it had been a very rewarding time. I built the Duke department from, really a very low research productivity and research funding, somewhere around, I don't know, 1.8 or 2 million dollars a year. Within the space of seven years, I built it up to around 12 or 13 million dollars a year, recruited a lot of investigators, who are still there and who are, basically, the reason for Duke's strength there today out of the people that I brought in during my time as Chairman.

LH: I would say that today, Duke's Department of Psychiatry would certainly be in the top ten.

BC: I think it's, actually in terms of funding, it's in the top five and, so, I take a lot of pride in that, but the administrative warfare that I endured got to be not worth it. So, I left the Chair in 1990.

LH: You were still pretty young when you took it, though.

BC: I was. In fact, I was not even fifty by the time I left it, so I guess I've done a lot of things early in my life. I was Chairman at the age of forty two at Duke and I left it before I was age fifty. And, I went back to being a professor.

LH: That's the way we do things, isn't it?

BC: Which was wonderful.

LH: The thing about a Chairman, I think, at least an ideal Chairman, has to be a great sense of altruism, because you have to spend so much time fostering other people's careers at the expense of adding more to yours and you must have spent a lot of time to get that funding multiplied so fast.

BC: Yeah, that is part of the job description is to be a generative presence within the institution or within the department and I could point to a good many protégés that I really helped to get

established. One, in particular, that I'm very proud of is Ranga Krishnan who I brought onto the faculty as a junior faculty person in 1984 and he is now the new Chairman at Duke as of the last three months. So, it's a great pleasure to see my own protégé, now, as Chairman of the department.

LH: So, what have you been doing since you've become a professor, again?

BC: Well, I rediscovered that being a professor is the best job in the American university life. That's the first thing.

LH: You're your own boss, huh?

BC: Right. And, I made a very successful transition back to life as a funded clinical investigator. As a matter of fact, in this period of my life, since leaving the Chair in 1990-91, up until now, I've actually had more federal research funding than at any other time in my life. As of 1998, I had a mental health clinical research center grant for studying geriatric depression. I had a RO- 1, which was to fund a longitudinal study of geriatric depression, which is really kind of the back half funding of the CRC. And, then, I have my neuroendocrine RO-1, which I've had, basically, since 1976. That's still going. We're doing some interesting new work on that. So, I would say, I really was able, after being Chairman, to get back into the clinical investigator research life and I was very pleased that I could do that. The last year, I've been giving away these grants, because I'm finding a further change in my life, which will happen at the end of this month. I will go emeritus at Duke and I will be moving to California to a new foundation, Pacific Behavioral Research Foundation, of which I will be the Scientific Director, and I will function, essentially, as a full time research consultant from that base. I'm very excited about this.

LH: This is located in Carmel, California?

BC: This is located in Carmel, California.

LH: Oh, boy, what a job!

BC: Right.

LH: That sounds wonderful. Now, the Dexamethasone Suppression test has had its ups and downs. Where do you think it stands now?

BC: The DST, I think, was a very important development for psychobiology, and not just because it was true, but because it was up there for something to be tested and in the process of examining the DST and checking it out, I think the field learned a great deal about how to think around the whole topic of biological markers of disease. The DST gave us, really, a very widely used "hands on" model to think about issues of sensitivity, specificity, Bayesian probability theory. You know,

within clinical psychiatry research, those were unused concepts, even as late as 1980. People simply didn't think in those terms. People thought in terms of correlations between biological variables and psychopathologic variables, where people talked in terms of group mean differences, you know, elevated serum cortisol in depression vs. mania, for example, but the idea of using biologic measures as discriminating or diagnostic tools was really brand new. And I will take the credit for introducing our field to that whole new field of language and terminology, sensitivity, specificity, positive predictive value, negative predictive value, diagnostic efficiency. We did not invent that. We found it in clinical laboratory medicine and statistics, that's where these concepts have been first developed, but we educated the psychiatric community about that. We, also, I think, educated people about the nuances of interacting between the dependent and independent variables in psychiatric research. For example, if you have a hypothesis that abnormal DSTs occur in mood disorder, and, then, you find patients that you think are schizophrenic with abnormal DSTs, the question arises, how do you interpret that? The face value way of interpreting it is to say, the DST is no good because it's non-specific and here are these schizophrenic patients showing up. The iterative way and the most-subtle way and the more, eventually, productive way to think about it is to say, oh, OK, let's follow the schizophrenics and see what happens to them, which I had done, to some extent in some early work, but the best example of that is Bill Coryell's work from Iowa. And his report that he still stands by is that patients that were thought originally to be schizophrenic with abnormal neuroendocrine markers like the DST, followed over time with blind reevaluations at two year and five year points in time, actually, then, thought to have affective disorder. So, the significance of the original marker was that our diagnostic assessment was not as strong as we thought it was and that, of course, is what we would predict if we think we have valid underlying psychobiologic measures. Now, I am not saying that explains all abnormal DSTs in all other cases, but it's an illustration of the way in which we had to approach the diagnostic nomenclature as a provisional nomenclature testing against the biology and going back and forth in that iterative way.

LH: Some people even proposed that we abandon the psychiatric terms of all diagnostic terms, and follow markers like the DST, regardless of what the diagnosis is in the patients and see how they fall out in terms of response to different treatments.

BC: There may be some validity to that. Certainly, across all diagnostic groups, but especially within mood disorders, having an abnormal DST is, by and large, a pretty bad thing to have for

longitudinal course. The data are that it predicts suicide. There's about an eight fold excess risk of suicide. It predicts a switch from unipolar to bipolar status, which is a remarkable prediction within the population previously thought to be unipolar depressed and it predicts about an eight fold excess of health services utilization in the form of inpatient hospital days over a five year to seven year follow up period. Those are some Swedish data. So, having an abnormal DST is not a good sign.

LH: Have you ever written this up?

BC: It's been written up, sure.

LH: I think it gives a somewhat different perspective, because so many people think the DST is valueless now. It's part of history.

BC: I think the DST is practically dead now, because work that other people and, then, we have done on dexamethasone kinetics and plasma levels has signaled clearly that there's a major confound in abnormal dexamethasone metabolism in some of the cases of nonsuppression. So, to have valid DST research nowadays, you clearly must control plasma dexamethasone levels. The average clinician is not going to get dexamethasone plasma levels and there's still no consensus on what are the valid plasma concentration windows, like the old idea of an antidepressant therapeutic window. There's no consensus yet on what that should be at different times of the day for dexamethasone suppression. So, because of that, it has pretty much fallen into disuse and even I never think about using it these days. Some of the younger people around come up to me and say, I want to do a DST on this patient, and I say, well, if you want to do a DST, go ahead, but I never think of doing a DST on my patients anymore. We've kind of moved beyond that.

TB: You did all through your career clinical work, besides your research, right?

BC: Yes, I've always kept my hand in, so to speak, as a clinician, and, in fact, you know, in many ways, the motivation for the DST work was that we were dissatisfied with clinical nomenclature and wanted to go to biology as a way to break through the Gordian Knot of these interminable debates about endogenous and reactive depression, melancholic and neurotic depression, etc., etc., from the 1960's. They were going nowhere.

TB: Did you treat exclusively patients with affective disorders?

BC: Well, no. At Michigan, we had a predominance of depressed patients. I started the clinical research unit at Michigan, the clinical studies unit, we called it, and it was basically a mood disorders program. By design, we would admit patients with other diagnoses, because we wanted

them as control subjects, control patients, but I would say two-thirds of the patients we treated at Michigan were mood disorder patients. And, I became very skilled at clinical work with recurrent unipolar and bipolar patients and I like to think that I'm a very good diagnostician. And, then, the last seven years, since I left the Chair, my clinical life, aside from the grants I told you about, my clinical life has been as Clinical Director of a hundred bed inpatient geropsychiatric service at John Umstead Hospital. And, in that setting, I do clinical teaching on all the patients that come along. We have a combined mood dementia service, because so many of our patients have co-morbid, either Vascular Dementia or Alzheimer's disease with depressions.

LH: I think vascular depression and dementia is underrated. You know, neuropathologists have been telling us for years that if you look at the brains of Alzheimer's patients, diagnosed with Alzheimer's, a viable number have a mixed disorder. They have Alzheimer changes plus vascular changes.

BC: Well, you know more of geriatric psychopharmacology than anyone else in the room, Leo, and you're right.

LH: Oh, no, that's your field.

BC: One of the great innovations that I introduced at our state hospital was, to insist that our dementia protocol include a MRI brain scan. Not only that, I insisted that the radiology department at Duke send us copies of the scans when the patient returned from the procedure. So, then, on a regular basis, we would have MRI rounds on my geriatric service. We would all look at the scans and discuss them and discuss the clinical aspects of the case. In a bootstrap kind of way, I taught myself a lot about neuroradiology through doing that and you're completely right in what you say, Leo, that co-morbid small vessel disease appearing as subcortical vascular lesions is extremely common in Alzheimer's and many cases of dementia NOS turn out to be vascular in origin. And, also, many cases of late onset depression turn out to be vascular in origin. This is one of the key contributions coming out of the Mental Health Clinical Research Center at Duke. Ranga Krishnan gets most of the credit for this. It goes back to an old idea of Felix Post in the 1960's in London, this idea of vascular depression. Felix Post was right, but he didn't have MRI's to prove that he was right, so in the 1980's and '90's, we discovered it and, now, we have essentially a new clinical entity, late onset vascular depression that people are really recognizing as a valid clinical entity.

TB: You had trained one of your successors. Is there anyone else, other than Ranga that you trained?

BC: Oh, yes. We had a big group of fellows that trained with the program in Ann Arbor. Elizabeth Young, who is one of the members of the college, here, right now, Meir Steiner, who is now in charge of a clinical research program in Hamilton, Ontario, Canada; Thanasis Zis, who is now the Chairman of Psychiatry at the University of British Columbia in Vancouver; John Greden really trained in research methodology under me and he is now a member of the college here and he was my clinical lieutenant on the inpatient unit at Michigan; Michael Feinberg, who is now with Hahnemann Medical College in Philadelphia; Roger Haskett, who's now with the University of Pittsburgh in Tom Detre's and David Kupfer's department, and some others, as well. But, those are the principal fellows that I trained at Michigan and, then, at Duke, I would say, Dr. Krishnan was my primary protégé there. As a matter of fact, when he came onto the faculty at Duke, in effect, I handed over the day to day running of my neuroendocrine RO-1 to him and we published many, many neuroendocrine studies together and that gave him the support that he needed and the freedom, and funding that he needed to get himself established as an independent investigator.

LH: That's the altruistic chairman. Are you sad that you passed up a career in clinical pharmacology or do you feel that you have?

BC: No, as I look around, clinical pharmacology, as a separate discipline, hasn't gone very far and many departments of clinical pharmacology closed in medical schools around the country.

LH: It has an identity crisis.

BC: It sure has. You know, it began with correlating pharmacodynamics and pharmacokinetics and that game was played out very well with some early classes of drugs, but gradually they did lose their identity.

LH: Well, you have certainly had a tremendous career and I guess now you're entering a new phase and we'll hear more of you.

BC: One of the things that I will be working on in the next period of time is one of the other strings to my bow, so to speak, which is psychometrics. I have always been pretty particular about psychometrics. One of my early Citation Classics was a paper published in 1973 in the Archives, about rating scales, a critical review of depression rating scales, and that, again, came out of a direct clinical study. We had the opportunity to study patients across the broad spectrum of clinical settings, general practice in primary care, a day hospital and an inpatient setting. So, we looked at

Max Hamilton's depression rating scale. That was our standard instrument and right around the same time something called the Zung self-rating depression scale had just come into vogue in the late 1960's and Bill Zung, who later was a very dear friend of mine at Duke, sent us copies of the scale and we checked it out in a number of studies in Melbourne. In the study across treatment settings, Hamilton's scores went step wise upwards, as you would predict, but Zung scales were exactly the same in the primary care patients as in the really sick inpatients. So, some alarms went off in my head and I took a very close look at the Zung scale and I realized what was going on, which was that this scale did have a fatal flaw. The fatal flaw was, you'd ask people to rate the frequency of their symptoms rather than the severity of their symptoms. So, people with persistent but mild symptoms rated themselves as high as people with persistent but extreme symptoms and the scale was unable to discriminate a primary care population of depression from an inpatient group who were mostly getting ECT. So, I said to myself, there has to be a better approach to this and, then, I designed the prototype of what has now become the Carroll Depression Scale and the first field testing of that was in Melbourne. I brought it to Philadelphia with me. In Ann Arbor, we set it up as a standard clinical scale and, then, it was picked up in the CRC at Duke, so, by now, I have a vast amount of data on this scale. We published it in 1981, in a series of three consecutive articles in British Journal of Psychiatry. And, a little historical note about that; I first offered that triplet of articles to George Winokur, for his new journal at that time, the Journal of Affective Disorders, and George, who I love dearly, got back in touch with me and said, "Barney, I think it's great, but I'm not going to publish three articles. That's too much." And, I said, "Well, George, let me think about this" and I persuaded the *British Journal of Psychiatry* to accept all three. And, then, later on when they were published in the other journal, George came up to me and said, "Barney you know, I really made a mistake."

LH: He sure did.

BC: Because, that's been another citation classic, that scale, and, lately, I have put a lot of work into some new analyses of the scale performance. That was my poster session here, Monday night, as a matter of fact, and I've also designed a new version of the scale, adding in some additional statements to cover the melancholic and atypical features of depression. So, now, this scale is really the only scale that has built into it a direct crosswalk to DSM-IV for diagnostic symptoms, all the diagnostic symptoms of depression, melancholic features, atypical features and dysthymic disorder with the algorithms built in to the scoring procedure. I hope that people will pick it up and use it.

And, then, I want to develop one further personal line of work, which is to take a fresh look at this entire topic of Suicide in Late Life. Now, this comes out of my work in geriatric depression the last seven years and I will be working, mainly, over the internet, getting into national and international databases on Late Life Suicide and trying to get some new insights into the correlates of that and the basic motivations of people. The numbers are staggering. The population base rate of suicide is around twelve per hundred thousand per year. In certain western states of the US, among men in their seventies and above, that figure of twelve rises to about ninety, so it's a very, very significant increase.

LH: Well, Australia's loss was our gain. We're so glad you came here and made a great many contributions. There aren't too many people who have that many citation classics.

BC: Well, you know, I just think I've been extraordinarily fortunate. I've had very good mentors, to begin, people like Sam Gershon, David Curtis in Canberra, Brian Davies in Psychiatry, Bob Mowbray in Psychiatry in Melbourne, Skip Martin in Endocrinology. I mean, these people, you know, really helped me a great deal and gave me the direct modeling of what it is to be a mentor and I have really tried to carry that through in my relations with Fellows and junior faculty over the years. And, right now, I still have two junior faculty people that I'm mentoring, Frederick Cassidy at the hospital and Eileen Ahearn in the department and with them, we are working on yet another field that I think is going to be extremely important. It's another combination of nosology and psychometrics. We have a model of mood disorder, a model of bipolar illness. It's called the Carroll-Klein model and it's basically my extension of Donald Klein's original thoughts on the fundamental biologic dimensions of mood disorder, reward disturbance, central pain dysregulation, and psychomotor dysregulation. We have taken that to bipolar illness and looked at it with the development of some new scales. We have a new scale for manic states. We published, January of this year, a very big and I think very important factor analysis of manic symptoms in Archives, showing really for the first time what is the factor structure of manic symptoms and it's nothing like the conventional wisdom that derives from the old Beigel-Murphy studies. And, now, we have developed a specific visual analog rating instrument for the patients to tell us where they think they are on these three orthogonal dimensions of illness and we have some very exciting studies coming along with that now. And, one of the other payoffs coming out of that is a new paper that we've just sent in proposing, from an actual database, what should be a revised set of diagnostic criteria for mixed bipolar disorder.

LH: A very important group.

BC: The existing criteria for mixed bipolar are, that you must have the full depressive syndrome. Well, when you actually look at the performance of individual depressive symptoms in the context of a manic episode, that's not an effective way to do it, so now we have, from our own data, a way of refining that definition and I hope that will be coming out soon.

LH: And, again, will tie into your interest in suicide prevention.

BC: Sure.

LH: Because, that's a highly suicidal group.

BC: That is a very high risk group. So, it's been a great twenty-seven years since I came here and a great time in Australia, even before that, and I'm extremely grateful to have had, you know, as good a shot at things as I have had. I've been very lucky and I come back to what I said before, young people starting out today usually don't have it as lucky as we had it back then.

LH: Barney, in knowing the history of Australian neuropsychopharmacology from pretty early on did you ever have any occasion to meet with, perhaps, the most famous Australian psychopharmacologist, John Cade?

BC: I sure did. John Cade was one of my teachers in psychiatry.

LH: Did he teach at the medical school?

BC: He actually taught at the medical school. I knew him well. His son, David, was in my medical school class and his other son, John, was two years ahead of us in medical school. So, I knew the Cades and I knew John and, in our clinical psychiatry training, Saturday mornings, we were taught at the Royal Park Psychiatric Hospital, which is about two miles from the medical school, the inner city state hospital that John Cade was director of, and we would go there, as medical students, to the auditorium on Saturday mornings and John Cade would teach us psychopathology and his style of teaching psychopathology was very Kraepelinian. He was up on stage with two chairs, one for the patient and one for him. An assistant would be hovering around and the patients would be lined up off stage. He would signal to stage right for a patient to be brought on and he would say, in a very Edwardian authoritarian manner, "Ladies and gentlemen, I'm now going to demonstrate a patient with schizophrenia", and the patient would be brought in and sit down and John Cade would put the schizophrenic patient through his hoops, send the patient off stage left, and he would signal again to stage right and he would say, "Ladies and gentlemen, I'm now going to demonstrate a patient with mania and you should pay close attention to the differences between them." So, this

was his style of a very autocratic old fashioned, but in many ways, effective style of teaching, descriptive psychopathology.

LH: Better than learning it from a textbook.

BC: Much better than learning it from a textbook. And, then, in my psychiatry training, I had some more encounters with Dr. Cade. I learned at that time that he had what can be called a divergent manner of thinking, a divergent cognitive style with lateral thinking and not always linear thinking. He published a paper one time in the Australian Medical Journal, a paper on his theory of the etiology of schizophrenia and this is in the late '50s, early '60s, was that schizophrenia was a disease that resulted from a deficiency of stone fruit, i.e., peaches, plums, etc. The epidemiological study found that most acute schizophrenics were admitted to the receiving hospital from the most densely populated parts of the city. They had the lowest density of fruit trees.

LH: What?

BC: From deficiency of stone fruit.

LH: That's as diverse.

BC: And, his evidence for that was epidemiologic data from the State of Victoria that the highest incidence of new cases of schizophrenia was in the inner city where there were no fruit trees.

LH: Epidemiological.

BC: Now, that's very similar in style to the thinking that led to his discovery of lithium. He had this weird idea that some toxin in the urine of manic patients was responsible. He thought it was a urate salt. Needing a soluble urate salt, he got onto lithium urate. And his one good scientific question was to ask was it the urate or was it the lithium? And, the rest is history. There was later on some data showing a higher incidence of psychosis in fruit growing regions in Victoria and this was related to organo-phosphorous insecticides.

LH: When he was teaching you, he had already made that discovery.

BC: He had already made that discovery.

LH: Why did it take so long to catch on? Was it because he had a reputation of being sort of a wild thinker and nobody believed him?

BC: No, no, Australians are very pragmatic and all through the 1950's, lithium was widely used, clinically, in Australia and it was picked up in England and through Mogens Schou, it was picked

up in Scandinavia and later in Europe in the '50s and the '60s. The resistance to lithium as a clinical agent was centered mostly in the United States.

LH: And, that was due to its use as a salt substitute for congestive heart failure.

BC: Exactly, and that's all being written up in Frank Ayd's book, *The History of Psychopharmacology*. But, I now have in my possession actual photocopies, glossy photograph copies of John Cade's original case notes of the first patients that he treated with lithium and, at some time, I will donate them to the ACNP Archives. They are very, very interesting.

LH: How was he also lucky enough to pick the right dose?

BC: Well, the dose was known, because lithium had been used for treatment of epilepsy and gout, so people already knew that lithium was safe. And John's description of his IND process, shall I say, was that after he'd completed his guinea pig experiments he, then, did a Phase 1 clinical trial on himself and the determining factor, when he treated himself with lithium for two weeks, was whether his wife, the long suffering Mrs. Cade, noted any difference, and Mrs. Cade did not notice any difference, so he, then, proceeded directly to treat a group of patients who were essentially chronic residents of the hospital. Today, we would call those patients, looking at the case notes, we would call them rapid cycling bipolar. They were in and out of manic and depressive phases of bipolar illness and to everybody's astonishment, they were all discharged within about four months of starting on lithium, so they truly were stabilized. John had complete freedom to do whatever he wanted in those days. There was no drug regulatory agency.

LH: And, he was the superintendent of the hospital.

BC: He was the superintendent of the hospital. He lived on the hospital grounds. I remember visiting his house to visit with his sons, who were in medical school at the time with me and going in by the back gate from the hospital grounds to the superintendent's house, there was a basket on the gate, and the basket was replenished every day with vegetables from the patients' garden for the consumption of the superintendent and his family.

LH: This is really old style, isn't it?

BC: And, he was, you know, he was really a beloved figure in the hospital and a very, very conscientious clinician.

LH: Now, that's a new element to your Australian training.

TB: So, really, you were in medical school about ten years after his publication on lithium, in the late '50s?

BC: I entered medical school in 1958.

TB: Just ten years after.

BC: That's correct.

TB: And, some already probably picked up lithium?

BC: Oh, yes, Sam Gershon was using lithium already in Australia then and in the pharmacology department in Melbourne a number of basic studies of lithium kinetics and distribution were under way and were published during the 1950s. Sam Gershon was already publishing his work on lithium.

LH: I think Gershon came to this country around early 1960s.

BC: Correct. I was with him in '61 and, then, he came across, well, actually, he had been here, I think, in '57-'58, and, then, he came back '59-'60-'61 to Melbourne and then, in '62, he came back again to the United States.

LH: Well, Sam would talk lithium to all the skeptics over here. I remember saying, "Well, lithium, that a good thing to kill you," because I had fresh in mind the idea of the cardiac people.

BC: Right. The last time I saw John Cade was at a very important event. It was the 1979 Conference on Lithium in New York, International Conference on Use of Lithium, and John, of course, was the featured person at that meeting, along with Schou. And, I remember being at the hotel, walking across the lobby the day that the meeting was getting underway and I saw John wandering around in a dazed and confused way and I knew immediately what the problem was. He was in his late seventies then and he was terribly jet lagged. So, I went up to him and I said, "John, how are you"? And, he said, "Oh, I'm alright, Barney, leave me alone." That was his usual style. And, I said, "John, you look as though you're not very well." He said, "All I need is a little sleep." I said, "Where have you been"? He said, "I just got off the plane from Australia." I said, "John, do you mean to tell me that you didn't break the journey anywhere between Melbourne and New York"? He said, "No, I just flew straight here." So, I admonished him and he was, frankly, in a traveler's delirium at the time with severe jet lag and disorientation and, so, we got him up to his hotel room and he slept that off and, then, he was back to his happy self for the rest of the meeting. I would take credit for helping to get John settled down in time for his public appearance that time.

LH: Well, that's an interesting side light on the aspect of major importance in history of psychopharmacology. Thank you, then.

BC: Thank you.

LH: Hey, I'm glad we caught that.

BC: Yeah.

## 10. JONATHAN O. COLE

LH: It's a pleasure to have you\* here for this interview on the history of psychopharmacology because I think you are probably one of the oldest historians, not in terms of actual age, but in terms of durations. Of course, you've been part of this wonderful ACNP. Tell me, how did you get started in medicine and psychiatry and psychopharmacology?

JC: My mother had a fixation on a surgeon, in my late adolescence, early, around twelve or so. And, then, she had manic or depressive episodes often, which may have contributed. And, my best friend in boarding school, had a father who was a doctor and somehow or other I ended up in medical school during World War II. And, at Cornell, I got under the influence of Harry Gold, who was doing double-blind studies of angina.

LH: Well, those Cornell conferences on therapy were really landmarks.

JC: Yes. I interned at the Brigham and did my psychiatric residency at Cornell. So, I got exposed to Harold Wolfe's neurology conferences, which were also pretty good. And, then, I went into the army for two years. When I got out I heard the National Academy of Sciences advertised to all the psychiatrists coming out of the service. They were looking for an MD to service about four committees they had at the academy. I applied and got the job with the help of George Thorne, who was my chief at internship. The National Academy had committees on stress, psychiatry, alcoholism, and drug abuse.

LH: Good for you, you got the job.

JC: Anyway, I got in my job some exposure to research and how committees review research. The committee on psychiatry was supposed to advise the army, on psychiatric research, but the And, then I went up to NIMH to find out what they were doing about reserpine and chlorpromazine, which just arrived at the time. They had given a grant to Ralph Gerard through the National

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\* Jonathan O. Cole was born in Boston, Massachusetts in 1925. He went to Harvard College and then onto Cornell University Medical School, graduating in 1947 and continued there in psychiatric residency at Payne Whitney Clinic from 1948 to 1951. After his residency he went into the U.S. Army. In 1953, he took a position as a Professional Associate to the committee on Psychiatry at the National Academy of Sciences in Washington, D.C. where he remained until 1956. Thereafter he served as Chief, Psychopharmacology Service Center at NIMH, from 1956 to 1966, and as Chief, Psychopharmacology Research Branch, NIMH, from 1966 to 1967. After he left NIMH, he moved to the Boston State Hospital from 1967 to 1973 and finally to McLean Hospital in Boston where he was active as a psychiatrist and a clinical investigator. He died in Cambridge on May 26, 2009. He was interviewed in San Juan Puerto Rico on December 11, 1994.

Academy to organize a conference and I did the legwork for the conference and, the army didn't want any advice. So, we were a committee without a function, as far as I could tell. eventually, edited a book on the proceedings, called Psychopharmacology Problems in Evaluation. And, then, Mary Lasker and Company dumped two million dollars on NIMH to run a grant program in psychopharmacology.

LH: What year was that?

JC: 1956, the same year the conference was held. They couldn't get Joel Elkes or anybody sensible to run it, so they ended up with me, because I'd run a committee. I knew something about research grants and something about committees and was handy and willing to take the job, so I ended up at NIMH running a program at age thirty-one or something like that.

LH: It seems to me I remember a meeting we had where you and Ralph came over and visited with the VA group.

JC: VA was doing a multi-center study and about that time, Nate Kline testified to congress saying that, "by-god, the NIMH should do a multi-center study", and sooner or later I did. It was an interesting time because we were getting money given us faster than we could spend it and could, in fact, do things like multi-center studies, because we had a lot of extra cash.

LH: The Psychopharmacology Service Center had another name, initially.

JC: No, that was the original name until it got changed to the Psychopharmacology Research Branch. I set up a scientific information operation under Lorraine Bouthilet, which, actually, did quite a job until it got expanded into the mental health information system and clearinghouse.

LH: So, you started The Psychopharmacology Service Center. In what year did you?

JC: In 1956 and ran it for eleven years. We, first, did the study in schizophrenia, in acute schizophrenia, comparing placebo with three phenothiazines in nine hospitals and that went quite nicely and produced highly sensible results. And we went on and did a second study without placebo in slightly less acute patients, which came out all right. Then, we did a study in chronic patients with high dose, low dose, placebo and, I think, doctors' choice treatments. Bob Prien wrote up most of that. Then, we did a study in depression, which was a bomb. I don't think it was, even, ever noticed.

LH: I once did an antidepressant study that was a bomb.

JC: And, we and Sy Fisher did, some stuff on Librium (chlordiazepoxide), placebo and what not, in anxiety. The Early Clinical Evaluation Unit (ECDEU) program started about that time. The name was changed to NCDEU and there is still an NCDEU meeting every Spring.

LH: Was the last one about the thirty-third?

JC: Something-like that, yes.

LH: I remember the first one; seems like it wasn't that long ago.

JC: I modeled the ECDEU program, or at least in part, on a program Nathan Eddy was running for problems of drug dependence. The program had originally twelve or thirteen grantees, but it turned into a meeting where industry and investigators could get together.

LH: It has become quite a big one now.

JC: Actually, it's less selective, but sometimes more fun.

LH: If I recall correctly, all the hospitals in your nine hospital study were non-academic hospitals. Weren't they state hospitals?

JC: No, we had a mix. We had Paine Whitney, Institute of Living, DC General, and the city's psychiatric hospital in St. Louis, whose name I forget now.

LH: Malcolm Bliss.

JC: Malcolm Bliss.

LH: You had one site in Louisville, didn't you?

JC: No, we had one in Lexington, Kentucky, and Rochester, New York, a State Hospital, Manhattan State Hospital and, I think, Springfield State Hospital in Maryland.

LH: In Springbrook?

JC: No, it was in Springfield, actually. That's where Gerard Hogarty came from to the PSC. He was the social work chairman on that project, actually.

LH: So, there were seven of them that were non-academia.

JC: Yes, I think we probably did a little better, with non-academic hospitals. Actually, the two lowest dropout rates were in hospitals where the principal investigator was the superintendent. No one dropped out from placebo. It was interesting. We, actually, had a tenth hospital, Stoney Park or Stoney Lodge, or something like that, up the Hudson, but they couldn't provide the patients, so we dropped them. We just went around at an APA meeting and approached people we thought might be interested and talked with them. We didn't put it out for bid or anything. We just sort of did it. Nobody complained in those days.

LH: Well, that was a landmark study, which allows me to say, I think, that we at the VA got robbed.

JC: We had more credit than the VA did and I think that was probably wrong, but it was nice.

LH: Well, between the two of them, certainly, it erased any doubts about the effectiveness of these drugs. There still were times when people weren't really quite ready to accept them. And, it was often cited that a sizeable number of the patients, I think, something about twenty-five percent on placebo, showed improvement.

JC: Yes.

LH: And, that was cited as a tendency to spontaneous remission. Do you think it could possibly be the case that many of these acutely psychotic patients weren't truly schizophrenic?

JC: Well, some of them were, undoubtedly manics, and a few of them may have had amphetamine psychosis. I wouldn't want to guarantee that the twenty-five percent got better actually were not schizophrenics. Some of the current studies, like the Hillside first episode schizophrenia study have lousy outcomes. Anyway, we had really great placebo-drug difference. Then the placebo group did better at two year follow-up than any of the others.

LH: Of course, because they were subsequently treated with drugs.

JC: We did a two year follow-up and found that there was a lower re-hospitalization rate in the placebo patients than there was in the drug treated patients, for some unknown reason.

LH: The VA had a similar experience. Well, you certainly did a series of landmark studies there and, then, you left the Psychopharmacology Service Center in when?

JC: 1967.

LH: 1967.

JC: Jerry Levine took over and I moved up to Boston to run Boston State Hospital, which in retrospect, I helped to put out of business.

LH: I think there is room for an asylum these days.

JC: People used to come in and say this was one of the best state hospitals, in the country and I used to have acute attacks of guilt, doubt and what not.

LH: Well, that was a movement all over the country. I remember in California that Governor Reagan decided to close all the hospitals and, of course, made no provisions for after care.

JC: We did fairly well on after care. Cooperative apartment programs and things of that sort. We were doing home treatment and other such things.

LH: So, after you ran the Boston State Hospital to non-existence, you went back to academia, did you?

J C: I took a year as chairman at Temple to get out of town. I was beginning to feel that I was doing enough irregular things that one of the old civil servants, who ran the business end of the hospital, was going to get me one of those days, if I kept on doing what I was doing at the hospital. There was no insurance for any of my acts as superintendent. The state would cover me for seventy-five hundred dollars

LH: Good grief.

JC: And, there was no purchasable insurance that would cover one's acts, as superintendent, in those days. For a year, there was a law that covered us and made us unable to be sued but, then, the change in the law lost that section. Anyway, I went to Temple for a year and my, then wife, said, "Try it for a year and if you like it, we'll move." By the end of the year, I'd figured I didn't like Philadelphia and I got offered a job at McLean. And I've been, more or less, there ever since, almost twenty-five years, now.

LH: You've been there a long time.

JC: McLean's, actually, been very nice till lately. The last year a few things have gotten kind of dismal and they were firing people and doing all kinds of things.

LH: That's because of budget?

JC: Yeah, we turned ourselves inside out to provide multiple levels of care and we were all ready for National Health Service, except that nothing ever happened. Nobody wants to pay for day hospitals and halfway houses and things, unless you have a private insurance.

LH: You'd think the insurance company would grab at it.

JC: They do, to some extent, but you'd better negotiate with them. We've done some business in halfway houses. At one point, we had one hundred and twenty patients in halfway houses. At Boston State that was fine because you had a fixed number of employees and, you could get rid of patients; and you could use the people for doing other things, but in private hospitals, these days, if you get rid of patients, you, also, get rid of beds and, then, you get rid of ways of earning money. Everything begins to sink. At the end of the slide, I don't think we're going to go broke, but it's going to be a rough five years.

LH: Now, who is in charge now after Fred resigned?

JC: Steve Marin took it over and is still running it. He now has an office down at Mass General and is looking more and more disinterested in the hospital. I got offered some money for a crummy little residency program, which works with a Catholic hospital in Brighton and I've now moved over there, half-time, teaching. I'm now director of residency training at St. Elizabeth's, like two or three days a week, and give them two days a week at McLean, as a senior consultant or something or other. I can't remember what.

LH: I think McLean always comes out on near the top of the list of psychiatric hospitals. Do you have as many people doing research there as you would a few years back?

JC: More, if anything. I think our research is gradually climbing over time.

LH: Is this due to successful grant applications?

JC: Mainly, grant applications. Sherv Frazier, once he got undepressed over the plagiarism nonsense, has raised something like twelve million dollars in endowments, so, we, even, have some endowment income to draw on. We keep body and soul together.

LH: So, it's still a major research hospital?

JC: Yes. Research is still going on, reasonably well.

LH: You mentioned Ralph Gerard, earlier. You were sort of his protégé, weren't you?

JC: I guess. I assisted him in organizing the meeting we talked about. But when I got my name first on the book he didn't like that very much. Then, he got a big grant out of me, somehow over my dead body.

LH: Did he use the grant for Michigan?

JC: Yes, Ypsilanti State Hospital. He brought Sam Gershon to this country on that grant. I wasn't quite sure whether I wasn't in conflict of interest or something or other, giving him the money. They used the money to prove to everybody's great satisfaction that simple schizophrenics are different from paranoid schizophrenics, to a great extent.

LH: Gerard is a neurophysiologist. How did he get interested in clinical psychiatry?

JC: I have no idea. I thought he was sort of getting more grandiose as he got older and having a great big program, in which he solved all the problems in schizophrenia. Then, he retired and went to California, I think.

LH: And, was lost forever.

JC: He was an entertaining and a creative guy, but I never understood what he did in zoology. He was a feisty, charming man, tough generally, to work with.

LH: Now, what would you judge to be your most significant contribution in your field?

JC: I suppose, probably, in getting the antipsychotic cooperative studies rolling. And, I'm given credit for inventing a metric for the abuse liability drugs

LH: You never trained in drug abuse, did you?

JC: Jerry Levine, who was my deputy for a while, did.

LH: Jerry followed you at The Psychopharmacology Branch at the NIMH. Did you have much interaction with some of the other people in that period of time, say like, Nate Kline?

JC: With Nate, I had a long friendly relationship. He never got much in the way of grants out of the feds. People like Roy Grinker, who was chairman of the committee, would look at the grant, and say, "Ah, Dr. Queen." The review committee went on from there to tear it to remnants. I finally understood that Nate was captive of a group of rather mediocre researchers. He was collecting his own civil service set, then, at Rockland State. He kept trying to put in big grants to get money for all of them and the results were these rather peculiar presentations that would turn up on my doorstep every now and then. But, I, generally, liked him.

LH: How about Heinz Lehmann? Did you know him?

JC: Oh, I knew him. Heinz and I and several other people did a site visit on Nate's Haitian Psychiatric Institute one time.

LH: So, you went to Haiti?

JC: It might have been one of the high points in my life, the week in Haiti, under old Papa Doc with whom we did business. The new clinic went up at Pompeu Bay, which was the old snake pit hospital wing.

LH: Nate was highly regarded down there, wasn't he?

JC: Yes. You also had some contact with Mike Gorman. I actually didn't dislike Mike, but I figured it was much easier to get along with people than to enter into a fight with them.

LH: Yeah, I don't think you ever had trouble with anyone.

JC: I, actually, like most people. George Crane was a little hard to like.

LH: George, if he could find you, he's going to get you.

JC: I know. I think my worst day at the Psychopharmacology Service Center was the day the Early Clinical Drug Evaluation unit people were meeting, and George presented this proposal that he wanted to analyze their data in some form or another and they all rebelled against him.

LH: You have to give him credit though that he was one of the first voices to recognize the antidepressant effect of iproniazid.

JC: Oh, yes, he, actually, probably deserved the Lasker Award for finding MAO inhibitors as antidepressants. He had observed the effect on tubercular patients on Staten Island, about the same time Nate was there.

LH: Was George working on Staten Island?

JC: No, but he was the psychiatric consultant to the TB ward where, iproniazid was first used. Patients got very happy and he felt it was an antidepressant. And, he and Nate presented at the same first conference on iproniazid. Nate got a prize for it and George didn't. You could see why. I couldn't figure out which one of them deserved it. I think it should have been split, in all fairness.

LH: That's right. Is George still around?

JC: I don't know. He was retired in San Diego like five years ago. He has a son, who looks remarkably like him, whom I met a couple of times, of course.

LH: Who else were some of the people who were there early on? Did you know Hy Denber?

JC: Yes. Hy was a little aloof, a little further out, a Mr. Cool, somewhat peculiar or something or other.

LH: What about Tweenie Saints?

JC: He never, actually, had a valid medical license.

LH: He didn't? I think he was from South America, wasn't he?

JC: Cuba or somewhere or other.

LH: What about Henry Brill?

JC: I much admired Henry Brill and also George Ulett. And I have a long friendship with Max Fink.

LH: Well, Max has been around for a long while. I've got to interview him. George Ulett got into acupuncture.

JC: Yes, he got into acupuncture.

LH: He sort of dropped out of sight. How about Fritz Freyhan, do you know him?

JC: I knew Fritz reasonably well. I never was quite sure whether I liked him or not or whether he liked me or not, but we got along relatively well.

LH: He wasn't an overly friendly fellow.

JC: He was at St. Elizabeth's for a while when I was in Washington.

LH: I knew he was at St. Elizabeth's when Joel Elkes started, probably about 1960, wasn't it?

JC: Yes. Actually, that had something to do with my leaving Washington, as a matter of fact. I left Washington in 1967. We had been pushing about where the psychopharmacology program may go, maybe to St. Elizabeth's and eventually, I was told by various higher ups that I could not extend myself that far. And, about the same time drug abuse was getting hot and Roger Meyer had come to work with me. Then, he moved over to run the beginnings of NIDA with a couple of other people and they separated drug abuse from psychopharmacology. And at that point, Milton Greenblatt invited me to come to Boston and run Boston State. My parents were getting older in Cambridge, so I figured this was a good time to leave.

LH: And, that's where you spent most of your life.

JC: Yes, in Boston. But, if they'd let me have the research ward at St. Elizabeth's and hadn't taken away responsibility for drug abuse, I'd probably still be in Washington.

LH: Well, that was a nice operation for a while. You trained quite a few people from all over the country.

JC: We had Max Hamilton in Washington for a year. Somebody finally looked at Max's personnel form, and down about the third page, there was the question, have you ever been a member of the Communist party? And, Max marked, yes; nobody had ever noticed it before. They debated about whether to deport him instantly or ignore it and they finally decided to ignore it, which was probably the wise thing to do. The shadow of McCarthy was still loitering around. Luckily, the bureaucracy proved a lot more workable than I would have thought it might this time. I owe a vote of thanks to Sherman Ross, who took a sabbatical the year I started PSC and helped me out in research design.

LH: Wonder what ever happened to Sherman?

JC: He was at the National Academy of Sciences in charge of their psychology section, the last time I worked with him, which was like ten years ago or so. He spread himself over so many areas in psychology that he never got himself a chairmanship or a really respectable position and, then, he moved to Howard. But, he helped me get started and found me Dean Clyde to run data analysis for me and Sy Fisher, who did a lot of other things with us.

LH: Well, he gave a lot of people their start.

JC: I'm still on friendly terms with Sy. He went to the University of Texas in Galveston but spends six months in Boston.

LH: So he spends some time in Texas and some in Boston.

JC: Yeah. He had a permanent rental of a condo overlooking Boston Harbor and one of the wharfs.

LH: Well, where do you think things in the field are going?

JC: I think antipsychotic drugs are getting better and better. I think we could use a new antianxiety agent. I just got through with a study on buspirone.

LH: Do you think that buspirone type drugs are important?

JC: They ought to be and I'm not sure why they're not. I tried to talk Mead-Johnson; recently into letting us restudy buspirone and see if we couldn't figure out a way of using it once a day and making it more user-friendly for primary care docs.

LH: It's never been quite as successful commercially as they'd hoped.

JC: It might be explained by the fact that it works slower than Valium (diazepam). But, I think something ought to happen in that area. You get someone better with a benzodiazepine and when you try to withdraw the drug you get back to where you started. People on Buspar, when you withdraw it, tend to stay well and maybe even get still better.

LH: I think there's a greater interest these days than ever before in Alzheimer's. Do you see that?

JC: Well, I don't know enough about the area to tell. But, people worrying so much about it, you would think that some drug would show up.

LH: Well, maybe, that Ronald Reagan's recent revelation that he's a victim of Alzheimer's would have a certain impact on that disease as Franklin Roosevelt had on polio.

JC: It may, in fact, get the funding rolling. In a certain way, the scene in Washington is not reassuring. You can't imagine that the people in congress are going to do a lot to increase the amount of grant money, around.

LH: Well, that's rather discouraging.

JC: Yes.

LH: Well, Jonathan, you've always been one of the friendliest and most jovial people in this whole field and it was a delight to talk to you and if you have anything else to say let us know.

JC: OK, I will. Thank you. I'm, glad that I might have been be able to contribute a little bit.

LH: OK.

## 11. JAMES V. DINGELL

LH: It's Tuesday, April 15, 1997, and we're here in Washington, D.C. to continue the series of interviews on the history of psychopharmacology, sponsored by the American College of Neuropsychopharmacology. Our guest today is Dr. James V. Dingell,<sup>4</sup> who has been long associated with the National Institute of Mental Health?

JD: Actually Leo, it was Heart, Lung and Blood, Cancer and Drug Abuse Institutes.

LH: Well, anyway, he's well known in his field, no matter which institute he works with and I'm welcoming you here.

JD: Well, thank you. Very good to be with you.

LH: I always like to know a little bit about how people got to where they, eventually, wound up.

JD: It has been an interesting story, punctuated by a great deal of good fortune. I began my training in chemistry at Georgetown University in 1950 and planned to go onto Law school upon graduation in 1954. However, this was the time of the Korean War and I had taken a double major, Chemistry and Military Science, to be prepared for my almost certain military service. But the first stroke of good fortune occurred when I took a course in Biochemistry in my senior year that changed my whole outlook on a future in chemistry. I was excited by chemistry and law school ceased to be a future plan. My good fortune was to continue as Georgetown had offered me a teaching assistantship in chemistry and the army agreed to allow Second Lieutenant Dingell to go on in graduate school. However, after about a year I found that things were a bit difficult living on one hundred dollars a month and I met Leo Gaudette, a fellow graduate student, who advised me that NIH offered opportunities for graduate students to do their studies at night and thesis related research during the day. It was in June 1955 that I went to NIH and after more than a dozen interviews had the good fortune to meet Dr. Bernard B. Brodie, who took the time to describe the exciting work that was underway in his Laboratory of Chemical Pharmacology, including studies on drug metabolism, reserpine, norepinephrine and the development of the

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<sup>4</sup> James V. Dingell was born on Detroit, Michigan in 1931. He received his PhD at Georgetown University and worked at the National Institutes of Health during this time. In 1962, he went to Vanderbilt University and in 1979, he returned to the NIH for the remainder of his career. He was interviewed in Washington, DC on April 15, 1997.

spectrophotofluorimeter with Dr. Bowman. I will always remember Dr. Brodie's words. He was not looking for civil servants but graduate students because he knew they would work harder!

LH: That was a wonderful opportunity. Out of eighteen interviews, this one caught you, right?

JD: Indeed! Dr. Brodie's enthusiasm was irresistible. Just remember these were the early days of the studies with the microsomal drug metabolizing enzymes, the revolutionizing drugs chlorpromazine and reserpine, and new instruments for the measurement of drugs and biogenic amines in biological materials. I will always be grateful for the opportunity I was given to become associated with scientists like Drs. Brodie, Axelrod, La Du, Burns and of course Jim Gillette who mentored my thesis research.

LH: Dr. Brodie must have been quite a charmer.

JD: He was indeed! He could be difficult to get along with but when you faced difficulties, as I know from personal experience, Dr. Brodie was the friend to have. He was devoted to his people and was always there and always ready to go that extra mile for his people.

LH: Now, you came there in 1955.

JD: In June 1955.

LH: Was that when Axelrod was still at the NIH.

JD: Julie had left. He got his degree in 1954, and he'd left Dr. Brodie but he left us a legacy with his early studies on the microsomal drug metabolizing enzymes. LH: So, of course, Brodie had been long in the field of drug metabolism.

JD: Actually, Dr. Brodie was probably the father of modern pharmacokinetics, modern pharmacology. He came down with that wonderful group from Goldwater Memorial Hospital with the founding of the Heart Institute in 1950. His most notable accomplishment before coming to NIH was his involvement with the anti-malarial program that had been going on at the beginning of the war. As you may recall, the first thing that happened, when the war broke out, was the Japanese overran Southeast Asia and with the loss of our source of quinine, malaria became a considerable problem. But there was an interesting compound, atabrine or mepacrine which showed promise but when it was used by troops showed considerable toxicity. Brodie and his group including Julie Axelrod developed a method for measuring the levels of the drug in plasma and determined the levels of the drugs, which had to be maintained in plasma to be effective against the invading organism. With an adjustment of the dosage schedule for the drug to provide adequate

plasma levels malaria ceased to be a major problem in the South Pacific. Some actually credited Dr. Brodie with a major role in winning the war in the South Pacific.

LH: Well, by golly.

JD: He was right up there with General MacArthur.

LH: There were more troops disabled by malaria than by bullets.

JD: Yes indeed! It was a wonderful time when I joined the lab, because it was spring for the NIH, things were in bloom! We had a sympathetic Congress; its members were interested in the development of science using those monies that had been spent during the war on other things, to develop and exploit. We had men like Lister Hill and so on, who were interested to develop and exploit the opportunities that we had for science, and of course, it goes without saying; we had a truly magnificent director of NIH in Dr. Jim Shannon.

LH: Well, Shannon was the one who brought Brodie.

JD: Indeed, and Brodie brought with him Julie Axelrod, Syd Udenfriend, John Burns, Burt La Du, all of whom deserve enormous recognition for their contributions.

LH: It sounds like a Who's Who in Pharmacology.

JD: It is.

LH: Now, was Jim Gillette part of that team?

JD: Jim Gillette joined Brodie, I believe in 1954. Jim was interested in the biochemistry of drug metabolism and his main interest, at that time, was the enzymatic mechanism of drug metabolism and he did the very early and very solid and, I hope, well recognized studies with, what was then known as TPNH Oxidase and led us into the Cytochrome P450 System. I was privileged to work with and learn from Jim Gillette the good habits of careful work in the lab, the importance of analytical methodology and the ability to work long hours.

LH: Now, that was the trademark in Brodie's lab, wasn't it?

JD: That was, indeed.

LH: And, unusual hours, too, if understand it.

JD: Yes we did. The graduate students, those of us at Georgetown would work all day and our classes were at night. Those at George Washington like Ronnie Kuntzman and Julie Axelrod took time during the day to attend classes and would work later hours at night.

LH: And, of course, Brodie was known for being on an entirely different rhythm.

JD: Yes, that's the other side of the coin. Dr. Brodie ran very strange hours. He would arrive, rather late in the morning, but you could be sure that if something hot was going on in the lab, you would receive a phone call at any hour of the morning, be it two o'clock or four a.m. in the morning, to hear about those hot results. He was a remarkable gadfly! He kept the lab energized from one end to the other; it was a genuine experience working with him.

LH: Well, he used to be able to throw out very interesting new ideas and be so enthusiastic about them.

JD: He did. He had a philosophy that if an idea struck you as having promise, to test it and to collaborate across NIH if necessary. This was the beauty of NIH in those days. The opportunities for collaboration were wide open, be it Evan Horning's people at the other end of the hall in organic chemistry or with Bob Bowman and his group for instrumentation.

LH: You must have a wonderful time to work in it.

JD: I think it was a truly remarkable time at the NIH.

LH: Now, what was your first assignment in the lab?

JD: Well, my first assignment in the lab was working directly with Jim Gillette on model systems for dealkylation. This was an enzymatic mechanism that stayed with me for a number of years and paid off well for me. We were able to come up with several nonenzymatic systems which effectively removed methyl groups from compounds such as aminopyrine.

LH: Now, did you do some of the early studies with tricyclics such as imipramine?

JD: Yes, and these were both interesting and very rewarding for me. After I finished my work for my master's degree at Georgetown, Dr. Brodie suggested that a new drug, imipramine, could give me some experience in pharmacology that would be of value if I chose to go into the drug industry in the future. As I recall, imipramine was originally synthesized as a potential tranquilizer. However, it was an astute clinician in Switzerland named Kuhn who recognized its antidepressant activity. Interestingly, Kuhn found that when the drug was administered to bipolar patients it did little or nothing to calm their excited phase but dramatically reduced their depressed phase. I well remember Dr. Brodie's words that although it might just be an interesting placebo, it was worth studying. He advised: "Why don't you take a look at this compound and see what you get?" Well, the obvious first step was the development of analytical methodology for the measurement of the compound and its potential metabolites. Experience told us that most likely the drug would undergo both hydroxylation and demethylation. Since the simple method for measuring the

formaldehyde formed on demethylation was at hand, I found that copious amounts of formaldehyde were formed on incubation of imipramine with preparations of liver microsomal enzymes. This was interesting since the tertiary amine methyl groups of imipramine were on a side chain and the prevailing thinking at the time was that for dealkylation to occur they had to be located in near proximity to an aromatic ring. Now for the analytical methods.

LH: Simple to do it today, wouldn't it?

JD: Yes, but these were the days before advances in gas and liquid chromatography, it was therefore, necessary to develop a fluorometric assay method that used solvent extraction to separate imipramine from its demethylated and hydroxylated metabolites.

LH: Hadn't Geigy already done some work on the excretion of imipramine?

JD: They had done some studies, as I recall. It was in the rabbit and they had found that hydroxylation is the major route of metabolism in this species.

LH: But what about dealkylation?

JD: They didn't know a great deal about dealkylation from their studies. But the story now became very interesting because my dear friend Fridolin Sulser joined Brodie's lab and was challenged by Dr. Brodie to find a way to unmask the antidepressant action of imipramine. The drug didn't reverse any of the drug-induced syndromes that were known at the time. In fact, it potentiated the action of ethanol and barbiturates.

LH: It wasn't, in that case, much different from chlorpromazine.

JD: Exactly. So, Fridolin and his technician Jim Watts, turned to the well-known depression induced by reserpine in the hope of finding a reliable model. I am sure, Fridolin has described in detail this interesting detective story, but they found that although a single administration of imipramine to rats potentiated the reserpine induced sedation, the chronic administration of imipramine before reserpine not only prevented but dramatically reversed the expected drug-induced depression. Their model actually mimicked what was seen in patients where there was a lag period of several weeks before the antidepressant action of imipramine became apparent. Their findings actually suggested that imipramine might act through an active metabolite. This fit hand in glove with results of my studies on the metabolism of the drug in rats. These studies showed that the secondary amine metabolite desmethylimipramine not only had a longer half-life than its parent compound in rats but accumulated in tissues including brain after the administration of imipramine.

LH: Wouldn't the hydroxylated metabolites be more likely to be short lived?

JD: Indeed, being conjugated with glucuronic acid or sulfate they would be rapidly excreted in urine and rendered inactive. Our attention now turned to the likely suspects, the dealkylated metabolites; and to make the story short, a generous sample of desmethylimipramine was obtained through the courtesy of Dr. Franz Haefliger of Geigy and tested in the reserpine model. A single injection of desmethylimipramine reversed the action of either reserpine or RO4-1284. Thus, desipramine was born along with an insight into the putative mechanism of action of tricyclic antidepressants.

LH: Desipramine was shared with Lakeside, wasn't it?

JD: That's another interesting story. As I recall it, the legal staff of Geigy in Switzerland was not aware of the holiday on George Washington's birthday and they were a day late in submitting their patent and had to share it with Lakeside. I think one had the patent on use and the other on the synthesis.

LH: That was a close call, wasn't it?

JD: Yes and there was a lot of money lost because of that.

LH: I think I remember Brodie thinking that the active metabolite desipramine would work much more quickly than the delayed action seen with tricyclics.

JD: Right.

LH: But, that didn't seem to be the case.

JD: It didn't, Leo, that's right. And, that's been an interesting story.

LH: But, it only takes a few hours before the dealkylated metabolites to accumulate.

JD: Indeed, we studied the metabolism of imipramine in several species and found marked differences in the pathways and rates of metabolism of the drug and its metabolism between species. Importantly, in rats where the anti-reserpine action was seen, the half-life of desipramine was considerably longer than that of the parent compound. But in rabbits where the anti-reserpine action was not apparent, hydroxylation was the main pathway of metabolism and desipramine did not accumulate in tissues. About this time the technique of Gas-Liquid Chromatography (GLC) was in its infancy and was being developed in the laboratory of Dr. Evan Horning down the hall from Dr. Brodie's laboratory. On a hunch I thought we might be able to further confirm the identity of the metabolite isolated from brain using GLC. With the blessing of my friend and mentor Jim Gillette I took a sample of the material isolated from rat brain to Dr. Bill

Van Den Heuvel, who injected it into their early gas chromatograph. Needless to say, we were delighted to see our first sample give us a beautiful peak characteristic of desipramine. We had confirmed the accumulation of desipramine in rat brain and the validity of our extraction assay. But back to your original point, we can only say that desipramine is an active metabolite, but whether or not imipramine acts through its metabolite remains an open question. Desipramine remains on the market, to my knowledge.

LH: Well, it's kind of unique among the tricyclics, being a specific uptake inhibitor of norepinephrine. It also seemed less sedative and anticholinergic.

JD: That's right. It's a remarkable compound and has been an important tool and this goes back to the philosophy I learned from Dr. Brodie. First, you got to have good methods. You've got to have methods that are both sensitive and specific for the compound. Secondly, drugs are the most formidable tools we have for probing the function of the central nervous system. And, when you think how naive some of our experiments were, grinding up the whole brain and trying to relate chemistry to function, I'll never forget Fridolin telling me, "Jim, we have to get beyond this, because a homogenized brain doesn't think."

LH: You mentioned Syd Udenfriend. I think, in this whole series, he's been neglected. I hope we can get hold of him, but what was he doing in this laboratory?

JD: Well, Sydney was one of the early members of Dr. Brodie's lab and he was Dr. Brodie's good right hand before Erminio Costa joined the lab, but Sydney developed further and later moved and took on his own lab, around the corner. You of course know of his development and leadership at the Roche Institute. That's kind of a capsule of my days with Brodie and Jim Gillette, an era that opened opportunities for me. We had Dr. Milton Bush in the lab doing his sabbatical, as I was finishing up my imipramine program and Vanderbilt was interested in developing a program in psychopharmacology, which takes us into the next part of my career and seventeen years at Vanderbilt.

LH: Did you move there at the same time that Fridolin did or before?

JD: Our paths crossed again and that's an interesting story, as well. I went to Vanderbilt at the end of October 1962. I remember driving to Nashville while the military convoys were moving to Florida during the Cuban Missile Crisis. I had left my wife and baby son in Maryland to move down. I went with the charge from Dr. Allan Bass, who was the Chairman of the Pharmacology Department, at the time, to help start the program in psychopharmacology. Allan Bass wanted to

develop some space that was available under the Department of Mental Health of the State of Tennessee at the Central State Hospital. Dr. Bass and Dr. Frank Luton, who was the Director of the hospital at the time, took me out to Central State Hospital to show me the area that I would have to develop as a laboratory. Well, I came home that night, after seeing the sorry state of where I would have to put a lab into a hydrotherapy room with all of the odors and things that permeated the hospital at the time. I went home and was physically sick that evening. But, not being one to turn tail and run, I moved out to Central State, started a lab with one technician and, lo and behold, things were going fairly well. Those were the days when I didn't have an awful lot of collaboration going on, so I'd have to keep several problems going at one time, so when I hit an obstacle I could shift the guns and move on to something else, waiting for that inspiration to solve the problem that had stymied me there. As things went well, another old friend and old hand from Dr. Brodie's lab, Danny Efron, came down to visit us, to see what was happening and what the potential was at Vanderbilt for development of a psychopharmacology program. Danny was taken with the possibilities of developing a program at Vanderbilt and suggested that we put in a center grant application. NIMH had money in those days and the amount involved was several hundred thousand dollars, which although modest by today's terms, was quite handsome in the early 1960's. I remember I worked with Allan Bass and Milton Bush and some of the members of that small department at Vanderbilt which at the time had only five members. We put together a center grant application, we were site visited and were funded with only a person, Jim Dingell in the whole program. The problem was then to find a Director to develop the program. After approaching several of the old timers in psychopharmacology, we came up blank. I well remember talking to Danny Efron on the phone suggesting one person who really ought to try for this position. He asked, "Who's that"? I said, "Fridolin Sulser." He said, "Jim, he's very happy where he is." I suggested he ought to give Fridolin a try... and behold, about two weeks later I got a phone call from Dan Efron telling me, "Jim, we found a Director for that program." I said, "Who is it"? He said, "Fridolin." We were able to start the program with an old colleague as my boss, which couldn't have been a better relationship. It was a very fruitful time for us.

LH: That became quite a department and still is.

JD: It was indeed that one small lab that became the Tennessee Neuropsychiatric Institute and when I left at the end of 1975 I think we had thirty or forty people. Allan Bass is a man of great wisdom and great foresight. I think Allan's philosophy was that, one must get competent young

people, give them the opportunities and support, which he did with me, with Fridolin and another outstanding scientist, who is now Chief of Medicine, Dr. John Oates.

LH: Now, what were you doing down there, once you got your laboratory set in these undistinguished quarters?

JD: Well, I worked on problems, such as the effects of calcium deficiency, on drug metabolism, effects of carbon tetrachloride poisoning on the microsomal enzymes. With Fridolin, we worked on the amphetamines. Fridolin's early days at Vanderbilt also offered the opportunity for us to renew our interest in the tricyclics. Other investigators had observed the ability of desipramine to potentiate the stimulatory action of amphetamine and had suggested that this action could provide a model for unmasking the antidepressant action of new drugs. We knew that because of its long half-life in rats desipramine accumulated in tissues and was localized in hepatic microsomes. It therefore seemed reasonable that the ability to potentiate amphetamine was a biochemical rather than a pharmacological interaction. That is, an inhibition of the metabolism of amphetamine by desipramine rather than an interaction at the receptor level. By using the original extraction procedure for amphetamine we were able to measure the levels of the radiolabeled drug in the brains of rats after administration of desipramine. What we found was a striking prolongation of the half-life of amphetamine in rats after pretreatment with desipramine. We later found that the ability to prolong and enhance the psychomotor stimulation of amphetamine by inhibition of its metabolism is not just a characteristic of antidepressants but was even seen with chlorpromazine.

LH: How did that work and which pathway was involved?

JD: Well, in the rat, it would have been the major pathway of para-hydroxylation rather than deamination which predominates in rabbits. This brings up an interesting side light to the matter. The first pathway of drug metabolism found in hepatic microsomes was deamination. This was found by Julie Axelrod using rabbit liver preparations to metabolize amphetamine. Since this was the research for his doctoral dissertation, he was fortunate that he had not chosen rat liver preparations to investigate the metabolism of amphetamine.

LH: We ordinarily think of drug interactions of this sort as being bad, but could some be of clinical value?

JD: Well, you certainly recall the history of SKF 525A. It was first thought that it would have value as what was called a prolonging agent, but later was found to be only an inhibitor of the

microsomal drug metabolizing enzymes. I think that a poor ratio of benefit to risk would doom the therapeutic use of drug metabolism inhibitors.

LH: You left in the mid-seventies.

JD: Yes, after finishing a series of studies on the metabolism and excretion of delta-9-tetrahydrocannabinol, I took the opportunity to return to the Washington area to work with Dick Adamson in the Laboratory of Chemical Pharmacology of the National Cancer Institute.

LH: So, you left Vanderbilt before Fridolin got interested in the effects of drugs on the down regulation of the beta adrenoceptor coupled adenylate cyclase.

JD: Right. That was his next area of interest. I didn't share those studies with him but was pleased to see them done.

LH: It was a good unifying hypothesis; unfortunately it left unanswered questions.

JD: Yes, you know, Leo, that reminds me of another "Brodieism." Discussing the importance of a hypothesis, Dr. Brodie made the remark that "you always have to start with a hypothesis that is so simple that it almost has to be wrong to begin with because any simple wrong hypothesis will, ultimately, evolve into a more accurate complex hypothesis."

LH: That's a good answer.

JD: And, words of real wisdom.

LH: So much of what you see written today is, what I call, a straw man hypothesis.

Now, I suppose you, like almost every other person in science that I've ever talked to, has no regrets at all about your career?

JD: None. My career was determined by good fortune, good fortune in meeting men like Dr. Brodie, Burt La Du, Jim Gillette, Fridolin Sulser, Dan Efron, Danny Freedman, Morey Lipton and so many others, men of enormous ability, willingness to cooperate, be helpful and so on.

LH: And, in a bargain, these were very nice people.

JD: They were, they were, absolutely, yes. Dr. Brodie was not always the easiest person to get along with, but, as I said, when you needed a friend and you had a problem, he was there. I would probably, had it not been for Dr. Brodie, ended my career in science in 1960, because the United States Army had decided that they were tired of granting me delays and called to active duty. Dr. Brodie decided that he would make every effort to get me transferred into the Public Health Service and keep me with him to finish up the imipramine problem, so, again, a man of great friendship.

LH: He gave you a practical opportunity.

JD: Indeed, indeed.

LH: Well, you mentioned Erminio Costa, in passing, and, of course, Brodie had a couple of people from Sardinia. Didn't he have Luigi Gessa?

JD: That's right, that's right and also from Italy, Rudolfo Paoletti.

LH: I remember, I guess it was in 1970, when the Nobel Prize was announced, that one of my friends bustling in and he said, "Guess who won the Nobel Prize." And, I said, "Brodie, Von Euler." He said, "You're wrong." This was won by Julie Axelrod. I said, "Brodie's heart must be broken."

JD: I'm sure it was. I think it was a very unfortunate occurrence. Dr. Brodie did so much in opening so many fields. The only thing that I think might have weighed in that balance was that Julie chose to stay with an area and kept moving on in depth. Dr. Brodie would open up an area and move on.

LH: Yeah, he was a pioneer.

JD: That was a time, Leo, when I was at Vanderbilt and being at Vanderbilt, everybody assumed that Earl Sutherland was going to get the Nobel Prize. And, I remember, lying in bed one morning and flipped the TV on to clear my head and wake up, and the news came on about the new Nobel Laureates and I was astounded it was Julie Axelrod and I'll never forget. I jumped out of bed just laughing my head off, because everything had been prepared for Earl. He had gotten the Lasker Award and it was almost assumed it would be automatic and here was this wonderful, gentleman, Julie Axelrod who was chosen. And I remember firing off a telegram right away, congratulating him.

LH: And, I remember the ACNP was meeting at that time, and Danny Freedman was president and he composed a telegram from the organization, congratulating Julie and I never saw an audience more sympathetic. You know, everybody was jubilant.

JD: Well, and you know Julie's history. Julie didn't get his PhD until he was about forty-five years of age and his plans to get into medical school in New York were thwarted because of quotas and so on, and, bless his heart, he worked as a technician.

LH: He had a tough life.

JD: And, the gods reward good people.

LH: Well, you had to work for your PhD, too.

JD: Yes, but I didn't have to face the hardships that Julie did and Julie was always a very kind and thoughtful and giving person and, again, one of those friends that you're really proud to have.

LH: One person that comes in mind, who won a Nobel Prize, who, as far as I know, didn't have a doctoral degree, was Gertrude Elion.

JD: Yes, wasn't that nice! With George Hitchings. Yes, I think that was another one of the good turns of science that will restore your faith in it, and that people, other than those that speak directly to God, can get the Nobel Prize.

LH: Well, a few years running, I had an opportunity to make nominations and the only winner I had, of course, I ignored the obvious winners like monoclonal antibodies, but I was trying to promote pharmacology and I put up Hitchings and Black because of all these methods for developing new treatments, but I had forgotten that Elion was such an essential part of the Hitchings team.

JD: Oh yes, but you know, and you recall that those people that were indispensable to one of us getting the Nobel Prize never get the recognition that they deserve. Well, we can think of names. I don't know whether we should mention them right now but in the case of Dr. Brodie, I think it was unfortunate. It would have been nice, looking back from the point of view of drug metabolism, if Brodie could have shared the Nobel Prize, perhaps, with Professor Williams from St. Mary's in London. But, so be it, those are days that are gone, Brodie had his share of recognition. If you recall, he received the Gold Medal for Science and I believe that was a reward for his work with the anti-malaria program and pharmacology development.

LH: Well, you were lucky, indeed, to be part of that wonderful team.

JD: Fortunate, indeed.

LH: I imagine that between the two of them, Brodie and Axelrod were responsible for more influence in psychopharmacology than any two people I can think of.

JD: And, the development of people. I, very humbly, admit that I was among the least of Brodie's graduate students.

LH: Well, I want to thank you for coming. It seems like we've been trying to get together for a long time.

JD: It's amazing how the time goes by.

LH: We talked about Brodie more than you, but that's good.

JD: Well, I think that's important. It's important that his enormous contributions be recognized.

My later years have been spent in administration in the National Heart, Lung and Blood Institute and the National Institute of Drug Abuse. Looking back it is hard to believe those many years have flown by so fast.

LH: Well, we are all getting older and that is why we are doing these interviews to catch us while we are still here.

JD: As you say, it's unfortunate that we don't have some of those old timers, who gave us so much and how wonderful it would be if we could have had Danny Freedman sitting here, Morey Lipton and Brodie, but you're fortunate, you've had Axelrod.

LH: I remember, after Danny became editor of the Archives in Psychiatry, I was talking to him once, and I said, "Danny, now that you're the editor, every time I send a manuscript in, forget it's me. Judge the manuscript on its merits; otherwise, my Presbyterian conscience will suffer." He said, "Don't worry; my Jewish conscience would suffer equally."

JD: Danny and Morey, to me, they were the epitome of what one should be in psychiatry — wonderful people.

LH: Well, that's the other pleasant part of our career, having known such lovely, smart, inspiring people. I can think of several dozen people, who could probably have interviewed you more intelligently.

JD: Thank you, my friend, thank you.

## 12. IRWIN FEINBERG

LH: Today is Friday, December 12, 1997, and we're in Kamuela, Hawaii, for the thirty-sixth annual meeting of the American College of Neuropsychopharmacology. As part of our historical series on people who've been in the field of psychopharmacology a long time, we're going to interview, today, one of the long time sleep researchers, Irwin Feinberg.\* Welcome, Irwin.

IF: Well, thank you very much, Leo, and it's a great pleasure to be interviewed by you, particularly, because I've admired your work for so many years.

LH: Oh, my, my!

IF: And, appreciated your friendship and support over the years. It's a great pleasure.

LH: Well, hearing that from somebody, who knows something about a field that I have very little experience with, I really like that. Tell me, when you started in this field, when was that?

IF: Well, I started off in sleep research quite accidentally. I was at the NIH and I was working in Seymour Kety's laboratory.

LH: When was this?

IF: I went to the NIH in 1957, having my draft number come up at that time and having the option of going, instead, into the Commission Corps of the Public Health Service at the NIH. And, so, I went to work in Ed Evarts' Section of Neurophysiology in Seymour Kety's Laboratory of Clinical Science in 1957. Ed Evarts became one of my closest friends and had the largest influence on my scientific development. Ed was a psychiatrist, who thought he would learn some neurophysiology because it would be useful for research in psychiatry. But, then, by the time I got there, he made many basic advances in neurophysiology. Although I had been hired to help him with his psychiatric work Ed said, "Well, I'm not interested in psychiatry anymore. I'm going to be a neurophysiologist full time, so go and find something to make your time useful and worthwhile.

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\*Irwin Feinberg was born in Brooklyn, New York in 1928. He received his MD from New York University. He trained in Psychiatry at the Boston Psychopathic Hospital, National Institute of Mental Health, Institut des Sciences de l'Education (with Prof Jean Piaget) in Geneva, Switzerland, and St. Elizabeth's Hospital, Washington, DC. At the time of the interview, he was Professor Emeritus, Department of Psychiatry and Behavioral Sciences in the UC Davis Sleep Research Laboratory. He was interviewed in Kamuela, Hawaii on December 12, 1997.

LH: Prior to that, you had completed medical school.

IF: Yes, I completed medical school at NYU in 1955. I interned at Boston City Hospital and I did my first year of residency at what was then Boston Psychopathic Hospital, later to become the Massachusetts Mental Health Center. Harry Solomon was the director of Boston Psychopathic Hospital when I was there. I think he retired at the end of my first year or shortly thereafter. But, anyway, I had only one year of residency training in Boston, because I had to join the Commission Corps of the PHS and, so, I.....

LH: You received your MD from what school?

IF: NYU, New York University Medical School.

LH: And, you then went into psychiatry right after internship?

IF: Right after my internship. I did my first year of residency at Boston Psychopathic Hospital and from there I went into the National Institute of Mental Health with Ed Evarts and Seymour Kety. Both of them had great influence on me scientifically, especially Ed Evarts because I worked closely with him and we became close personal friends. I had tremendous admiration for him as well as for Seymour Kety and Louis Sokoloff.

LH: Evarts did a lot of work on the motor system, didn't he?

IF: Yes, he ended up focusing on the motor system. But he also did pioneering work on sleep. He did some of the best early work on differences in neuronal activity in different parts of the brain in REM, NREM and waking, measuring activity in the same neurons in all three states. Part of that work involved pioneering microelectrode techniques for single unit recordings in cats. Later, Ed moved to monkeys when he started to do his research on motor system. So, there I was, kicking around in Ed Evarts' lab. I was interested in hallucinations, which is an interest I still have, and was studying hallucinations in schizophrenics at St. Elizabeth's hospital when Bill Dement came through the NIH and gave a talk on REM sleep. Having by this time some knowledge of the history of thinking about hallucinations, it occurred to me that I could use REM sleep to investigate Aristotle's hypothesis that hallucinations come about from a disturbance of the mechanism that normally produces hallucinations during sleep, i.e. dreaming.

LH: Hallucinations as a kind of REM sleep awake.

IF: Right. So, I embarked on what I thought would be, at most, a six month study to compare REM sleep in hallucinating and non-hallucinating schizophrenic patients. The reason I had only six months to collect the data was that I was scheduled to spend a year with Piaget in Geneva. I

was in fact able to collect the data in six months in collaboration with Fred Snyder and Richard Koresko. So after collecting the data, I went off to spend my year in Geneva. When I returned, I found that analyzing these sleep EEG records was not as simple or straightforward as the literature had led one to expect. And so the study that I thought would only be a six-month digression took two years before it was finished. It turned out that there was really no important difference in REM sleep between hallucinating and non-hallucinating schizophrenics. However, there was a substantial difference in the amount of Stage 4 Sleep or deep sleep between the schizophrenics and my normal controls. Fifty percent of the schizophrenic group had no scoreable Stage 4. The other fifty percent had perfectly normal Stage 4 Sleep. Therefore, as a group, the schizophrenics averaged half the stage 4 levels found in age-matched controls. What this means is still a very interesting research problem. This is especially so because to this day the stage 4 abnormality remains the most consistent brain abnormality demonstrated in schizophrenia, even though it is present in only half of the patients. This stage 4 result has since been replicated several times.

LH: Is there any clinical difference between the two groups?

IF: A good question that I can't answer. By the time the data were analyzed and I recognized this finding I no longer had access to the patients. I had completed the data analysis many years later and no longer had access to the patients. They had gone their various ways. But medication was not a factor. These were essentially un-medicated schizophrenics and that was an unusual aspect of the original study that one cannot now duplicate.

LH: Not today.

IF: Not at this time. So I had by this time put several years of effort into sleep research. After much effort I now had, essentially, a negative result with respect to REM sleep in schizophrenia. By this time I was hooked on sleep because I was convinced it must do something important for the brain. Because we often dream about what happened to us during the day I reasoned that REM sleep might be related to memory processing. To study that question, I selected a group of elderly patients with dementia of varying severity and varying etiologies. I compared their sleep to that of a group of elderly, age-matched normal subjects. In both groups, there was a correlation between the amount of REM sleep per night and independent measures of cognitive function. A positive finding at last! However, this study of elderly normal controls led me to assemble data on sleep and aging. I had elderly normal subjects as controls for the demented patients and I had data on normal young adults who were controls for the young schizophrenics. To use these normal data

to construct age curves for EEG sleep measures over a broad range I recorded sleep in a small group of children. In graphing these data, I discovered what had already been mentioned in the literature, although less well documented. There are many changes in sleep EEG with ageing. The finding that intrigued me the most was that there is a huge amount of deep, stage 4, sleep in children that decreases very steeply across adolescence. Stage 4 then continues to decline, at a very much slower rate, to a plateau in late middle age. I'm now going to skip ahead a decade to the interpretation of the biological significance of the huge decline in deep sleep across adolescence. This interpretation turned out to have some influence on psychiatric research. It became evident to me that the change in sleep across adolescence was one component of a major brain reorganization that is taking place over adolescence. During adolescence there is a great loss of brain plasticity. This is shown, for example, by diminished ability to recover from brain lesions, particularly notable in lesions that cause aphasia. There is also a substantial decline in cerebral metabolic rate. In adolescence there are rapid advances in cognitive function that traditionally had been assumed were entirely due to education. But I thought that these biological changes in the brain might contribute to it as well. I summarized this evidence in 1982-'83 and proposed that the brain changes across adolescence might all be explained by a genetically programmed elimination of synapses; a few years before, in 1979, Peter Huttenlocher had demonstrated a reduction in synaptic density in human frontal cortex over adolescence.

LH: That would be a second pruning.

IF: Indeed, that would be at least the second, and one coming quite late, at an age when brain development, except for myelination, was thought to be complete. In this paper, I also proposed that a defect in this late pruning process might cause some kind of mental illness, notably, schizophrenia, which often has its' onset at the end of adolescence. This hypothesis was the first modern neurodevelopmental model of schizophrenia and I was led to it by attempt to understand the enormous change in deep sleep EEG across adolescence. This change remains one of the most fascinating unsolved problems in human developmental neurobiology. One can also state the issue more generally: sleep is very tightly linked to age over the human life span. Inherent in that tight link must be clues to both the function of sleep and the nature of brain aging. And, so, that was one direction that my research wandered into.

LH: This was all done in Evarts' laboratory?

IF: No. I have been excessively peripatetic, perhaps, the most peripatetic of the sleep researchers. After seven years at the NIH, I went to Downstate Medical Center and worked there in Brooklyn for five years, very near where I grew up. I then left to go to San Francisco as Chief of Psychiatry at the VA Hospital and Professor in the Department of Psychiatry at UCSF. And, so, this last set of studies that I described was done in San Francisco. Now, you mentioned, at the beginning, that I have been, somewhat, contrarian in the sleep field. That is absolutely correct. I've taken my own direction in several respects. One example, in which my deviant thinking was, I hope, valuable and influenced the field, was my emphasis on the importance of deep or Stage 3, 4 Sleep. This was at a time when sleep research was all agog about REM which had more recently been discovered. Although non-REM sleep occupies 75% of total sleep, as compared to 25% for REM sleep, REM was considered biologically more important. This position was maintained even though, the priority activity of the brain, in falling asleep, is deep sleep. Most of the night's deep sleep occurs in the first couple of hours after falling asleep. In contrast, the highest proportion of REM is at the end of the sleep period. Among other arguments, I pointed out that - if REM sleep were the most important component of sleep- it would come first, because in nature the organism doesn't know how long it will be possible to remain safely asleep.

LH: Yes, but I think the reason that REM caught on, especially at that particular time, was, of course, that Freud made such a big deal about dreams that here we could now find out when people were dreaming. Don't you think that was it?

IF: That was a very major influence. Yet another aspect is the physiology of REM which is so dramatic. In REM the organism is asleep but neuronal activity in several parts of the brain, such as visual cortex and lateral geniculate, is explosively active. The same is true for various brain stem structures that mediate arousal. So not only was REM related to dreaming (almost exclusively it was thought at the time) but there was also a striking paradox: intense neuronal activity, including in the motor system, in a sleeping subject. In the 1960s, Jouvet called REM "paradoxical" sleep, a term that is still used, though mainly in animal sleep research. Again, the paradox is intense activity in many brain structures when the organism is asleep and behaviorally quiescent. Prior to the discovery of REM, of course, it was thought that the brain simply shuts down during sleep.

LH: At the same time that the body was paralyzed.

IF: Right. The body needs to be paralyzed during REM. If it were not paralyzed the intense neuronal firing in the motor cortex would cause movements that produce waking. These dramatic features, along with its relatively recent discovery and, as you mentioned, its apparent relation to dreaming (now known to be much weaker than originally thought) caused the rapidly developing field of modern sleep research to focus on REM and neglect non-REM sleep. However, there were several considerations that led me, in 1974, to propose that if there is a component of sleep that is homeostatic for the brain it's much more likely to be slow wave sleep or deep sleep than REM sleep. The most important of these considerations is that slow wave sleep rather than REM sleep is correlated with how long you've been awake. If you take a nap early in the morning, you have essentially no deep (slow wave) sleep, but if you take naps later and later in the day, you have more and more, slow wave sleep. If you are deprived of sleep, the amount of slow wave sleep increases still further. This was, primarily, the work of Wilse Webb and Ralph Berger, who demonstrated the relationship of slow wave sleep to prior waking duration. In contrast, REM is not related to how long you've been awake. The amount of REM increases the longer you've been asleep. And, if you extend sleep beyond habitual levels in college students as we did by keeping them in bed for 12 hours, they double their normal amount of REM sleep. But this doubling has no effect on the amount of REM they have on the following night, or on its timing. In striking contrast, the amount of slow wave sleep that occurs in a late nap gets subtracted from slow wave sleep on the following night. These and other considerations led me in 1974 to propose the homeostatic model of delta sleep. An essentially identical model was published eight years later (without attribution) by Alexander Borbely in Zurich. Borbely added a circadian factor that controls sleep timing and he also quantified the model, which got it more attention. These two proposals regarding delta as the homeostatic component sleep remain the operating models for basic sleep research and theory. Another area, in which I was a contrarian, was on the issue of REM latency and depression. I was contrarian in two respects: with respect to diagnostic significance and to biological meaning. First, I pointed out very early that short REM latency was not specific to depression but also occurred in schizophrenia.

LH: Narcolepsy.

IF: Right, it occurs in narcolepsy and in many conditions of abnormal or disturbed sleep. To this day I am puzzled by the fact that expensive research projects are being supported under the assumption that early REM onset is a specific marker of depression. My other contrarian position

with respect to REM latency is one the field now pretty well accepts. It concerns the biological (as opposed to pathophysiological) significance of REM latency. After all, what is measured in REM latency? It is the amount of non-REM sleep that occurs prior to the first REM period. If REM latency is abnormally short, does that signify an abnormality of NREM or REM sleep? The assumption had been made, in the context of the overemphasis on REM that we discussed earlier, that a short REM latency must indicate increased REM "pressure."

LH: Could be the other way around?

IF: Exactly! It could be the other way around. In fact, we, now have very nice experimental evidence that it is the other way around in normal subjects. That evidence, which I alluded to earlier, is that if subjects take a late nap, the slow wave sleep in the nap is subtracted from the slow wave sleep that night. Where does the subtraction take place? In the first non-REM period, i.e., shortening REM latency.

LH: By virtue of the fact that you have less non-REM preceding it.

IF: Precisely! Moreover, you can show this relationship is nicely quantitative.

LH: That's a very important observation, I think.

IF: Of course I agree. Nevertheless, it is still usually ignored by the sleep researchers who currently investigate clinical populations. However, it has not been ignored by some very good sleep scientists, like Kate Benson at Stanford or Mario Guazzelli in Pisa (Italy). Nevertheless, at present, these points are ignored by the majority of American sleep researchers.

LH: Well, you know, unfortunately, a body of knowledge gets accepted and becomes dogmatic before anybody really took tries to test it out. Of course, one of the mysteries about slow wave sleep is that benzodiazepines, in particular, seem to wipe it out. And, if it has a restorative function, why aren't people who take benzodiazepine sort of impaired? And, I think you found an answer to that one, too, didn't you?

IF: Yes. This paradox is extremely important, particularly for clinical psychopharmacology. It is also relevant to some of the recent advances that were discussed this morning in the symposium at the panel on metabotropic glutamate receptors, and I'll return to this point later. As you noted, benzodiazepines and other GABAergic modulators like barbiturates, instead of increasing the amplitude of delta waves in deep sleep, depress these wave amplitudes and decrease or even eliminate visually scored stage 4. Nevertheless, these drugs indisputably promote sleep. They make normal individuals sleepy and they help insomniacs fall asleep. However, they actually

increase total sleep time only slightly, as measured by the polygraph. They increase subjective total sleep time much more strongly: the patient usually feels that he has slept much more soundly and awakens more refreshed. So, it remains a puzzle that garden-variety insomniacs, for whom most sleeping pills are prescribed, don't have much of a reduction in total sleep time when studied in the laboratory before treatment. And yet they report "I still feel I was awake all night long. I remember everything I thought about during the night." Well, one aspect of sleep is that there is much more mental activity going on during sleep than is remembered. This is because memory systems normally shut down during sleep. That's why we don't tend to remember much of the dreaming that we have during the night; memory consolidation does not take place unless one awakens shortly after the dream. In 1982, I proposed that the inconsistency of the subjective complaints of insomniacs with the EEG evidence that they get almost a normal amount of sleep could be explained by a failure of insomniacs' memory systems to shut down normally during sleep. Insomniacs therefore remember much of the mental activity that goes on during sleep that normally is not remembered or consolidated. They interpret this as having been awake and this memory is correlated with the subjective experience of un-refreshing sleep. However, the failure of memory systems to shut down is not discernable in the polygraph, which makes it a poor tool to study insomnia. With this background, one can understand why benzodiazepines and other GABAergic brain inhibitors improve subjective sleep of insomniacs. These drugs depress arousal and cause a relative amnesia. They suppress the ability to remember by reducing brain arousal level by increasing cortical inhibition. This improves subjective sleep in insomniacs.

LH: How consistent are the amnestic effects of those benzodiazepines!

IF: Extremely consistent, and one can show this effect by using benzodiazepines to suppress memory in animal learning studies as well. So what had been considered a side effect of benzodiazepines, namely, their amnestic effect, appears to produce their therapeutic effect on insomniacs' sleep.

LH: Now, when you get back to the apparent loss of slow wave sleep, I thought, you proposed awhile back that you don't lose it; it just shows itself in a different fashion.

IF: Yes, I did show that there's no net reduction in the number of delta waves. If you measure delta waves after administration of benzodiazepines with computer analysis, as we showed in a Science paper in the late seventies, you may find no scoreable Stage 4. The stage 4 classification requires that delta waves of criterion amplitude be concentrated in short epochs of sleep.

LH: Yeah, it's an artificial categorization.

IF: Totally, artificial. And, if one measures each delta wave by computer after administration of GABAergic hypnotics, one finds that the number of delta waves is not reduced. They are simply more spread out so they don't meet the stage 4 criterion.

LH: Don't cluster up so they don't look like Stage 3 or 4.

IF: Right. However, there is a net reduction of delta wave amplitude due to the fact that these drugs suppress brain metabolism. As you know, if you give a large enough dose, you can induce coma with a profound reduction of brain metabolism and EEG amplitude. With larger and larger doses, the EEG gets almost flat. I'm glad you brought up the question of these effects of hypnotics because this brings us to the most recent work that I've been doing, which has been with glutamate antagonists and sleep. If you think about it, all of our GABAergic hypnotics work by increasing neuronal inhibition. What about the alternative way?

LH: Of decreasing excitation.

IF: Yes, logically at least, decreasing neural excitation should have some of the same pharmacological effects as increasing neural inhibition. One of the first public discussions that I've heard of this approach was at this morning's panel on metabotropic glutamate receptors. Our own lab has been doing experiments in this area for six years. It would be laborious to go into the details of all of these studies. In brief, antagonizing glutamate (excitatory) neurotransmission has produced huge increases in deep sleep that last for a relatively short periods of time (three to eight hours). Afterward, the EEG returns to normal. This is not the case with GABAergic hypnotics. The EEG remains abnormal for days to weeks after these drugs. Even a single nighttime dose leaves the sleep EEG abnormal for a couple of days. We believe that reducing brain excitation with glutamate inhibitors is a promising area that may have clinical potential.

LH: Glutamate inhibitors as hypnotics.

IF: Right. As I just mentioned, this possibility was discussed this morning by an investigator from Eli Lilly at the panel on metabotropic glutamate receptors. So this is a very timely issue. That's pretty much the way my career has gone. A lot of it was accidental. For example, I always maintained my early interest in hallucinations and schizophrenia and it was because I retained that interest that I put together the pruning hypothesis of schizophrenia in the early eighties. It was because of my work with Ed Evarts that I formulated a model in which auditory hallucinations are caused by a defect of corollary discharge control mechanisms in the motor systems of thought.

Briefly, we know that the motor systems' commands are monitored as they're emitted by the brain and this monitoring informs sensory systems and allows feedback to occur even before the action takes place, before the muscles have responded. This is called feed-forward or internal feedback or corollary discharge. Hughlings Jackson emphasized that thinking is simply the most complex of our motor acts. If so, it might maintain the feed forward or corollary discharge mechanisms present at simpler motor levels. These mechanisms might inform the brain that we have initiated a thought. We have always assumed that we know our thoughts are our own because we "will" them. In fact, most of our thoughts are not voluntarily "willed" by us. Usually, our thoughts just pop into our minds. Some of those spontaneous thoughts can be quite bizarre but we still recognize that we have produced them. It may be this internal thought-monitoring mechanism that is impaired in schizophrenia. The schizophrenic, after all, has thoughts (voices) or neural activity which he does not recognize are produced by his own brain.

LH: Leading to a totally bizarre experience or reality?

IF: Yes, when the schizophrenic doesn't recognize that these are his thoughts he interprets them as coming from the environment, which may not be unreasonable given the way his brain is functioning. So the schizophrenic interprets voices or thoughts as coming from the TV or from radios implanted in his head. It seems to me that this must indicate impairment in the brain's self-monitoring mechanisms, i.e., in the corollary discharge mechanisms I hypothesize exist in the control systems of thought. Evolution is conservative. We might therefore expect that efficient control mechanisms known to be present in simpler circuits will be retained as more complex circuits evolve. These ideas were stimulated by the work of Evarts on motor control systems. In any event, I believe that the question of how we know our thoughts to be our own is at least philosophically interesting. I am also convinced that it bears on psychopathology.

LH: How long has it been since the Kales and Rechtschaffen classification of stages of sleep was proposed. That was in 1962 or some distant date, wasn't it?

IF: It was. Your memory is very good. It was 1962.

LH: Now, is that still operating?

IF: It is still used exclusively by people who don't do computer analysis. But I think there is very little excuse not to do computer analysis which is now quite inexpensive.

LH: That's why I raised the question. Is it time to rethink that classification?

IF: Yes. Visual stage scoring is a grossly inadequate kind of arbitrary classification. I don't blame Rechtschaffen or Kales for this. What they were doing was trying to standardize widely different visual scoring procedures that different investigators were using.

LH: So, all would speak the same language, at least.

IF: Exactly, and that was a very valuable contribution at the time. But today its arbitrary and unsatisfactory nature is grossly obvious. As we discussed, for an epoch to be scored visually as stage 4 it must be made up of 50% of delta waves with amplitudes of fifty or seventy-five microvolts peak to peak. If the 50% criterion for stage 4 is reached, the entire epoch is classified as stage 4, whether it consists of 100% or 50% of these delta waves. Much information is being lost. Even more information can be lost when studying age effects with visual scoring. In a child, delta waves might average 500 microvolts in amplitude, rather than 50 or 75 microvolts. But a stage epoch made up of 50% 500 microvolt delta waves gets the same visual score as one with 50% of 75 microvolt waves. Visual scoring simply does not recognize that huge biological difference. Another problem with such scoring is poor reliability. No matter how hard one tries to train individuals to perform reliable visual scoring, reliability remains limited. Even my very best visual scorer could not reproduce the same scores on the same epochs when I gave her blinded records that she had scored 6 months earlier. These limitations of visual scoring led me (and others) to embark on direct computer measurement in the 1970s and this has been an extremely productive approach that has now been adopted by many investigators. The computer is of course almost perfectly reliable.

LH: So, inter-rater reliability with visual stage scoring is very limited...

IF: Yes. Because it was unsatisfactory in the very best of hands I pursued the development of computer analysis. We now use a fine program written by J.D. March of Delta Software. He's selling it commercially. It is the only program that simultaneously performs both period- amplitude (time domain) analysis and power spectral (frequency domain) analyses. It also manages efficiently the huge volumes of data generated when one analyzes, for example, 1500 epochs per night with each epoch getting over 100 measurements. Nevertheless, in spite of the strengths of computer analysis, there remains a need for some visual processing, of the EEG because computer pattern recognition is still not satisfactory. We still need visual inspection to classify an epoch as REM, non-REM or waking and to exclude artifact. Once the classification has been made, one can perform computer analysis to quantify the EEG in each stage.

LH: Well, that's drastically different.

IF: Yes, but necessary. With this approach, one can determine exactly how many delta waves are present including also their amplitudes and periods. One can do this for all the other waves in the EEG spectrum, and of course, do this separately for REM and non-REM sleep.

LH: Why don't you propose to the Sleep Disorders Association that they reconsider the computer scoring of sleep epochs in view of the technological developments that occurred in the thirty something years?

IF: That's a very reasonable question. I have proposed this but so far made little headway. There are several reasons. One is that many clinicians have invested in commercial computer systems that do not do wave measurement but try instead to reproduce visual sleep stage scoring. This is what many clinical sleep labs want because it saves money. But commercial sleep scoring systems have never been adequately validated even with respect to stage scoring. Moreover, the best they can do is to produce visual stage scores that lose the information I just described to you. But I think the situation will change soon because small ambulatory recorders that do both stage scoring and EEG wave measurement are being developed. But right now the clinical labs are sticking to stage scores.

LH: They don't want to spoil the business, huh? Whatever happened to Aserinsky? I can't think of any situation in science where somebody has been part of a dramatic discovery and walked away from it so quickly.

IF: Well, I don't know the whole story. After Aserinsky discovered REM sleep as a grad student for Kleitman in 1953, he took a job in a physiology department in one of the medical schools in Philadelphia. I don't remember which one, maybe Temple. I would rather not comment on that development because I think that Aserinsky may have been treated unfairly. I don't think he walked away from his discovery willingly. But, he certainly did make the seminal observation and it was his alone.

LH: Now, of course, Kleitman was the father of the sleep studies, I guess, and, as I understand it, Bill Dement might have just come there at the time they discovered this and he took it up and ran with it and did a tremendous job.

IF: My understanding is that Bill Dement was Aserinsky's research assistant while Bill was a medical student and that is how Bill got into sleep research. And, he made a number of important

contributions, including the best first early description of EEG cycles across the night (with Kleitman). Bill was also the first to demonstrate REM sleep in the cat. LH: And, the PGO Spikes. IF: Yes, he described the PGO spikes though I think it may have been Jouvet who first discovered them. But Bill used them in several studies and emphasized their importance. A tremendous part of Bill's contribution was as a popularizer, a person who emphasized the importance of sleep to medicine and to basic physiology. However, I believe he went a little bit overboard in the establishment and promotion of the sleep disorders clinics.

LH: Overused.

IF: Overused, particularly at a time where costs of medical care are sky-high. And the use of the sleep laboratory is not helpful for many conditions but is always very expensive. Sleep apnea is the most important condition that has been discovered by clinical sleep investigation. The care of patients with sleep apnea is not something that psychiatrists or psychologists are qualified to do. It requires pulmonologists. The field has been too slow in sifting out of what is valuable from what is not valuable in the sleep disorders area. For example, many sleep disorders clinics would refer patients with a simple complaint of insomnia for sleep laboratory examinations. As I mentioned earlier, most patients with insomnia have fundamentally normal polysomnograms, typically with only a slight increase in the sleep latency. So, these are very expensive tests with limited value for diagnosis or therapy of most sleep disorders. I hope there will be an evolution to a more focused and limited use of sleep laboratory examinations.

LH: Gosh, I wish you would publish something called, What I Have Learned in Thirty-Five Years of Sleep Research, because, you know, you've had more original ideas, I think, than anybody I ever talked to in the field. And, yet, your ideas don't get publicized as much as they should.

IF: Thank you Leo. I must confess that has been frustrating to me. It is an example of the need to market research findings. There's a regrettable aspect of modern science, which is, that if you have an interesting finding or idea, you are not likely to get recognition for it if you only publish it once.

LH: Repeat it.

IF: Unfortunately it appears one has to keep publishing it over and over in different forms to maintain priority and get recognition. And, I have always found it boring to write a second paper with the same finding. I'm more interested in writing new papers on new things and that has, in the reality of this world, cost me a lot.

LH: I expect it has. But, I think you're right. I remember, many years ago, I asked a well-known scientist "Harry, why do you publish the same damn stuff? Why do you keep repeating it?" He said, "That's the only way to get your ideas across."

IF: And, that's unfortunately true. Another way one can do it is with a book where you summarize a point of view and an approach. I do hope to do a book on sleep and one on schizophrenia, but I keep putting them off.

LH: Well, I have been just a little bit discouraged about the way that programs of this ACNP organization are being driven toward neuroscience exclusively. I was going to propose to the Program Committee that they send around an announcement to all the members and say, "Look, if you want to be on the program, send a one page summary of what you want to talk about, either work you have in progress, work you've done or for review for the whole field that you know," and see what comes out of it. You know something like a summary of what we've just talked about. I think it would be a very eye opening experience for a lot of people.

IF: Well, I would certainly love to do that but I don't think it will happen.

LH: Well, I would change it from the top down model to the bottom model.

IF: When you can, I will be happy to be a part of it.

LH: Well, I hope you will be and it's been very nice talking to you, Irwin. I knew this was going to be stimulating and it certainly has been for me.

IF: Well, thanks a lot, Leo. I appreciate it.

LH: You might call it an eye opener.

### 13. SILVIO GARATTINI

LH: I'm Leo Hollister and today, December 12, 1995, it's my privilege to interview Silvio Garattini.\* Dr. Garattini is the Director of the Mario Negri Institute in Milano, one of the pre-eminent pharmacological institutes in the world. Welcome to San Juan.

SG: Thank you.

LH: You were quite a young man when you became Director of Mario Negri. How did that happen? What was your training up to that point?

SG: I was born in 1928. I went to school during World War II and had to resume my education after some interruption. At the time no one in Italy knew what was going to happen, so my father said, "It would be best if you study something that will provide you with security" so I started my career in chemistry. Chemistry was considered a safe occupation and I went to study and got the title of Certified Chemist. I had an excellent training in chemistry because at that time the teaching of chemistry in Italy was not only theoretical but included some laboratory work and I enjoyed that very much. Then I worked as a chemist in a steel factory, but I wasn't happy. After the war ended I decided I would like to get a university degree and in 1948 I passed the admission examination. I decided to enter medicine with the idea that with my training in chemistry, a training other medical doctors would not have, I could combine medical with chemical knowledge. When I was taking my examination in pharmacology, I realized that it appealed to me very much. Pharmacology studies the biology of chemicals, the interaction between chemicals and the living organism, and I decided I would like to pursue pharmacology as a career. My family could not afford to keep me while I was at the university, so I had to work while I was studying. So, after that examination I started my career in the Pharmacology Department of the University of Milan, while I was following the courses and taking the examinations necessary to get my medical degree. I got my MD in 1954.

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\* Silvio Garattini was born in Bergamo, Italy in 1928. He received a diploma in Chemistry and his MD at Milan University where he served in the Department of Pharmacology until 1962. In 1963, he was founding director of the Mario Negri Institute for Pharmacological Research. The Mario Negri Institute, under Garattini's leadership, has contributed to the world scientific literature on topics ranging from cancer and its treatment to tumour immunology, neuropsychopharmacology, and cardiovascular and renal pharmacology as well as the education and training of scientists. He was interviewed in San Juan, Puerto Rico on December 12, 1995.

LH: What did you do after you got your MD?

SG: In 1955 I got a Libera Docenza – a sort of between qualification - in chemotherapy and in 1957, I earned one in pharmacology. For a short period I stayed on as an assistant professor in the Department of Pharmacology at my university, and then I moved to the Department of Pharmacology at the University of Milan. The head of the Department was Professor Emilio Trabucchi, a well-known pharmacologist, who played an important role in my professional development. In Milan, I had the opportunity to organize a team of young pharmacologists to work with me on psychopharmacology, while I continued my research in the laboratory, publishing papers. 1957 was a significant year in my life because I had the opportunity to spend three months in the United States and to visit laboratories, including laboratories at the National Institute of Mental Health and at the National Heart Institute, and to meet many people I knew from the literature, like Bernard Brodie, Julius Axelrod and others. I was very impressed that research was already a profession in the United States unlike the case in Italy. At the time in Italy research served as a means of collecting credits to improve one's career at the university, and for publishing papers, but it was not a profession in itself. I was also struck by the variety of institutions doing research in the United States. There were public universities, state universities, private universities, private laboratories, and research laboratories of the pharmaceutical industry and of foundations. I found the idea of a "foundation" especially attractive because a foundation is a relatively free organization that is not subject to the anonymous bureaucracy that is ever-present in Italian universities. Since foundations are not for making profit, one should be able to work in a foundation in the interest of the public. This was another attraction for me. In a somewhat naïve way of thinking I saw foundations as private places at the service of the public. So after I returned to Italy, I got together my team in the department and told them that if we are serious about our intention of doing research, we would have to decide whether to move to the United States and work there or create a facility that has a different organizational structure from any of those in Italy. We decided that we should stay and create a suitable setting for our research. Then, as a naïve young man I went around asking people for their help to establish a foundation.

LH: That wasn't so naïve.

SG: Well, it was something very simple but apparently some people responded to it favorably. In fact while doing the rounds asking people for support I met, by chance, Mr. Mario Negri, an

industrialist in Milan who was primarily in the jewelry business, who had no children but was always interested in young people. And when I asked Mr. Negri, like I asked everyone, "Why don't you help us set up a foundation where we can do independent research?" he responded simply, "Why not?" Then he added, "But you are too young. Let's think about it. Let's see what can be done." After that we had many meetings at which we discussed, not only what should be done, but what kind of research we should do, how an organization of this kind could obtain support, and what kind of rules of operation the foundation should have. After a series of such discussions I was quite confident that he was ready to do it. But then, tragically, he got cancer of the liver. I was shocked. My dream, that seemed so close to materializing, was fading. But then, about a couple of weeks before he passed away, he called me and asked me to visit him in the hospital. When I went, he told me, "Don't worry. I have done what we discussed and whatever happens to me everything will be fine." Mario Negri died in April 1960. When they opened his will, everything we had discussed was written there-each single point we had talked about was there. He named me as the director of the institute to be established, that he wanted to be called The Italian Mario Negri Institute of Pharmacological Research. So my dream became reality.

LH: That was very noble of him.

SG: It was also something extremely risky for him to do. It was a difficult task to create a research foundation in Italy, where most research at that time was done at state universities, and even at drug companies, research was in a very early stage of development. Mr. Negri left the equivalent in Italian lire of about 1 million US dollars for the creation of the foundation and how we had to decide what to do with the money. One possibility was to put it in a bank and use the interest to fund some of our research. The other was to use the capital to build an institute that would then have to survive by competing for grant support. To do something significant in Italy we knew we would need a building, so we decided to use the money Mario Negri left to build the institute we envisaged. By the end of 1961 the Institute was recognized as a non-profit organization by the U.S. Treasury. We needed this recognition in order to obtain support for our research from the USA. We were already collaborating with American groups.

LH: So, it was established as a foundation to get tax-exempt status.

SG: Exactly. First, we were recognized by the American government and then, later, by the Italian government. In February 1963, 20 researchers moved into the Institute in order to set up laboratories so we could continue our research. We had three groups of researchers: one group was

working in cancer, one in psychopharmacology, which at the time was just starting to develop, and one in cardiovascular disease. It was a difficult start. We actually got much more help from foreign than from Italian groups. We represented something new and unusual in Italy, and were asked again and again, "What kind of organization are you? Are you a university? Are you industry?" Our answer, of course, was that we were neither university nor industry. It took some time before people recognized that this type of organization had not existed in Italy before. I would like to acknowledge here the strong support we got from Sir Henry Dale, the chairman of Burroughs Wellcome. I had the privilege to discuss our initiative with him and he was very sympathetic and encouraging about our project. Then we also got support from the Gustavus and Louise Pfeiffer Research Foundation in New York. To operate the Institute we implemented three simple rules. The first is that we don't spend money that's not available. We thought it was important to resist the temptation to borrow money, so as to avoid running into problems. The second rule is that in order to maintain our freedom we do not accept any donation, grant, or contract that is more than 10% of our total budget. In this way, we thought we could avoid becoming dependent on any single body. The third rule is that we never check people's working times. We thought that everyone would do what they possibly could and that self-discipline was important. These are three simple rules that I believe are important regarding the operations of the Institute. As soon as the first scientists moved in we started research. Then, to complement the research with educational activities, we established two schools, one for technicians, and one for post-doctoral fellows. These schools are still operative. It was also an early decision that all scientific papers from the Institute would be written in English.

LH: A wise decision.

SG: Well, we saw, that at that time English was the language of science and if we wanted to communicate our findings to the scientific community we would have to do it in the lingua franca of science. We use Italian when we process data in the Institute but English to communicate our findings with the world. So far we have six thousand scientific publications. We also decided that not only the scientific community but also the physicians in the community and the public should be informed about our findings. This was quite unusual at that time. But we felt it was important for people to be informed, so we wrote articles for newspapers, talked on the radio and appeared on television. In Italy, it was considered improper for academics to talk to laymen. But we were convinced it was important to let the public know about progress of science and problems in

science. In Italy in those years people were not accustomed to make donations to support science. Donations were usually given to the church or to the arts or humanities. By communicating with the public directly we tried to convince people that it was just as important to contribute to scientific institutions.

LH: Did you get on any list of organized charities over there?

SG: No, we did not, but now we have a number of institutions that support our research with grants. An important one is the Agency for Cancer Research. Right now, we have maybe 20 or 30 organizations, helping support various kinds of research in different fields.

LH: Do you have anything comparable to the National Institutes of Health?

SG: No, not really. We have the National Research Council, but that organization has much less money to distribute than the NIH. Actually, we have been very lucky because at the beginning we had several grants and contracts from the NIH. There was a period, I believe, between 1965 and 1970, when the Mario Negri Institute was receiving more grants from the NIH than any other European organization. After 1970, the Institute gradually became accepted by Italian academia and we became part of the Italian scientific scene. But the beginning certainly was very difficult in this respect. In the meantime, the Institute was growing so fast that the building that we built in the beginning was no longer sufficient to accommodate all our researchers. So we added first a new floor, then a six-floor extension, which we called "the tower", because we needed more space for laboratories. We also got a grant from an American foundation to build a guest-house where people from other countries who were working with us could stay. Later we built another building to accommodate epidemiology and molecular biology, two areas of research we became interested in. We also set up a second Mario Negri Institute in Bergamo, concentrating on renal diseases. We built it in Bergamo because we were able to arrange collaboration with the local hospital so we could build a bridge between laboratory research and clinical work. Then, we built an institute in the south of Italy, because we wanted to help young researchers in the south to get involved in scientific work. Just recently we established a clinical research center devoted to rare diseases near Bergamo. Why rare diseases? Because I think that people with rare diseases are twice unlucky; they are unlucky because they have the disease and unlucky again because it is such a rarity that industry is not interested in developing a treatment for it.

LH: Can we focus in on that rare disease center?

SG: We were able to extend our activity into this area and remodel a splendid building in its own enormous park, thanks to the generosity of the Daccò family. In gratitude the building is called the Aldo e Cele Daccò Center. There are about 5000 rare diseases and they represent more or less 10% of all pathology. The clinical research center serves as an information center where people - physicians, parents and relatives or anyone - can get information on all the different rare diseases we know about. In addition to a small hospital, the Center also has an outpatient clinic and a school for rare diseases. The rooms in the hospital are the old bedrooms of the villa, very nice and decorated in lovely colors. So patients can walk out from their rooms into a park and beautiful surroundings.

LH: Sounds like a palace.

SG: Yes. Physicians usually see not more than one or two cases of any of these rare diseases in their whole career. So our idea is to have 20 people with a given rare disease together in one place. It's something no one ever did before.

LH: People with rare diseases are scattered all over the place.

SG: We will have room to receive foreign scientists interested in one or other of these diseases, so they can stay for a week or so to do studies that could help these patients. The place is already tidied up and within the next year it will start to operate. This is what we have so far. We started, as I told you, with about 20 researchers in the Milan Institute and we now have about 900 people. So the family has grown.

LH: Maybe your use of the term, naive, at the beginning was correct, because I don't think anyone except a naive young man could have dreamed such an empire could develop.

SG: I should say I've been very lucky with my colleagues. Some of my early collaborators have, unfortunately, passed away, including Professor Alfredo Leonardi, who became the General Secretary of the Institute. He was an M.D., but he took care of the administrative aspects of the organization. You might have known Professor Valzelli, because he was involved in psychopharmacology and did a lot of work on aggressive behavior. Each of my collaborators has his or her own scientific personality. They work on their own grants. The Institute is a composition of different independent researchers.

LH: It's an amazing development. Now, let's talk about psychopharmacology. You have a book here that was published in 1957.

SG: Psychotropic Drugs is the book you are referring to. It is the proceedings of a meeting held in Milan in the early years of psychopharmacology. A lot of clinicians and scientists involved in psychopharmacology from all around the world attended it. At that time we already had chlorpromazine, reserpine, meprobamate, iproniazid, and obviously, amphetamines.

LH: Some of the prototype drugs.

SG: One of the opening presentations was given by Professor Blaschko, a well-known biochemist and enzymologist, who reviewed all the various forms of monoamine oxidases known at that time.

LH: Now, when was this conference held?

SG: In Milan, from May 11 to 15, 1957.

LH: Well, didn't you have at the opening session, besides Blaschko, also Ab Hoffer, Erminio Costa, who must have been a very young man, Hi Denber, and Ernst Rothlin from Sandoz?

SG: Yes. Rothlin was there from Sandoz because Sandoz had LSD and some other hallucinogenic agents. We had many important people from the field of psychopharmacology at that meeting.

LH: I think your book was published in the same year as Abraham Wikler's book "The Relation of Pharmacology to Psychiatry."

SG: Well, the Milan Symposium was a very interesting meeting in that one could sense from the presentations the direction psychopharmacology was taking and the tremendous amount of work that still needed to be done to understand brain function. I see psychotropic drugs as tools to understand how the brain is functioning, to generate knowledge that could provide ideas to open new avenues for developing new drugs, more than just treatments. Actually, only a few psychotropic drugs proved to be of importance in treatment.

LH: Neuropsychopharmacology is a bootstrap operation. We get ideas from our drugs, which we use to treat our patients for developing new drugs.

SG: Exactly. And the brain is so complicated that probably there are no other ways but using drugs for learning about its functioning.

LH: I imagine you still have a large division devoted to psychopharmacology?

SG: Yes and our research in this area is not restricted to psychopharmacology but also includes neuroendocrinology and neuroimmunology. These are newly emerging areas of research. Our work in psychopharmacology ranges from basic molecular biology, to clinical work in psychiatry that we do in collaboration with other people because we ourselves have no clinical

arm. We are doing research with drugs in biochemistry, neurophysiology, behavioral pharmacology, endocrinology, and immunology. We also do research on psychiatric epidemiology, as well as on evaluation of psychiatric service in general hospitals because, as you probably know, we no longer have psychiatric hospitals in Italy.

LH: So the psychiatric service is provided in the general hospital?

SG: It is provided by general hospitals. So, it is very important to see how the psychiatric service works in general hospitals. So, in psychopharmacology we have quite a wide spectrum of activities. Serotonin has been a continuous interest of mine. In the proceedings of the Milan symposium we reported our findings on measuring serotonin in the brain. At that time, to do one measurement of serotonin in the brain we needed ten brains from mice. Now, with new techniques like isotopes, ultra-radiography and mass spectrometry, we can do a hundred examinations on a single brain.

LH: Major changes.

SG: Yes, there have been a lot of important changes during the past 40 years but there is still a great deal of interest in serotonin in the Institute.

LH: It was interesting that during the 1960's, most people in this country put their bet that the important neurotransmitter in depression was norepinephrine, and serotonin was kept alive mainly in Europe. But now we've come around to thinking more about serotonin, especially with the new class of serotonin uptake inhibitors.

SG: Yes. I think that both chemical transmitters are important in depression, and possibly also some of the other neurotransmitters.

LH: We know of many transmitters now.

SG: We know that there is an interaction between serotonin and norepinephrine, and also between these and some of the other transmitters. If you touch one neurotransmitter you induce a lot of interactions.

LH: Then, in addition to neurotransmitters, we also recognize receptors and receptor subtypes.

SG: Plus transport mechanisms. There are new micro-analytic techniques that are becoming important. Before, we could measure only a mixture of serotonin, free and bound in vesicles, together. Now, with microanalysis, we can measure the serotonin that is free and is acting on receptors or various other targets. We now have ways of measuring serotonin release that causes changes at the presynaptic or postsynaptic receptors.

LH: Bernard Brodie didn't live long enough to see the resurrection of serotonin.

SG: Yes. I learned a lot from Bernard Steve Brodie. I had the privilege to be in contact with him and spend time with him. He was certainly an exceptional man, one who was able to ask the right questions. I will always remember hours of discussions I had with him. It was a way for him to get new ideas.

LH: Well, I'm glad there's a laboratory dedicated to his memory in Cagliari.

SG: Yes, there is a laboratory in Cagliari dedicated to him. And I'm very glad that we have this laboratory in Italy, because he was always very interested in science in Italy.

LH: He trained a lot of people from Italy, like Gessa, Costa.

SG: Exactly. In 1959, about two years after my first visit to the USA I had the opportunity to see Steve Brodie again, and at that time he told me, "You should come and stay with us for a period. Why don't you call me?" I would have been very interested to spend time with him. But then in 1960, I felt obliged to follow the directions in Mario Negri's will. Shortly after the will was opened I went to Miami for a meeting where I met Steve and told him that I would not be able to come because I was committed to building an institute. That was when I introduced Erminio Costa to Steve Brodie.

LH: Oh, is that right?

SG: And so in a way, Erminio Costa...

LH: Took your place.

SG: He was senior to me, but that was the occasion at which he met Steve Brodie for the first time.

LH: What a small world!

SG: Yes.

LH: So, as you look back on psychopharmacological experiences in your laboratory, what would you think are your major achievements there?

SG: Well, we were probably the first to show the antagonistic effect between serotonin and chlorpromazine but we didn't get any recognition for it because we were obliged by the university to publish in Italian. We were doing experiments at the time with serotonin in isolated organs.

LH: So you followed up on Gaddum's old experiments with serotonin and LSD?

SG: Yes, exactly. We tried chlorpromazine, among many other substances, and were surprised to see the great antagonism between chlorpromazine and serotonin. We did our experiments in several isolated organs and also did some studies *in vivo*. But our findings on the mechanism of action of chlorpromazine were not recognized because they were published in Italian.

LH: Let me interrupt a minute here. This antagonism of serotonin by chlorpromazine, along with its dopamine blocking action, makes chlorpromazine somewhat similar to the newer atypical antipsychotic drugs?

SG: Exactly. There is really no difference between chlorpromazine and the new atypical antipsychotics except that chlorpromazine is also very active on norepinephrine. I don't know if that is significant or not, but in any case there is this difference.

LH: Interesting.

SG: Another contribution was based on research that I did with Erminio Costa. We were the first to show the antagonism between reserpine and imipramine, the first tricyclic antidepressant. Imipramine was considered to be a chlorpromazine-like drug.

LH: Neuroleptic.

SG: Neuroleptic, but Dr. Kuhn in Switzerland recognized that it had antidepressant activity. Although there was already some experience with iproniazid, a monoamine oxidase inhibitor, which seemed to have an effect on mood, you may recall, there was some skepticism in those years about whether a drug could have antidepressant effects. There was no animal model for depression we could use to show antidepressant activity. So since some clinical experience indicated that reserpine might have caused depression in some patients treated for hypertension, we used some of the behavioral effects of reserpine as a model for depression. We induced changes like hypothermia and ptosis in the animal with reserpine and tried to see if imipramine antagonized these changes. It worked, and reserpine reversal became an important pharmacological test for screening and developing new antidepressants. Later reserpine was replaced by tetrabenazine, a benzoquinolizine derivative with similar pharmacological action to reserpine in the test because it could be given intravenously, so it was easier to work with. It was interesting to see that imipramine was an antagonist of reserpine and that chlorpromazine was not. So I think the development of an animal model of depression that could be used in screening for antidepressants was also an important contribution we made.

LH: Yes, indeed.

SG: In the late 1950s we studied the effects of electroshock and showed that it produced changes in serotonin. Later on this was also shown by others, using more sophisticated techniques.

LH: So you found changes in serotonin after ECT.

SG: We made contributions to the understanding of the mechanism of action of benzodiazepines too. We have done a lot of work to characterize what was present in the brain after the administration of a benzodiazepine. For instance, diazepam is metabolized to form methyl oxazepam that is metabolized to oxazepam. These metabolites are at least as active as diazepam. So, when using diazepam, or benzodiazepines in general, one must always be aware of the possibility that the drug might have active metabolites which might be just as active or even more active than the parent substance.

LH: Methyl oxazepam has actually a much longer half-life than diazepam.

SG: Exactly, so it stays there for longer and that explains the longer duration of action of diazepam than would be expected from its half-life. We worked in several animal species so we learned that not all species metabolize diazepam the same way. We also did a lot of research with benzodiazepine receptors at the time the first reports on these receptors were published.

LH: That was in '67?

SG: Yes, some time in the late 1960s. We also invested a lot of research in the area of anorectic agents.

LH: Fenfluramine?

SG: Fenfluramine, and dexfenfluramine, the active metabolite of fenfluramine. We did a lot of work with these drugs in various animal species, studying their mechanism of action, and showed that there was an increase in serotonin that was responsible for the anorectic effect.

LH: It creates a feeling of satiety.

SG: Yes, and we could distinguish between amphetamine-like and fenfluramine-like mechanisms of action in anorectic effects. There are several other agents that are not yet used clinically that have exactly the same effect as fenfluramine, for example methylchlorophenyl piperazine, an agonist of 5HT1C receptors which is a trazodone metabolite.

LH: That's a trazodone metabolite.

SG: Well, it's a trazodone metabolite. And that was another of our contribution.

LH: It was developed in Italy, wasn't it?

SG: Yes, it was developed in Italy. In the 1970s, we were studying the effect of drug metabolites in the action of drugs and found that in some cases the action of a metabolite differed from the action of the parent substance. For instance, if you take buspirone, it is its metabolite that explains the anxiolytic activity of the drug. Buspirone itself is not an  $\alpha 2$ -agonist but its metabolite is. So unless you know exactly what you have in the brain, in terms of chemicals, you don't know what to expect from your drug.

LH: We need to know the active metabolites

SG: Another example of this is dexfenfluramine that has an active metabolite, dextrorfenfluramine that accumulates in the body differently from the parent substance. It also differs from the parent substance in that it is a 5HT1C agonist, so it has its own action on serotonin too.

LH: So, there are lots of chemicals to be tested. Do you think fenfluramine damages the serotonin system? Is that a real concern?

SG: Well, with excessively high doses there is a long-lasting decrease of serotonin. If one looks into the brain with various techniques, including antibodies against serotonin, it is a fact that one cannot recognize serotonin in the brain. One interpretation of these findings is that there is selective neurotoxicity with fenfluramine. There is a lot of discussion at present about what the dexfenfluramine-induced disappearance of serotonin means. My opinion is that it would not have been a clinical problem and it only appears at much higher doses than those used in humans. I think it would be a very interesting area of research to establish what the neurotoxicity is, because even if serotonin is not present for a long time after the administrations of fenfluramine, all its functions seem to be present, and that implies that serotonin synthesis is going on.

LH: There are probably hundreds of thousands of people taking fenfluramine, and if they don't have a serotonergic system, it doesn't seem to cause any harm. It makes one wonder about the role of serotonin in brain function.

SG: At the time of the Milan symposium, when I started my research with serotonin, it looked like we would progress rapidly in understanding how the brain functions and develop drugs to take care of all psychiatric diseases. After almost 40 years, though, I must say these expectations have not been fulfilled. It is certainly fair to say we have made a lot of progress, but maybe less than what...

LH: What we hoped for.

SG: If we look back at the last 40 years we have not developed any antipsychotics that are clinically more effective than chlorpromazine. In the anxiolytic field we have added benzodiazepines and buspirone to meprobamate but they don't seem to offer major advances. None of the new antidepressants are superior to imipramine. The selective serotonin uptake inhibitors might have a different side effect profile from tricyclic antidepressants, although even on looking carefully through the literature that is not completely clear. In any case, what we have in new drug development is rather disappointing at present. Maybe studies now going on in laboratories with peptides, cytokines, and so forth will lead to advances in treatment.

LH: One of the problems is that we used the drugs as tools, as you said it, to find out what they do, and then we used the drugs for which we had some understanding of what they do in screening to pick up new compounds. If one picks compounds this way, they are bound to have action similar to the drugs we started with. But one might think that as we are accessing post receptor mechanisms and going all the way down to third messengers, we should find new points in the system that drugs might attack. Who knows whether it will be any different blocking the system somewhere downstream rather than blocking the receptor?

SG: We will probably have to look for drugs in the future that don't have the same wide range of activity as the drugs available today, and if we do that, we might be able to develop drugs that are more selectively effective for certain subgroups of patients. In other words, we might develop drugs for a certain type of depression but not for the treatment of all depressions. But to do that will require changes in our approach to drug development because industry will not be interested in developing drugs without a sufficiently large market to get back their investment. I see this as a problem that needs to be solved. In order to progress we need to find a way to dissociate the development of the drug from the question of profit. There is a conflict between our needs and what the companies are developing and that will have to be resolved.

LH: It could be done in an independent pharmacological institute.

SG: Well, yes, that's true. I think we shall have to find a way in the future to bring together the know-how of industry with the know-how of independent research institutions and reconcile their interests with the interests of the public. Possibly we shall need help from the government because if we don't get these know-hows together and don't reconcile the different interests we will still have difficulty developing new drugs. It is time to think in a different way about how to develop psychotropic drugs. Take as an example the field of antihypertensives. If you are a drug company

and develop an antihypertensive you want a drug for the whole spectrum of hypertensive patients, to widen your market. But maybe what we really need is a range of anti-hypertensive agents, each addressing only one mechanism that may be present in only a fraction of hypertensive patients.

LH: We have so many antihypertensives that work through different mechanisms.

SG: But we don't take advantage of that to prescribe the specific anti-hypertensive agent for each group of patients. This is more or less what is happening in psychopharmacology too, when we talk about the use of neuroleptics in schizophrenic or other psychotic patients. We have many neuroleptics and one or other of these may be more selectively effective in one subpopulation of patients or another.

LH: I spent about ten years of fruitless studies on how to pick the right drug for the right patient.

SG: Maybe all the drugs we have are similar because they have been detected by the same tests. Some time ago I organized a meeting in Milan on New Tests for New Drugs, because if we continue with the same tests as today we will just have more chemical entities of the same type. So, as I said, we should probably work to develop drugs that are selectively effective for one or more subpopulations of patients.

LH: Let me ask you a personal question. You look 20 years younger than your chronological age. How do you do that?

SG: That is a compliment. Time is equal for everybody: I have no secret. I am lucky to have good health and I am interested in my work, which is a privilege.

LH: It is a blessing to enjoy one's work.

SG: I hope to see other developments in the field of psychopharmacology.

LH: I hope you will. You have contributed a lot to the field; starting as a young chemistry major you have built quite an empire, and a very good one. Silvio Garrattini, I wish you all the best.

SG: Thank you.

## 14. ANGELOS E. HALARIS

LH: Today is Thursday, December 11, 1997. I'm doing an interview today with Angelos Halaris,\* who is the Chairman of the Department of Psychiatry at the University of Mississippi, Jackson, for ACNP's History project. I'm Leo Hollister, the interviewer. Welcome to the project.

AH: Thank you.

LH: Well, where did you begin life?

AH: That's a long story. Life began in Athens, Greece.

LH: I figured with a name like Halaris, it had to be Greek. Were you actually born there?

AH: I was born and raised there through high school. I attended a Greek-American school in Athens, so I learned English as my second language very early. But, then, I switched course. After graduating from high school, I went to the University of Munich in Germany on a scholarship awarded to me by the Bavarian government, which was a nice thing to have, at the time.

LH: My goodness, it must have been quite an honor.

AH: It was. It came rather unexpected. But, it allowed me to enter Medical School. As you probably know, European medical schools are a straight six years in duration. The scholarship covered my education about half way, what we could call pre-med, here, and, then, because I'd done rather well, I got a second scholarship from the German government. And that really saw me through my entire medical school.

LH: So, you got a degree, then, from the University of Munich?

AH: Yes, the University of Munich School of Medicine. And half way through my studies, I joined the Max Planck Institute of Psychiatry in Munich.

LH: That's another prestigious place.

AH: The idea was to do a doctoral dissertation there. We had the option of doing a literature review or a basic science dissertation, so I opted for the latter. And, I started with some

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morphological studies. I learned how to use the electronmicroscope and, at the same time, I did some work with lipids, some lipid research on Tay-Sachs disease and that was my dissertation theme. Then I met another scientist, Dr. Norbert Matussek, who played a major role in my shifting gears and getting me into biogenic amines, as a new field of studying the biology of depression.

LH: Who?

AH: Norbert Matussek.

LH: Oh, Matussek!

AH: You probably know him.

LH: Yes, yes. He is a fine man.

AH: He's a wonderful individual. I consider him as my first true mentor. He worked at the Max Planck Institute for Psychiatry in Munich, Germany and had just returned from NIMH, where he had spent some time working with Biff Bunney and the group that Biff had assembled, at the time, at NIMH. That was right around 1965, the landmark year that saw the publications about the noradrenergic hypothesis of depression. Norbert had just been exposed to that thinking, so when he returned to Germany, he set up a laboratory at the Max Planck Institute to pursue similar work.

LH: What did you do, shift from lipids to monoamines?

AH: Yes, I shifted from lipids to monoamines.

LH: Go with the flow.

AH: Go with the flow. It was more exciting and, so, I started working with Norbert, doing some research on the side and we were interested in looking at the effect of reserpine on depletion of biogenic amines. And, since, I had learned how to do electron microscopy, we treated rats with reserpine, and some other shorter acting drugs, and looked at the hypothalamus to see if we could visualize the depletion of biogenic amines following reserpine treatment. At the same time, we were measuring the level of biogenic amines and correlated the depletion of biogenic amines with the disappearance of dense core vesicles from hypothalamic tissue prepared for electron microscopy.

LH: So, you could do microscopic structural work, along with biogenic amine analyses.

AH: Exactly. And that was what I was doing with Norbert, while trying to finish medical school, which I did, and everything went fine. Actually it went very well. Another major encounter in my life occurred in 1970 when I met Daniel X. Freedman at a conference on drug abuse in Zurich,

Switzerland. I had been following Danny's work and I was fascinated by all of his theories about serotonin and psychotomimetic drugs and model psychosis.

LH: That's still one of the better explanations for experimentally-induced psychosis.

AH: Well, there have been better ones since that time. Danny helped me get a research fellowship through the Foundations' Fund for Research in Psychiatry. So, I joined him in Chicago in 1971, after discharging my military duty in the Greek Army.

LH: Oh, you had to do some obligatory service in the Army?

AH: I had to. I was obliged as a Greek citizen, at the time. I had exhausted all of my deferrals and they caught up with me and they said you're going to have to spend some time with us before you can go anywhere else. And, Danny was patient enough to wait for me to get released from the Greek Army. A month later I was in Chicago to start my Research Fellowship. I don't know if you remember the Foundation's Fund for Research in Psychiatry. They were offering fellowships back in the early seventies. After spending two years as research fellow, while I had a staff position waiting for me in the Department of Psychiatry at the University of Munich to work for Hans Hippius, Danny asked me to stay on and work in his department at the University of Chicago. "OK I said, I am honored by the invitation to stay, but I really want to do a residency in Psychiatry because I want to become a psychiatrist." Frankly, he wasn't too keen to see me train to become a psychiatrist stating, "Anybody can become a psychiatrist; you can be a successful researcher."

LH: Up till then, you'd been doing mostly laboratory and no clinical research?

AH: I wasn't even licensed to do clinical work in the United States, at the time. So, I sort of struck a deal with Danny that I would stay on and continue to work in the lab and pursue a common interest that he and I had in psychotomimetics, but I insisted that I wanted to do a residency. And, he said, "Well, I'll arrange for that." And he did. And for a while I was doing residency and working in the laboratory at the same time.

LH: Interesting. A lot of people did that. I think Jack Barchas and a number of other people combined lab work with their residency.

AH: I think George Aghajanian has done something like that.

LH: Well, I think even Sol Snyder did it? I remember the first I met him, he was still in the lab, but he was nominally a resident at Hopkins.

AH: Well, it was a bit tough, especially, during the time when I had to do my inpatient rotation, which was a rather demanding rotation, but the lab was almost right next to the ward, so I could go back and forth very easily and I had some technicians that I had already trained, so the lab kept running. And, we had already obtained sizeable grant support and in the long run it all worked out. Looking back now, I am very, very glad that I did what I did back then. I didn't drop research to get specialty training and I didn't drop training to pursue research. I did both for a while and that proved to be a very wise decision. I also had to get a permanent license to practice medicine in the United States. That was a tough time having to study hard while working full time as a resident and researcher. As an international graduate, I had to take the FLEX, a grueling three day examination covering the entire field of preclinical and clinical medicine.

LH: And, you were already out of school for several years. That makes it really tough.

AH: Indeed, but it all worked out, eventually. The first time I went to take the test I was totally unprepared and I flunked it, but then I wised up and studied for it and I passed it. And so, Danny wanted me to stay in Chicago, which I did. He gave me a faculty appointment and I became an Associate Professor toward the end of the seventies, at the University of Chicago. I began to pursue some other research interests of mine, which I had started in Munich with Norbert Matussek, and that was the role of biogenic amines, serotonin, and norepinephrine in the action of antidepressants. By that time I had begun to suspect that dopamine might also play a role.

LH: In depression.

AH: In depression. As a matter of fact, Danny and I wrote a chapter in one of the books that he had edited.

LH: And that was before the days of bupropion.

AH: That's right. So, when bupropion was ready for clinical trials as a potential antidepressant, I linked up with Burroughs Welcome and Dr. Warren Stern who was the organizer of the clinical trial program to develop bupropion as an antidepressant.

LH: He was sort of the honcho over it.

AH: He was the organizer of all clinical studies and I jumped at the idea because people thought that bupropion acted through dopamine.

LH: Did you actually join the company?

AH: No, I just did several studies for them and I'm proud to say that I was the first one to do the first open label study of bupropion in depression. I was very impressed with the response I saw in

the first six or eight patients I studied. And I called up Warren and said, "Warren, you've got a potential winner here." And, as you know, the drug eventually came on the market and it's....

LH: Is it proved yet just how bupropion works through dopamine?

AH: Probably as an uptake inhibitor, but I think it's a dual dopamine and norepinephrine uptake inhibitor. It looks like its major metabolite, hydroxybupropion, inhibits norepinephrine reuptake whereas bupropion itself inhibits dopamine reuptake. So, I was excited because it confirmed my idea that dopamine is involved, at least with some aspects of depression, and drugs that enhance dopaminergic transmission could exert an antidepressant effect. That work I had started while I was still in Chicago. In 1980 I moved to UCLA and I was given the opportunity to set up a laboratory at the Brentwood VA.

LH: At the VA Hospital affiliate?

AH: Right. I was given an inpatient ward to run and I was supported to build a laboratory in the same building, right underneath the ward, so I was able to do much of the same thing that I had done during residency. The ward was upstairs where I was Ward Chief and the laboratory was in the basement where I was Lab Chief, and I could run up and down and ride two horses at the same time.

LH: If you didn't mind running upstairs, it was ideal.

AH: So, that was an interesting situation.

LH: There were a number of other labs at that hospital, wasn't there? Sam Eiduson was there and Ed Geller.

AH: Ed Geller, Ted Van Putten.

LH: Oh, yes, Ted; he was one of the clinicians.

AH: He was a clinician. Phil May was there too. Phil May's laboratory was down the hall from my laboratory. Steve Marder is still there and Art Yuwilier is probably still there.

LH: I think he was there about the same time as Sam Eiduson was there.

AH: I don't know if he's retired or not. Art was very active in research. I spent almost five years at UCLA and during that time I made a major change in my research approach. I began to look for a marker for depression and because of my interest in dopamine I wanted to develop a blood test and measure dopamine or HVA in blood as an index of central dopaminergic activity.

However, everybody was looking at MHPG at the time, and measuring it in urine or CSF and CSF wasn't easy to obtain, then, as you know.

LH: Not a trivial way to get a laboratory specimen.

AH: No, and we wanted to have something that anybody could do, and rather easily. So I thought, how about a blood assay for MHPG? I was fortunate to hook up with a young biochemist, Ed DeMet, who had come to work with me while I was still in Chicago. We set out to develop a gas chromatographic technique for measuring plasma MHPG and we did it. It took us over a year to work out the method and, then, we had a method that we could apply to studying depressed and manic patients.

LH: It's probably the one still in use, isn't it?

AH: Actually we've replaced now gas chromatography with HPLC. It's simpler, cheaper and faster, but we started out with a huge gas chromatograph. It was an old model but it worked. It was a rather cumbersome method, but we were able to get some samples and I'd draw some samples from manic patients and, lo and behold, MHPG was very high and got some depressives and that was variable, sometimes was low, and sometimes was the same as in normal healthy subjects, much like everything else in depression.

LH: I remember the MHPG era. Mostly the determination of MHPG was done in twenty-four hour intervals or time periods, and I was curious as to what the reliability was. I didn't think very much of it.

AH: You know, if you measure twenty-four hour output, you can't very well assess what happens from hour to hour and that was my thinking at the time. We needed something that would allow us to do that.

LH: To get it right.

AH: If the amount of blood isn't too much, one can sample blood more than once a day. And, that was the idea of doing our assay in reducing down to a small blood volume and we were able to do that, especially, after we switched to using HPLC. I was a little disappointed that I couldn't get a clear picture about how high or low or normal the level of MHPG was in depression. But, then, I thought, well, maybe it's not a matter of too much or too little, maybe there is a dysregulation in the output of norepinephrine by the brain, by the nervous system. That was a theory that Larry Siever and others had put forward. I modified that theory and started talking about a desynchronization theory and got into biological rhythms and discovered a diurnal rhythm for plasma MHPG in normal volunteers by sampling six or eight times, during a twenty-four period.

LH: Well, the endocrinologists pioneered techniques where you could do continuous sampling.

AH: That's right. Well, we needed ten ml of blood per draw. And, so, the most we could do was about sixty to eighty ml in a day. That was pretty much the limit, but that allowed us to construct a diurnal curve, using sophisticated statistics called the cosinor model. We applied that model to our measurements and we came up with an impressive sinusoidal curve and we described that and published it a few times. Then, I said, "Okay, now that we know there's a normal rhythm, if our desynchronization theory is correct, as far as depression, if we applied the same methodology to depressed patients, we should not see that nice sinusoidal curve." And that was exactly what we got. We, basically, got garbage, nothing anywhere like the clean sinusoidal curve that we had seen in healthy subjects. So, yes, we can say now that MHPG production is desynchronized in depression, but what does that mean I don't know.

LH: Well, of course, nobody knows what changed rhythms in depression really mean, whether they're a secondary phenomenon or whether they're of primary importance. You stayed with the catecholamines for quite a long while.

AH: I stayed with the catecholamines for quite some time.

LH: Did you go into the HVA now?

AH: No. We played a little bit with the method, tried to simulate our plasma MHPG method and develop a plasma HVA method. We had, for some reason, more trouble getting consistent results with HVA and, then, there were serious questions raised about how much plasma HVA reflected brain dopamine activity. So, we dropped that approach altogether, believing we had gone as far as we could go. And, then, we got excited by the  $\alpha$ -2 receptor theory and began to work with platelets. I started that work in 1983-84, while I was still at UCLA. And, then, I moved again. At the end of '84, I moved to Case Western Reserve University, Cleveland, Ohio. I took a medical directorship and vice chairmanship in Cleveland, but always under the stipulation that I could have a laboratory. So, I packed up some equipment that I owned and moved the laboratory to set it up in Cleveland.

LH: You get hustled into administration too early.

AH: Well, that got me into administration, probably a bit too early, but I was determined to pursue research at the same time. I was fortunate to find a young scientist, Dr. John Piletz, whom I recruited at UCLA. He had just finished his fellowship in molecular biology and he had expertise that I didn't. He wanted to do research in neuroscience. So, that was a good marriage and he's still with me now. So, I made the transition from plasma MHPG to platelet  $\alpha$ -2 receptors, hoping

that this might prove to be a reliable marker for depression. And, when we reviewed the literature the findings were quite discrepant. There were studies that showed  $\alpha$ -2 receptor up regulation in depression, studies that showed no difference, and studies that showed fewer  $\alpha$ -2 receptors, so everything was possible. And, we couldn't sort this thing out until one day by serendipity, one of our technicians in the laboratory made a mistake in mixing up the buffer for the incubation of the platelets that made a ten-fold difference in the magnesium concentration. It was simply a mistake but the mistake resulted in resolving two binding sites on the platelet when we constructed the Scatchard plot. And, that was a very positive finding. After a lot of work, at least a year, we figured out that the assays that people had been using to measure  $\alpha$ -2 adrenoceptor on the platelet, was actually two binding sites lumped in one. If we changed the concentration of the buffer, we could separate out these two binding sites. One of these sites was the  $\alpha$ -2 adrenoceptor, but the other one was something else. Eventually, we identified that binding site as an imidazoline site, the site that also binds clonidine and clonidine-like compounds, but it is not an  $\alpha$ -2 receptor binding site. What struck us was that depressed patients showed very clear and consistent and statistically significant increases in this binding site.

LH: ...which were not  $\alpha$ -2 receptor binding sites?

AH: The  $\alpha$ -2 receptor sites continued to show some increases of minor degree, not always significant, but the imidazoline binding site was always unmistakably elevated. Encouraged by this finding, we launched several studies of depression. We now have a total of five studies and more than one hundred patients, some of which were done in Cleveland, and some of which in Mississippi. And, we have gotten consistently the same results. So, we now have an imidazoline receptor theory of depression.

LH: And, you think it's a fairly reliable marker?

AH: Well, it has been confirmed in five studies by us. It has been confirmed by Garcia Sevilla in Spain, and probably others, who are working on that story. It looks true and reliable.

LH: The trouble about depression these days is, that it is not clearly defined what kind of depression are you talking about, psychotic, melancholic, or whatever.

AH: Well, we use by DSM-III and DSM-IV diagnoses.

LH: So your findings are in major depression.

AH: Primary major depression, non-psychotic, unipolar, but even those groups are probably mixed bags. But, we've gotten this consistent information from this type of patient population.

We treated the patients for six to eight weeks, and in the first study, we treated them with desipramine; and at the end of treatment, we saw a normalization of the binding site, of the imidazoline binding site. It returned to normal levels. We think those patients who respond to treatment show the normalization of imidazoline binding sites. Then, I thought, maybe a non-adrenergic antidepressant might not show us this effect, so we did another study using fluoxetine and, lo and behold, we got the same thing after eight weeks of treatment. Then, I said, "How about doing, yet, a third study and let's use a different antidepressant drug." So, we picked bupropion. Of course, bupropion has mainly a dopaminergic effect, but it's a very different molecule.

LH: I always think of it as a tamed down amphetamine.

AH: Yes, very much so.

LH: The structure is so similar.

AH: Absolutely. And, bupropion gave us the same result. So, that's been our focus for the past seven or eight years, now. I moved from UCLA to Mississippi in '93 to become chairman of Psychiatry at the University of Mississippi, and, again, I moved my lab from LA with me. I feel like a turtle, who, always, takes his house and belongings with him.

LH: Your gypsy life began in Greece, went to Germany, Chicago, Los Angeles, Cleveland, and then, Jackson.

AH: And, I think that's probably the last stop. Now, in Jackson, I was given lots of resources by the medical school. And I set up ten laboratories where there was nothing before. I was given, very generously, an entire floor in the brand new Research Building that the University built back in '93. It was just opened as I was arriving there. So, Psychiatry has a sizeable basic science operation at the University of Mississippi. I'm very proud of our accomplishment.

LH: And, your clinical facilities are in the University Hospital?

AH: Yes.

LH: So, they're not too far away, either?

AH: No, it's three minutes, walking distance. The laboratories in the new Research Building adjoin the Hospital and the medical school, the Hospital is right down the hall. It's all clustered together very nicely. I can walk back and forth easily.

LH: So, in your recruiting for faculty, you are research minded.

AH: Yes, yes. We have ten PhD basic scientists in the department.

LH: Oh, that's pretty good.

AH: Yes. They each have their laboratory. They direct their own laboratory. A lot of them choose to work on different aspects of depression, but I leave them alone. They can do as they wish.

LH: That's the way to do it. Let them follow their own ideas.

AH: And, they've been very successful, all but one have independent funding from NIMH and NIDA.

LH: And, that's tough to get these days.

AH: Yes. I'm pleased to tell you, too, that I continue to have an RO1 myself. In fact, I just got my renewal grant application funded two weeks ago.

LH: I guess it'll go into two figures, a high two figures before you're through. One of the people you recruited was one of the residents at Houston, when I first came there, Peggy Pazzaglia, and she spent some time with Bob Post, and then, I guess she went to your place after that.

AH: Then she came to Jackson.

LH: And, then, you got a fellow, a travel recipient award.

AH: For Craig Rush, yes. He came from Hopkins. He had done a fellowship with Higgins. He is a behavioral pharmacologist. One of the things I wanted to set up was drug abuse research and I recruited Bill Woolverton from Chicago. Bill Woolverton had trained with Bob Schuster and he was an Associate Professor in Chicago and very successful, but he wanted to leave. He's from Alabama and he wanted to come back to the south.

LH: There's something about the south that's attractive, anyway, especially, when you've lived in Chicago for a while.

AH: So, Bill came down and he brought fifty monkeys with him. So, we set up a drug abuse laboratory and I said, "Well, this is fine. This is for basic animal research, but we need to add two more components to complete the picture." I thought we need to have Human Behavioral Pharmacology of the kind that Bob Schuster and Uhlenhuth had set up in Chicago. I learned a lot in Chicago and a lot of my models go back to the Danny Freedman era. So, we recruited Craig Rush from Hopkins and he set up a wonderful, very successful laboratory. Now, we're looking for someone to do the third component, which is a patient based program and we're working on that right now.

LH: Sounds like you've got a good blueprint.

AH: So, it's been a good twenty-five or so years, starting out in Chicago, and, before that, in

Germany.

LH: Well, it's nice to hear that Danny Freedman played a pivotal role in your career. He was such a remarkable person.

AH: He taught me an awfully lot and not just in psychopharmacology and "aminology."

LH: He was always so much fun to be around, too. I remember, after he got to be editor of the Archives, I said, "Danny, just because we've been friends, I want you to treat every manuscript I ever send in as objectively as if you didn't know me at all. Otherwise, my Presbyterian conscience would bother me." And he turned to me and said, "And, so would my Jewish conscience." I understand his wife died very soon after him.

AH: Yes, a few months later.

LH: I was dumbfounded to hear that.

AH: Yes.

LH: Well, you were probably at that seventieth birthday party for him that was in Washington?

AH: Yes, I was.

LH: I was there, too.

AH: That was in Washington, and, of course, you know, he moved to UCLA. I preceded him about a year. And, we overlapped for a year and a half, and then, I moved to Cleveland. He stayed behind. He did quite well at UCLA and then one morning, shortly after I had moved to Jackson, I believe it was in '93, I got a call from Steve Pachl. I don't know if you ever met Steve Pachl. Steve Pachl was Danny's right hand since the Yale years. Steve was a lab technician, who had administrative skills that Danny appreciated tremendously. So, when Danny moved from Yale to Chicago, Steve came along, and was elevated to administrative assistant. Steve's office was right next to Danny's. And, so, whenever Danny was out of town, he was out of town a lot, Steve was minding the shop. So, Steve called me up and said, he tracked me down in Mississippi, and he said, "You know, there's some sad news that I need to report to you now. Danny just died last night in his sleep."

LH: Did he have a cerebral hemorrhage?

AH: It looks like it.

LH: I never knew him as hypertensive.

AH: I didn't either. But, you know, he was chain smoking for years, non-stop, several packs a day.

LH: Well, I remember, after Danny died, writing to Mary and saying how great a time that seventieth anniversary party was. You know, you always find you have to pay the tributes to him and give him a good night and, then, I guess, within a year he died. Well, you've got a lot of future ahead of you. You shouldn't be on a history project yet. I ought to get you another twenty years from now.

AH: Well, I hope so. I hope so. I don't feel I'm anywhere near, even pre-retirement. I hope I can be active for at least another fifteen years.

LH: I would think so. How old are you now?

AH: I'm fifty-five. I just turned fifty-five last month.

LH: Oh, well, another twenty wouldn't be bad; although, we do, do die. No question about it. AH: But, you, also, have become a little more thoughtful, a little wiser with age. You don't jump the gun as quickly, and you don't jump at what appears to be a hot idea, as quickly as we used to in our youth.

LH: Was it Oscar Wilde who said, "Experience is the name we give to our mistakes"? So, I think most of us develop a lot of experience over the years. It's been nice talking to you.

AH: I don't know very much about this History project.

LH: Well, the project, I think, was Oakley's idea. He thought that before it becomes lost, completely, we ought to try to recover some of the history of this organization, because, now, after thirty-five or thirty-six years, it's getting a little long in remembering. So, this is just one facet of the bigger project, but the idea of doing video tapes is very attractive, because it's easy and it gives any future historian some source of really direct quotes. I usually try, in our interviews, to elicit information about people as well, who the interviewee knew, but who are now dead and try to let the dead speak through them.

AH: Right.

LH: So, the idea is to get older people. That's why I say, you're almost too young for the project, because the whole idea was to try to get people before we lose them, and you have to be realistic that nobody's going to last forever and, so, you want to try to get these things on record before it becomes lost. Already, we've missed a few chances, but, as I say, you're much too young to be part of history.

AH: Well, I hope I have offered a little bit of insight into Danny's mentorship. I see myself as being, basically, his brainchild. He raised me. What I have gotten from Norbert Matussek in

Germany was very, very useful and very good, but Danny really shaped me, and so, I have a lot to thank him for. And, he was patient with me.

LH: I think we're blessed to be in the field where you can get so much intellectual satisfaction and get paid for it.

AH: Right.

LH: That's pretty hard to beat. It's been very nice talking with you.

AH: I've enjoyed that. I enjoyed our conversation, too.

LH: Your story is of the classical success story in every respect and I hope it will continue that way.

AH: I hope so, too. OK.

## 15. JEROME H. JAFFE

LH: We're in Las Croabas, Puerto Rico for the annual meeting of the American College of Neuropsychopharmacology and we have with us, today, Jerry Jaffe,\* who is a long time member of this society, and also, a very prominent figure in the field of neuropsychopharmacology. I, also, have with me, Tom Ban, on the other side of the table and I'm Leo Hollister. Jerry, you've had such a remarkably diverse career that it's hard to tell where to begin. Why don't we begin with how you got into medicine, and more explicitly, how did you get into drug abuse?

JJ: I got into both, more or less, by accident. I hadn't planned to go into medicine. I became involved in psychology, as an undergraduate, much influenced by the Chairman and the Professor of Psychology, Hubert Hamilton, a wonderful man, but under appreciated by others because he studied animal behavior. I got very interested in it. Toward the end, I thought I wanted to do research in psychology. He advised me that, I guess this was back in '52, '53, there's not much support for that. If you want to do research, you should probably go to medical school.

LH: You were, then, an undergraduate at Temple?

JJ: I was an undergraduate at Temple. There were others that I knew that were influencing me in that direction. It was not something I looked forward to. I looked at it with the thought that pre-med was much more intense. But, I decided that I would apply to medical school, and then, found out that you had to take an exam a year before. I hadn't done that. So, I was left with some time left over, and I continued with some work I was doing and took a master's degree in Experimental Psychology. But, just about that time, chlorpromazine came out, and reserpine. The psychopharmacology was beginning just as I was making that decision, and the work I was doing on animal behavior looked like it would apply. And so, I went to medical school with the idea that I'd get the degree, and I'd do research in psychopharmacology. LH: That was in 1956?

JJ: I entered medical school in '54.

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\* Jerome H. Jaffe was born in Philadelphia, Pennsylvania in 1933. He received his MD degree from Temple University School of Medicine in 1958. Under the administration of President Nixon, Jerome Jaffe was the chief of the Special Action Office for Drug Abuse Prevention (SAODAP), an executive agency created by President Nixon. During his career, he popularized the use of methadone treatments for heroin addicts. He was interviewed in Las Croabas, Puerto Rico on December 1, 1998.

LH: '54. Boy, you really came in just at the hour.

JJ: Exactly at the beginning. I mean, I remember they were still talking about chlorpromazine as an anti-emetic. It was really at the very beginning.

LH: That was good.

JJ: Right. And in medical school, I didn't have any great direction about where I was going to go, how I would pursue that research. I got into trouble with the people in psychiatry, because it was an analytic school, and I was still using these scientific methods of deciding how you decide what is true. They did not like that very much. I would ask questions and they did not fit very well.

LH: Conflict between philosophies.

JJ: But, somewhere around '57, I was in the library and I came across Abe Wikler's book and that was a magnificent review.

LH: Oh, you mean that paper bound, *The Relationship between Psychiatry and Pharmacology*?

JJ: The paper bound, *The Relationship between Psychiatry and Pharmacology*.

LH: That was a classic.

JJ: It was a classic, and by that time, I'd had a summer fellowship in psychopharmacology. There was one professor; he was an assistant professor of pharmacology, Sidney Ellis, who felt I had some promise, allowed me to work for the summer doing something and that was a good experience. And then, Wikler's book came along, and I was pretty well set that psychopharmacology was where I was going to go. And then, it was just about the time that you had to choose your internship, and I thought, gee, Wikler is at Lexington, and that's, obviously, the place to go to study with Wikler. But, I didn't know enough about the bureaucracy, and when I signed on the dotted line, I realized that I had committed myself to the clinical division and they were going to use me to help staff the hospital at Lexington. And, I didn't realize that, actually, Wikler was in a separate division, the Addiction Research Center, the same building, but administratively quite distinct. But, after my internship in the Public Health Service, I was assigned to Lexington. At least, that much was fortunate, and I did get to meet Wikler, and that was sort of the beginning of how I got into that role.

LH: Lexington was the field of all those giants in the field.

JJ: There was Wikler, Isbell. Bill Martin was there, but then, there were people doing even work in the sociology of addiction. Jack O'Donnell was there. It was really quite a remarkable place.

LH: And, you had the good sense to go there. So, I guess, prior to going to Lexington, you were, generally, interested in psychopharmacology, with Lexington steering you to go into the addiction field.

JJ: I think that's so. I didn't start out being interested in addiction, in any way, but once I got there, I sort of, I was still interested in psychopharmacology, in a general sense. And they wanted me, at the time, you committed yourself to a residency, and the more time you put in, in the residency, the more time you put in various assignments within the Public Health Service. I looked at what Wikler had done with his career, and I spoke to others, and it's clear that he studied basic science before he really got into psychiatry. And I decided that I wanted to study more pharmacology before I got into dealing with, what was then, I guess, the dominant dynamic perspective of psychiatry. And then, Sid Ellis, who was that professor at Temple, who gave me that summer fellowship, suggested that I look into Al Gilman's department. Now, that was kind of awesome, because we had used Goodman and Gilman as a textbook. And I, when I was leaving the Public Health Service, applied to what was then an interdisciplinary program in the neurosciences at Einstein, where Bob Gilman was Chairman. And, much to my surprise, they said, "We'd like to have you." That was very nice, and I met Sid Sharpless and Murray Jarvik, and it was really a new world, really bright sharp minds. And Al Gilman said, "You know, what would you like to do"? Well, nobody ever said that to me before, what would I like to do? And, you know, I got to talking with Sid Sharpless, and he'd already been working on plasticity in the nervous system, on the concept of supersensitivity, changes in neurosensitivity with deprivation of input. And then, we began to elaborate the notion that, maybe, some aspects of opiate withdrawal or, maybe, withdrawal, in general, were due to denervation supersensitivity, or at least, functional reductions in sensitivity. And, that was great. We elaborated on it. We came up with a series of experiments and that's sort of how I proceeded.

LH: I see where, in 1969, you and Sharpless wrote a book chapter on "Withdrawal phenomena: the manifestations of supersensitivity."

JJ: Well, actually, we started even long before '69. We began this in about '61. We got our first experiments done, and we actually published an abstract in about '63, on "Barbiturate withdrawal, innovation supersensitivities." But, just as we were about to say, "gee, isn't this a terrific idea", Inland published a review in Pharmacologic Reviews, I think, on denervation supersensitivity in the central nervous system. He'd been working with the salivary gland as a

model, but he, obviously, saw the implications for the CNS. If you pharmacologically block the actions of an agonist, you get a change in the sensitivity of the post-synaptic element, and so, we recognized that he'd gotten there first. But, we proceeded to talk about this and to work on it, and you know, it was clear that probably the changes were not just at the receptor. There might be some intracellular changes that probably accounted for the changes in sensitivity. But then, some other things happened.

LH: Now, this is about the time that a number of theories that still are, I guess, standard in the development of tolerance and dependence. I think, Avram Goldstein presented one, Joe Cochin, and Lew Shuster, all three of them, almost simultaneously.

JJ: And they all presented at a meeting that Abe Wikler convened on the addictive states. It was published in 1968. I think it took place in about '66 or '67. And, we, also, presented the notion of supersensitivity as one of the phenomena that might explain withdrawal. And it was a great meeting, and Abe was there, of course. But what had happened in those intervening couple of years, was that we had a small heroin epidemic in New York, and the number of people, who knew anything about addiction then was very, very limited. You might recall that, basically, doctors were supposed to stay away from addicts.

LH: Psychiatrists wouldn't even take alcoholics as patients.

JJ: Exactly, and so, because I'd come from Lexington, everything that came up to do with addiction was referred to me, even though I was still a post-doc, and at this point, a fellow; but I decided that while I was studying this, I ought to go back and finish off the psychiatry. I had one year, and so, I simultaneously managed to get it all done. So by '64, I had finished a residency in psychiatry, was still working with Sid Sharpless, still in Gilman's department, and then, you know, it seemed like the world was changing. Addiction became a major issue. I got involved in clinical things, and then, some of the issues that had to do with Lexington continued to come back. For example, Bill Martin published on his work with cyclazocine, so there was an antagonist that allowed one to test Abe Wikler's theory, which was a theory of conditioned phenomena as an explanation of withdrawal.

LH: Conditioning, abstinence, and withdrawal.

JJ: Yes. And possibly, you could block the re-initiation of physical dependence with an antagonist. After a while, there would be no reinforcement, if people relapsed and took the opiates. And then, here at last, was an antagonist that you could use to block the receptors.

Now, that was stirring. I'm not sure we knew there were receptors, then, but we knew you could block the effects of opiates, though.

LH: Well, Bill Martin was then beginning to focus in on the multiple receptors.

JJ: Well, he said that in '67, but the notion that there really was a receptor wasn't particularly clear, as this was '64. We knew that it blocked the actions of opiates. And the nature of regulatory processes, at that time, was such that, in a matter of three or four months, I was able to get an IND and get some cyclazocine from the company. And I had all these people, who knew me at Lexington, who'd come back, and they were calling me up, saying, "Don't you have anything that we could do; what kind of treatment can you offer?" And we, actually, tried cyclazocine, got it published in '66, and that was the first clinical trial on cyclazocine ever done. And, the amazing part was that here was a drug that didn't give you any real reinforcement. As a matter of fact, it had some adverse quality.

LH: It was a mixed agonist antagonist, wasn't it?

JJ: Yeah, it was, but people wanted to quit badly enough that they would try it, and that didn't surprise me. I met a lot of people at Lexington who worked, and I thought were likeable people. I didn't have any of these kinds of images of addicts that the world had, because I had met some of them. So, somehow, by '66, I was so deep into the notion of working on addiction, I mean, on the basic science side. I had won a research development award to work on the basic mechanisms of physical dependence, perhaps pursuing the notion of supersensitivity and what are the post-synaptic changes. And then again, fate intervened. I met Vince Dole. I was trying some things on whether or not addicts do, indeed, develop so much tolerance to opiates that you have to escalate those, item for item. I did a study, not well known, as I never published it, where we were providing intravenous opiates to a select group of addicts. I got visited by the Bureau of Narcotics about every two weeks. They were quite respectful, but they wanted to know exactly what I was doing. And just about that time, this was about 1965, I guess, I heard of Vince Dole, heard him give a talk, met him, and tried methadone, and there was something very, very different about the addict's behavior; so, it sort of confirmed what Vince had found out. On a single oral dose of methadone, they felt different. It was a lot easier. You weren't spending all your time negotiating doses, and so, I did some work with methadone. But, I realized that the issue of people coming back every day, and I did probably the first stabilization on methadone, at that time. This was still at Einstein, but when I left Lexington, Wikler, Isbell, Frazier, Martin, they gave me the

reprints. These were, I guess, in '63, '64. There was about twenty-five years' worth of reprints and I read them all, because I'd been asked by Gilman, at the time, to write this chapter in his textbook. When the third edition came out, it was multi-authored. So, I was the first person to write on opiates in the multi-authored text. I was pretty junior, so I tried to read everything I could, and I read all of these reprints and I came across a drug called l-alpha-acetyl-methadol. It had been totally forgotten. People thought it was too toxic, and I realized that if you gave this drug every other day or every third day, this could be even better than methadone, because it would reduce the compliance work for the drug user. So, I thought, gee, isn't this wonderful? And, I tried to write up a grant, and it was a good grant, but then, I said, so where will I do this treatment? I'd done this cyclazocine, actually, in Sam Barondes' office. He had this little room, tiny little room, maybe eight seats outside of his lab, and he'd allow me to use that to do a little group therapy on the cyclazocine. But, I couldn't imagine people coming back every single day to pick up the drug. And, I didn't think one should give it out for self-administration. I tried to find a place where I could do this study, and this was, I guess, about '66, and nobody in psychiatry was interested in addiction. It was not something that they wanted to get involved with, and I looked around to try to find a place where they would allow me to do it. At the time, we had an empty TB hospital. It had been a TB hospital. TB was no longer a problem. It had all these empty floors. I tried to get one room where I could do this, and "No, we don't have any room." They had rooms filled with old iron lungs, but they couldn't find any space, so, I could put in this grant, but I was not about to put it in if there was no place where I could, actually, implement it. So I said, "Maybe this is not the right place to do it." And again, chance intervened, and Danny Freedman asked me to come to Chicago, and that came about because I had a chance to put on a symposium on drug abuse, and Danny was the obvious man to talk to about LSD. He was the world's expert on LSD.

LH: But, hadn't you published on acetylmethadol before that? I see a citation here with Bob Shuster and Paul Blatchly.

JJ: Yes, that was in, I think, '68 or '69. But, what happened was, by the way, I also had the drug, because I knew Paul Blatchly. He had a supply left over from the analgesic trials in the early sixties, so this was only the mid-sixties, so he still had some, and we were going to collaborate on that, but there was just no place that I could do it. I don't think he had enough heroin addicts out where he was, at that time.

LH: He was in Portland, wasn't he?

JJ: Yes, that he could do it. And Danny met me during the symposium, and he had been offered the Chairmanship in Chicago. Illinois had nothing going in this area, and he asked me if I would come out. And I said, "Yes", because there were some things I wanted to do. I was moving, obviously, into some interest in clinical psychopharmacology. But, one of the things that I wanted to do was to study LAM. That's what we called it at the time. And by '67, I got out there, and the rest of it has to do with the Illinois Drug Abuse Program.

LH: But, before we leave LAM, isn't there something of a frustration for you to be one of the first people to use it, and then, find that it takes another thirty years before it can come into general use?

JJ: It was only about twenty-four years, I think.

LH: Well, I thought the general use of LAM was only a few years ago.

JJ: Well, I think it was only from about '68.

LH: And, you were studying it from '68?

JJ: Well, it was a tremendous frustration, but I guess, you learn that government doesn't always see things with the same sense of urgency that the clinician does. And, as you recall, I got an opportunity to actually expand the use of LAM, briefly, in the early seventies. And then, for a variety of reasons, it sort of got put on a back burner, and it only, I guess, in '93 or '94, got approved for use.

LH: I think so. I had a little later date in mind, but it was somewhere in the nineties.

JJ: But even after that, the problem was that it still had to be approved at each state level, because it was still a Schedule I drug; so, although the Federal Government finally said, "Now it's approved", it took work at every state legislature to get it into a schedule, from Schedule I to Schedule II, where it could be used. Yes, it has been a very, very slow process, but it's used in some other countries now, and it'll probably be used here, at least, to some degree.

LH: Now, before we go into the Chicago part of your story, tell us about Abe. What sort of a person was he? He must have been a remarkable man.

JJ: Well, Abe had this notion that was different from most of the people in psychiatry, who felt that addiction was a manifestation of some underlying psychiatric defect. That was the dominant view, at the time. But, Abe said, you know, "Whatever its origins", and he had some views on its pathophysiology, but once it developed, it was *sui generis*. It was a thing unto itself. And I always said, I actually wrote one of the obituaries for Abe, Abe was *sui generis*. He was in a class by

himself, a man of incredible intellectual capacity, intellectual breadth and depth. He seemed to have read everything, remembered everything, and critiqued it.

LH: And that book of his that got you started, it was phenomenal that one person could do all that.

JJ: Yes, that was the amazing part of it, that anybody could have completed that review, to have read all those papers, to have summarized them, to have seen their relationships, and critiqued them. Now, you would have expected some kind of sort of distant, scholarly, introverted person; but Abe wasn't that way. Abe was, actually, quite humorous, a man, easily approachable. I don't think you wanted to ask a stupid question in front of Abe.

LH: He didn't suffer fools.

JJ: No, he did not suffer fools, gladly, but he was helpful and encouraging and a good teacher, altogether, somebody I admired and was much influenced by, not just in terms of that he sort of led me into whatever paths I've walked, but because he was smart, funny, and inspiring in some way.

LH: Yeah, well, I'm glad to hear you say that, because it's evident, from that book that he was a real scholar.

JJ: Well, the thing about him, when you got to hear about it, is that he'd, actually, set out to study with some of the best people in the world, including when he was trying to understand conditioning and how learning played a role in the actions of drugs, he went to study with Pavlov. He learned Russian to do it.

LH: Oh, God.

JJ: No, he learned Russian, he read Russian, and there were equally impressive number of people that he'd, actually, taken fellowships with. I'm trying to remember some of them, really great physiologists. There were some at Yale that he went with for six months studying neurophysiology. Because, when you look at some of his early work, you see some of the work on reflexes at the spinal level, and a lot of it reflects some of the work that he did at Yale and other places, when he took these sabbaticals and studied for it. They were not sabbaticals. They were part of his self-training for the Public Health Service, to prepare himself. That's who he was, he knew basic physiology, as well as anybody else, but he had this vast wide range of knowledge of things, remarkable things.

LH: Well, you were lucky to have had him as a mentor. Okay, so Danny invited you to come to Chicago, then?

JJ: I guess he invited me in early '66, just at the time that I was concluding that Einstein really did not have enough interest in addictions to help me move the obstacles out of the way, so I could start a clinical program. And, with some reluctance, I said, "Yes." And then, Danny had been asked by the Governor's Advisory Group to provide them with advice on what to do about the addiction problem. And, by this time, I had become aware of at least three major ways you could deal with heroin addiction. There were maintenance approaches, methadone, LAM. There were conditioning approaches, drugs like cyclazocine, and perhaps, its successors. I think naloxone was just coming out. Naltrexone had not yet come out. And there were therapeutic communities. I had met the people at Staten Island. David Deitch was quite courteous to me and I'd learned there's something special going on here. This is not psychotherapy, but it works. People changed and they got better. And, then, of course, there was detox. We had detoxed lots of people at Lexington. I took care of about three thousand people during my year of exile.

LH: But, the recidivism rate was very high.

JJ: The recidivism rate was very high, but it wasn't a hundred percent.

LH: Some people were very visibly shaken, right?

JJ: Some people got better. Now, why? And, given that you have these four approaches, how do you decide which one you to use, tell someone to spend a year in a therapeutic community; do you put them on methadone; try antagonists; or just do detox? Well, that was a major question when you had more than one approach as to which one might be best, and basically, that's what I told the Illinois Drug Abuse group. Danny had many, many interests, as most people know. I mean, he was a major mover and shaker in the whole world of psychiatry, and particularly, in the research aspects of mental health. And so, he didn't attend all of these meetings, himself; I don't think he attended more than one. So, I was, sort of, the representative of psychiatry at this meeting, and they first considered civil commitment. That was the thing in '66. As you know, the Federal Government decided, oh that was another route, by the way, compulsory treatment, and the Federal Government had just passed the Narrow Act in 1966, which should have required people to stay six months at Lexington, after which they had supervision. And, that was still another approach to treatment. And, Illinois was considering that; they were considering therapeutic communities. They had not considered methadone, and they were just debating which of these things they should do. And I said, "I don't see that there's much debate. There are no facts. The only thing you can do, in terms of a statewide level, is decide what is appropriate for

the people in Illinois. Or you can build, at least at some level, all of them, and try to develop a program that would compare them. And then, when you see which is most effective, scale it up."

LH: That was a novel idea.

JJ: It seemed so logical that I couldn't believe it was novel, but as it turned out, it was novel. But, it was absolutely logical. How do you decide which of several treatments you use? You do an experiment. Well, apparently, states and governments don't usually do that, but they pondered this, and no matter what they came up with, they concluded, "You know, this is logical." And so, they put in a bill to the state legislature. Now, this was early '67, or maybe, late '66, and it was a little strange, because it really said, we want money to do this, and they weren't proposing a single program, but they were proposing something called a program that would compare the alternatives. And, at the time, they had asked for, what was then, a lot of money. It was about a million dollars, and that was big money then. And, I had had my Research Career Development Award to study things, and Danny had given me laboratory space, and I was prepared to do that. I was a researcher from the laboratory, giving advice based on some peripheral reading about treatment, and what I was told by the Chairman of this Narcotic Advisory Council is, "We'll do this, but only if you'll agree to run it." I didn't know how serious he was, but I saw it as the major moral dilemma of my career or my life, as a matter of fact. I had a Career Development Award to work in the laboratory. But, by this time, I had met lots of people. I was going back out there, over the months, giving them this advice, I guess, from mid '66 to the beginning of '67. And during that time, I began meeting people in Illinois, addicted people who had partially recovered, and they were decent people. And Illinois did not have one single place where you could get outpatient detoxification. If you wanted to get detoxed, you pled guilty to an offense, they put you in the jail, and a kindly nurse would give you some chlorpromazine, something like that. That's all they had. There were no facilities, no long term, no short term. There was nothing. So, I felt it was sort of on my shoulders whether or not Illinois would change, and I felt that I really didn't have a moral option to just go back to the lab. And so, I said "okay." And that put me in a position of starting, as sort of an N of 1. How do you get enough people to implement three or four different modalities, build them, so you can scale them up, so that you can then compare them? And, that was not an easy task, and I guess, within a year, it became quite apparent that you cannot be competent in the laboratory, build that, pursue that, be the head of a state government program, and also, the only clinician trying to train everybody else in how to do all of these things. And I

gave up the Career Development Award, and Danny was kind of angry. He said, "You don't do that."

LH: That was altruistic.

JJ: Well, no, it was not altruistic. I mean, how can I send in annual reports on work I haven't done? The work, trying to build this thing, was an eighteen hour a day job. When do you want me to spend time in the laboratory? Yes, he was a little unhappy, but I thought it was the honorable thing to do, and that's what I did. And, I was the Director of the Illinois Drug Abuse Program and built it. And, we did a lot of innovation and Danny was very supportive, actually, except for giving back the money.

LH: It's so hard to get.

JJ: Well, I didn't know that. I mean, you have to remember, I was only about thirty or thirty-one. I didn't know how hard it was to get money. I'd never had any difficulty with that before. I mean, I was on this post-doctoral grant when I was with Al Gilman, and I put in this Research Career Development Award and I got it, and so, I had no idea it was hard to get money. And then, when I came to Illinois, they gave me a million dollars to do this, and I just had no appreciation of it. But, Danny was tremendously supportive in terms of finding me space to do all of this. We had space for a laboratory to do drug testing. We even had the university find us space to put in the first methadone clinic, and we found further space, and the state helped. And, we even found space within the hospital to run a detox ward.

LH: Was this in the Billings Hospital?

JJ: In Billings.

LH: So, you were working all over the South Side?

JJ: Yes, originally, it was supposed to be on the South Side. We had a methadone clinic, we had a detoxification unit, where we could use cyclazocine, and I was recruiting, and I brought some people in, to start a therapeutic community. We didn't get any help from NA. NA was just not interested in being looked at or evaluated. So we started our own, using people who had trained in those methods, found a place, and began to build that. And within a year, we had a model of a therapeutic community; we had detoxification, using cyclazocine, still, because there was no other antagonist, and we had methadone going, on an ambulatory basis, and probably, within that next year, I was able to recruit some good people, Bob Shuster, for example, and Pat Hughes.

LH: Ed Senay?

JJ: Ed Senay was already there. He was head of Consultation Liaison. Ed did not, actually, take a real interest in drug addiction for another two years, because he still had a major role with Danny, running the Consultation Liaison service. And so, we were doing these things, but within a year, we had conducted the first experiments on LAM. So, things were really moving along and that we continued to innovate, build it, and expand it, and we, actually, did a random assignment study of randomly assigning people to therapeutic community, methadone, or the detox unit. But, it turns out that was really a naive idea. You can't really assign people to something they don't want. I mean, they've heard of something. They know what it is. That's what they want. You can't assign them to something else, even if you have a monopoly, and the only treatment available, the ethics of it is questionable, I think.

LH: Different strokes for different folks.

JJ: Well, the point is that, that's what we were trying to find out about, but the drug users, themselves, already had some firm ideas about what would work for them. A lot of them had no interest in spending a year in a therapeutic community. They would rather stay on the street. And, others knew that methadone would help. And others didn't want methadone; they only wanted detoxification. And, to randomly assign them, was equivalent to saying they were going to drop out of treatment. And, we did that for a while, but it became so apparent that the attrition rate was so high that when we'd start to look at the data, this data didn't mean anything. And, this is before they talked about intention to treat as a major design issue in psychopharmacology.

LH: It was due to a lot of untreatable...

JJ: No, it was intuitively clear that, and I tried to present that data, Paul Lashley had a later conference and we showed them the preliminary stuff. I said, "But, it doesn't mean anything if people vote with their feet for a particular treatment, and absolutely refuse to participate in another, then you can't really directly compare them." And so, we expanded and continued to build that program, and the amazing thing was, we didn't think there were that many drug addicts in Chicago. And the number of people, who came forward seeking treatment, was incredible, really quite surprising. And, we had waiting lists and things of that sort. And it seemed like, not that the research became secondary, but the research had to take a sort of a parallel role. As you said, our responsibility is to expand this, because people were getting better. You could see lives change, people who had been in and out of Lexington, and things of this sort, changing their lives. And this was sort of unusual because it deviated from the usual psychiatric dictum that you maintain

distance; you don't get involved with the patients. We got involved in their lives. We got to know their families, their children. The line, that was the great insight that you got from the therapeutic communities, you cannot maintain this very sharp bright line between who's staff and who's a patient. If you did, you sort of generated what happens in the jail. It's us vs. them. But, if you blur that line, some of the former patients became staff members, and really high ranking staff members, eventually. People saw themselves as participating in a joint enterprise to get people better, and there was a kind of an esprit de corps that was quite remarkable in the program as it expanded from several hundred to several thousand. And, that's what happened in the course of a few years.

LH: How closely was Danny affiliated with it?

JJ: Well, Danny knew about it. He saw it, and he allowed me to be simultaneously, you know, on the faculty. Nominally, I was a state employee. I was the Director of the Illinois State Drug Abuse Programs, but Danny was, in his own way, running interference for us, he was sort of like the forward line behind some kind of running back or quarterback, that he found space for us; he got the university to back us. The university has a lot of power in Chicago, and that was important. I didn't realize how important it was, at the time, I think, but there's no question.

LH: Even getting addicts admitted to Billings was quite a feat.

JJ: Oh, yeah, that was something. That was really quite an achievement. But, remember, the University of Chicago is sort of surrounded on that side, and it viewed itself as an institution that tried to do good for the community, as well as to be a scholarly place. And, this certainly was doing a lot of good for the community. So, there was a certain synergy of mission. But, I did, actually, continue some research at the laboratory level, and Danny and I published this study on cannabis together, and a few other things continued.

LH: Well, somewhere along that line, you must have attended a CINP meeting. And, when Tom Ban asked me to review that meeting and I looked over what you had to say about substance abuse. And thirty something years later, it's still true, I mean every aspect of it, just change the names of the drugs a bit, but it is still true.

JJ: Well, Abe was the one who asked me that at a CINP meeting. Abe keeps reentering my life. This was in a '66 or '67 meeting. Abe asked me to come to it. I wrote this paper, and we talked about all the ways that people were approaching the problem of addiction, from civil commitment, compulsory treatment, to detox. I said, "You know, this is the mission, to find out

what works best for whom." And, I guess we're still at it, in one way or another, and I don't know that we've actually solved that simple problem of giving a patient, what you think will work best.

LH: Well, that's true of all psychopharmacology. You could use a dart board.

JJ: It may be what you've learned. What we have learned is that all of them work, to a certain degree, and you have some notion that if the patient really wants to do something, maybe that's a good reason to select that one first. You really have a number of effective treatments.

LH: The same way with antidepressants, if the patient had a good response before, it's foolish to try something else.

JJ: So, yeah, that was an interesting paper, I don't know, but I'm surprised anybody remembers that paper, but that was back in '67.

LH: It could be published today by just changing the names of the drugs and it would be very contemporary. Well, I guess, you must have gotten some fame, but how did you come to President Nixon's attention?

JJ: Well, the Illinois Drug Abuse Program, actually, became one of the models. Remember, the state was putting up money to be able to say that this is really the way it ought to go. New York was putting up money, but its' great thrust was, remember, they were building large buildings for civil commitment. And the city was putting its money into therapeutic communities then, under Henry Brill's influence, actually, and they made sure that they had enough money for methadone, as well, with Vince Dole. I should mention that, in the interval between leaving Einstein and going to Chicago, Vince Dole invited me to spend six months working with him. So, I went down there and I talked to them, so, I got to know those people reasonably well, Vince and Marie, and they were very kind to me. But, what happened was that then the government, I guess this must be about '68 or '69, was finally implementing a small piece of the 1966 Narcotics Act, and by '68, the government was beginning to give grants for community based treatment. Well, we were there ahead of this. We got one of those grants. Now, we had money from the Federal Government for community based treatment and the state government.

We were, I suppose, viewed, because we had gotten this early start, as a place where new grantees should come and see what we're doing. Now, I guess, the unique part of Illinois, that made it distinct, I say, from New York, is that there was not this sense of bitter rivalry. There were people, who were taking methadone, working methadone programs, who actually came from therapeutic communities, and they needed to learn how to do group therapy. And, so, they went to the

therapeutic community we had set up, to see how they did it. And, there were some people from the therapeutic community, who realized, you know, if someone didn't want to come in, they shouldn't just say, well, go out and die on the street. They'd say why don't you go in the methadone program? So, we used to have these meetings together, with people from varying perspectives, sitting together, talking, not just civilly, but as colleagues, of how we're going to deal with the problem, how we're going to help most people. And, that was very different from New York, where there was bitterness between methadone and therapeutic community and even the civil commitment. And, some of that persists, even today. And, in fact, there's a kind of a resurgence of that bitterness between different treatments. In New York, the mayor is currently saying, methadone is not appropriate. I guess this happens from time to time. So, people would come to Illinois, and we would show them what we were doing. For example, Griffith Edwards came early; Benny Primm came; Bob DuPont came; I guess Herb Kleber came; and we were happy to show them what we were doing. We didn't view this as sort of academics, so much as practical application of what we were learning, for the public health. And, they went back and built their own programs. Bob DuPont built a scaled up, with some help from the White House, a major program in Washington, D. C. It was, mostly methadone, as I understand it, but his support came through the city of Washington, D. C., which, in turn, was encouraged to do something about crime, because, I guess, it was '68. Nixon was elected in '68.

LH: I think it involved a Nader report that crime was diminished among people who were getting methadone. That went well with the White House and they went all out for it.

JJ: Well, I'm not sure there wasn't something going on to help Bob get started, but you can ask Bob about that. But, there's no question, that then, there were some supportive people in the White House. Once they got the Controlled Substances Act finished, there were some young people, Jeff Bonfield, Bud Crowe, who were saying, you can't stop here. There's something that can be done on the, so called, Demand side, actually, dealing with addicts, themselves, instead of just trying to keep the drugs out of the country that we ought to look at. And Jeff Bonfield was sent out on this reconnoitering mission to look at programs, and Bob said, "Be sure to go to Illinois." I'm not sure we would have done that, but for Bob. And, I'm sure he visited New York, and he saw those programs, and I guess, he visited a number of places. And, he came out there, and I treated him pretty much the way we treated anybody else who was coming to visit, a long stream of them. I would say, "Take a look; here's what we do." Then, he asked very pointed questions about how

we decide what we're doing, and I told him our perspective on building that which worked, keeping track of it. We had a fairly efficient way of funding things and looking at them and managing them. We were very early in getting into computerized data. And, Jeff went back, made his report, and then sometime around September 1970, he called and asked me to write a report for the White House on if we were given more money, what we would do about the drug problem, and he wanted it in six weeks, and it had to be absolutely secret. "If it leaks at all," he said, "It'll be of no value." And, in my range of acquaintances, I didn't know very many people in the scientific community who would want to work for the Nixon administration, No. 1, and No. 2, who could keep their mouth shut that long. But, I tried. I called. I didn't think it could be done in six weeks. I persuaded him to give us eight weeks and this was a fascinating group, because it was almost a sub-group of the ACNP. Okay, who do I get? Okay, Sid Cohen, Jack Mendelson, Jonathan Cole; I got Jack O'Donnell. There might have been some more ACNP members, who came. But, it was a really fascinating group, and we got together and we tried to write this report, as best we could. Ed Brecker, who wrote that book for Consumer's Report, Illicit Drugs, came sort of as our scribe. LH: He was a very good reporter.

JJ: Yes, and we sat for about four or five days, Helen Knowles, I think, was part of that, as well, and we wrote this up. We wrote a report, and then, I worked for another two weeks, Ed Brecker and I, trying to put it in some kind of neat form. We didn't have that much support. We typed it up and sent it in, and it differed from the report that the White House had solicited from its various agencies. At that time, the dominant thinking was probably a combination of, I think it was more sociological, that addiction springs from poverty, deprivation, and joblessness, unless you do something about that, change society, you can't do much about it. And, their view of methadone, I think, was that it's an interesting experiment but it's only an experiment. Whatever you do, don't expand it. Now, this was, remember, we're moving now into 1970. Vince Dole had been expanding. We had been expanding. Other people had been expanding, but without any formal support from health authorities, because you can't support experimental work on a large scale. And, so, even though the demand for that kind of treatment was overwhelming, literally thousands of people have said, "You know, I would rather have that treatment than continue using heroin." The government was saying, it's only an experiment, we can't do anything. At least, it was that part of the government that was chaired at the time by NIMH. I could go into the personnel, who were writing that report, but I'm not sure that's really germane.

LH: Don't mention names.

JJ: We had this report that said, look, if you have this much money, the first thing you need to do is to stop the pretense that something that is treating, I don't know, five or ten thousand people and has been used for five years, is only a small experiment, and you ought to make it available to all those who need it. And, then, there were a whole bunch of other things that we recommended; that basically, what we were recommending was NIDA, that there ought to be some organization in government, not just a little piece of NIMH, but an entity that has both the intellectual capacity and the staffing to look across what government is doing; what's happening in terms of prevention; what are you doing about research; what are you doing about finding out what works; what are you doing about basic research. I mean, all of that needs to be coordinated in some coherent way, so you know what you're trying to achieve. And, we felt, maybe, this would be somewhere in, at the time, Health, Education and Welfare. And, that's pretty much what our concept was, and that's what we recommended, and I think that if you interviewed Jonathan Cole, he'll probably have the same memories of it and Jack Mendelson, as well. They were key people and there wasn't very much dissent. We all saw it that way. And of course, we had to deal with marijuana, LSD, and all the other drugs, as well. Sent it in, didn't hear much. (I got a thank you note, by the way, somewhere in January. It said, thank you. It was very kind, but non-committal.) In April of that year, as I recall, maybe late April, I got a call from the White House to come down. By that time, I guess, I became one of their experts on drug abuse and they had asked me what I would do about the heroin use in Vietnam.

LH: Oh, dear, that was a hot ticket.

JJ: It was a hot issue. We had not known about it when we had written that report, which was late in December 1970, not a mention of a problem of drug use among military people in Vietnam, a total shock. And then, Congressmen Steele and Murphy, I think, from Illinois, reported that they had visited Vietnam, and fifteen percent of the servicemen were addicted to heroin. That's a big number. And, at the time, they were going through this demobilization of bringing back a thousand every day, to turn loose in a country that doesn't have adequate treatment. Most people could not get treatment, so you were turning those loose, and there were all these dire predictions of what happens when heroin addicts make other heroin addicts. I mean, there was this mystique or mythology that heroin addicts would run rampant through society, and certain congressmen were talking about expanding a major compulsory treatment program, civil commitment for two years

for everybody. All kinds of things were said. The military tried everything it could. It had, obviously, resources to control supply, add electronic things and all kinds of things that were aimed at the war effort, but they simply could not bring the heroin under control; they could not control the supply of heroin.

LH: I've made a number of bad predictions in my life, but one of the best ones was that this epidemic is a situational thing, and will subside when they get back, except for those who were addicted before they got over there.

JJ: Well, that was the point. Except for those, you know we did not know what would happen when they got back and nobody knew.

LH: Well, you know, there's something that nobody has ever brought up. Where did they get this entirely, ninety-five percent pure heroin? You know, that's not easy to make.

JJ: Well, apparently, it was coming across from Laos, Cambodia. The golden triangle was still there, and there was traffic there and they just weren't cutting it very much, but that was the situation. And, I had some notions. It was pretty much to me, almost self-evident, about how to compare treatments, and I just told them, okay, what I would do. Well, I said, first of all, I found out what they were doing, they were offering amnesty to people, who would volunteer that they were addicted. Well, sure. You wouldn't be subject to court martial, but you would get the worst jobs possible, thereafter, and nobody was volunteering for amnesty, to speak of. And, one of the issues was what you could do to identify those people who were dependent, to deter those people who are not already dependent, and to get some feeling as to whether the numbers that have been bandied about, fifteen percent addicted, had any relationship to reality. And, what I suggested was a method that would accomplish all of those, that would get the epidemiological data, that would act as a slight deterrent, and that would identify those people that require treatment. It was fairly simple. I don't know why it wasn't obvious. But, I said, "What you need to do is to test people; do urine testing, and when you find someone who is dependent, you will detoxify them, and after a while, when you have gotten that much done, begin random testing. That will give the message that you really can't use heroin with impunity, and that when you find somebody who's used, you either put them in treatment or put them under a condition that if they ever test positive again in the next six weeks, then there'll be some consequence, as you might have in any employment situation." Well, they said, "Wait a second." I said, "Well, but you'll have to make some changes. As I understand it, if you find somebody who's heroin positive, you court martial them." That was

the code of military justice, at the time, and people were getting dishonorable discharges and bad conduct discharges. There were all kinds of horrendous consequences for drug use. And I said, "So, you'll have to change the code of military justice. You can't do that testing, unless you make this a medical procedure."

LH: Now, by this time, had you been appointed to this special office?

JJ: There was no talk of this special office.

LH: Were you still a consultant?

JJ: I was a consultant. I was head of the Illinois Drug Abuse Program. I was just giving some advice. I said, "This is probably what you ought to do." Now, I had one special tool that I knew of, that the military didn't know of, because they did not know very much about rapid drug testing. They were using only gas chromatography and things of this sort, but I had learned a little bit from Vince Dole about rapid screening. I think I was coming back from a CPDD meeting, I think it was, and I sat in the plane next to Avram Goldstein, another member of the ACNP. Avram told me about an invention, which allowed you to do, basically, an enzyme based identification of heroin, which would do it in a minute.

LH: Enzyme linked absorbance assay. I think it was Synthex and Zacharoni's company.

JJ: I've forgotten which one it was, but Avram had worked with these two companies. One of them, I think, made electronic stuff, but Avram had one machine. He said, "There are no other machines." I said, "Gee, I'd love to get one for Illinois," and I bought one, and the state of Illinois had one on order that would be coming in. So, I knew that you could actually do this screening, physically, using these essays. And, if you could do one a minute, you didn't have to have sixty machines in Vietnam, and the White House should have bought into this. They sent me over to present this to the military, and I told them this is what I think you should do, and they said, "Well, we don't need it. Maybe we'll get around to it sometime." And, I had the idea that the President wanted this done right away. He didn't like the idea of addicted people coming back with no treatment. I mean, I was in a room full of generals, with the Secretary of the Army, and they thought I was saying something that I really wasn't saying. They thought I was saying, "If you can't get this done the way I want it done, I won't mix my fire anymore." That wasn't what I meant at all. But, Nixon had that reputation. He doesn't like somebody, who can't get it done. So, he went in the other room and they broke up the meeting. He came back five minutes later and said, "We'll get it done in two and a half weeks." And, I had, about a week before that (it was Sidel,

the corporation that made it, by the way), on the chance notion that this might go through, I called the guy up and said, "If you were to put people on double time and have them working around the clock, how long would it take for you to make another machine, in addition to the one that I have on order for the State of Illinois?" He said, "About two weeks." So, "That's fine, why don't you do that." And, if things go wrong, I knew I could pay for it out of the Illinois Drug Abuse Program. I said, "I can't tell you what this is all about, but I'm calling from Washington." So, when they agreed, I already had the Vice-President (his name was Bill McGaugh) ready to go to Vietnam, with a consultant, and with these machines. The most amazing things happened in those two and a half weeks, including the decision that if we have to make policy it must span not just treatment within HEW, but also the Veterans Administration, because what does one do with those who are addicted in the Army. The decisions had better be at the level of the Executive Office of the President, so that the person put in to coordinate all of this has authority over all the relevant agencies. And, that's the origin of the Special Action Office for Drug Abuse Prevention.

LH: And, you became the first Drug Czar.

JJ: Yeah, I became the first Drug Czar, but that's another story, totally unexpected, not predicted, but, basically, what they did is they dug out our old report from 1970, and said, here's what you need to do. It emphasized the evaluation of the effectiveness of treatment; you need to fund research. Sometime, I guess, in the very first week of June, I got a hint that they were going to develop this thing, which I thought was still going to be a part of HEW and give it some funding. A day or two before June 17th, at a Presidential Press Conference, they said the program was going to be in the Executive Office of the President. Such developments, at that age, you don't think much about, you don't even dream about them; I'm not sure I'd even met the President by that time. Sometime during this period, and I'm still kind of confused in my mind as to how it all happened, I met the President. The next thing I knew, he'd called the members of the Congressional leadership, the Senate, and the House, and he said, "I'm going to set this up. I'm going to have a major initiative on drug abuse." This might have been the day before the Conference, but again, I am a little confused about the details, and I was sitting there thinking, well, he just wants me to observe it. And, he said, "Dr. Jaffe is going to run this." And, I was absolutely dumbfounded because nobody, not at that age, says, "Mr. President, who told you I would?" And, we had a press conference the next day. Somebody went out and bought me a shirt; they bought a shirt that was about one size too big, you know. And, I was sort of thrust out

in front of the Washington Press Corp, not prepared for most of this. Now, what are you going to do? Yeah, I could have said, "How do I know what I'm going to do?" But, I knew what we had to do because of this nexus between crime and addiction and treatment. I sort of said, "I don't know how these things happened, but it came up without much thought, that we're going to make treatment so available that nobody can say they committed a crime, because they couldn't get treatment." If you think about that, that satisfies all sides of the equation. We don't want people to commit crimes; we don't want them to use their addiction as their excuse; we don't want judges to say, "Oh, you poor fellow. You committed a crime; therefore, you're excused, because you're addicted." But, mostly, we wanted people to have the option of getting treatment before they got to that point. And, that sort of became the central thing that we wanted to do, at least, over the first year or so. I mean, there were lots and lots of things that needed to be done, but to expand treatment to the point that there were no waiting lists. In addition, what came with it was the great opportunity to put a real base into treatment, because the amount of money that was going into the basic science of studying drugs of abuse was minimal. I don't think there was more than three or four million dollars. A lot was named drug abuse, but when we really examined the books, it was leaking into all kinds of other activities, which is typical for government. But, we decided, and you can ask Jerry Levine about this, that, "Look, we're not here to punish people for past sins. Just make sure this money," we put up, I guess, twenty million dollars within a matter of six months, "Just make sure this is devoted to research relevant to drug abuse."

LH: This was before NIDA?

JJ: This was before NIDA.

LH: So, you were working through Levine's operation?

JJ: Well, as it turns out, all of the money that was designated, "Drug Abuse," most of that was being spent by Jerry Levine on research. And, we said, if we move all of that, then, there's no psychopharmacology. I said, "Look, let's do this. You keep it all, okay. We're not going to say anything about it. But, I'm putting up new money. You don't touch it. This is for Drug Abuse." And so, basically, we made that hold. I didn't say anything to anybody higher up. This is the way things worked. And so, we kept the psychopharmacology budget intact and put up brand new money for Drug Abuse research. And Sol Snyder said, "Gee, this is the money that allowed me to move ahead with receptors and things of this sort." That's very gracious of him to say that, and if it's true, that's terrific. But we knew that if you're going to make progress, you needed to have

basic and clinical research funded for real. And so, we put all of that into place, and we began changing that division of drug abuse, of narcotics in NIMH, into what then became NIDA. That was the transition that took place at the beginning of it, on day one. And so, that's how I sort of got into that. It was not something that I had planned.

LH: How long did you stay in that position?

JJ: Two years.

LH: You really got things going. Again, you must feel awfully disappointed, after your wonderful accomplishments, but we still are fighting attitudes about addiction now.

JJ: Well, you know, the pendulum swings. It's much easier to fight some external anima, you know, it's the narco terrorists, or something that it isn't, than it is to say, there's some aspects of life that are difficult to deal with and sometimes the best we can do is to provide some treatment. Treatment for addiction has never been that popular. It's very hard to build a constituency for it. The families don't like to speak up. The stigmatization of being addicted to illicit drugs does tend to reduce the number of experimenters and people who are using them. So, in the name of prevention, we stigmatize, but in doing so, we also make those who do become dependent seem less worthy of treatment, and that's the dilemma we're going to have, I think, for a long time to come. But people are not willing to put up the money that it takes to subsidize treatment, and most of the people who become dependent don't have the money to pay for fully effective treatment. So, what we have now is a much diluted form of what we had in the early seventies, because it's simply not adequately funded per person. There's just not enough to give people first rate treatment, or even second rate treatment.

LH: Well, at the last meeting of the CPPD, which you attended, I think, Barry McCaffrey got up and said some words, but I'm rather heartened by the fact that he was coming around to the idea, that maybe, treatment is the way to go, rather than interdiction.

JJ: Well, it's not an "either/or." I mean, you can't ignore the fact that the more drugs that are available, the more likely people are to use. But, to say a treatment doesn't work is, not just short-sighted, it's simply ignorant of the facts; there are people, who for whatever reason, at the policy making level, in the past, have said that treatment is ineffective. It's just not so. Treatment for dependence is probably as effective as treatment is for any other chronic illness, and certainly, it's as effective as treatment we have for most of the other psychiatric disorders. But, we did get a lot accomplished, in terms of psychopharmacology, during those early years. Certainly, we

initiated the studies of LAM; we got, what was then the National Academy, to study naltrexone, and those are major accomplishments. And I think, the other major accomplishment, however, is that we conducted a major study of the natural history of heroin addiction, which I got Lee Robbins to do.

LH: Of the Vietnam people?

JJ: Yes, and there were a lot of obstacles to get that done. My office actually assigned someone, specifically, to make certain that there were no roadblocks for getting that done. I think the Department of Defense was, literally, I don't want to say terrified, but they were most uneasy about doing a follow-up that might show there were really, really dire, long term consequences of the heroin addiction in Vietnam. And, I knew that I'd spoken to the President about this. And, he said, "You find out what happened from this. Write a book about it." And, I said, "I can't have a more direct authority than that." So, anytime the generals put roadblocks in Lee's path after we designed the study, I would get a report back, and I would call up directly from the White House and open those paths again because I thought that was a critical study. It's a landmark, and I was pleased to have been able to see that one through. And, that's one other legacy of that office, that some good research was done.

LH: But, the military was very slow to come around.

JJ: Well, once they saw how good it was, they were proud of that. Once they saw they were getting good results, they had the press conference on Lee's study in their place. And, I was happy to let them do it.

LH: I remember once, some general that was connected with the army's program came to visit the VA Hospital in Palo Alto, and I took him over to our methadone ward, and one of the people there showed him around and told him all about the program. On the way over, he's saying how awful these people were and that they should have their buttons stripped off and be dishonorably discharged. So, on the way back, he said, "See, that was a very attractive, very intelligent informative guy that was showing us around," and I said, "Yes, Sir, he's on forty milligrams of methadone a day." And, his face just dropped.

JJ: I don't think the prejudice has changed much. I don't see any dramatic breakthroughs in dealing with those issues, but one has to pursue it. I think the pendulum swings.

LH: What was your impression of Nixon? Your account sounds like he was pretty much with it.

JJ: He was very sharp. You know, we, for the first time, brought to that level the notions of

incidence, prevalence, and epidemiology. And we needed to find out more about the extent of the problem. I mean, how do you plan for treatment if you don't know how many people are using, with what consequence, or how long?

LH: You have to do market research.

JJ: In a sense, you know, we had to do these initial studies. The household survey had to be continued. DAWN (Drug Abuse Warning Network) had to be initiated. I mean, all of this stuff had to be done, and he instantly grasped it. And, I heard him give a presentation once, not even glancing at his notes, in which he accurately understood all of these concepts and talked about them. I was very impressed with his sharpness on these issues. And, frankly, Lee Robbin's study, that Vietnam follow-up study, would never have been done if he hadn't been so direct in saying, "You write a book about this," which I took as a directive that says, move everything out of the way. Make sure you find out what happened about this. So, he understood something about war and medicine, and the progress that sometimes happens. He said, "You know, some of the greatest advances in medicine have taken place as a result of what we learn in times of conflict and war." So, my impression of him is as a very astute man, much more than that, I don't think that I need to say.

LH: Now, your career has always alternated between the academic role and the public service role. Since then, you became the Director of the Addiction Research Center.

JJ: Yeah, I spent a few years there. I wrote the first national strategy at my kitchen table. I had somebody from the DEA come over, the law enforcement side, and we argued about things. One of the things we argued about was whether I was allowed to mention alcohol and tobacco. He said, "Well, you deal with illicit drugs." I said, "No, we're going to deal with all drugs." And, we finally got to where it was just barely mentioned; but from the very beginnings of my first chapter in Goodman and Gilman, I included a little section on nicotine as an addiction and alcohol was in there. I mean Al Gilman was not happy to see nicotine labeled as an addiction, and he always shortened that paragraph, using his prerogative as editor. I was a chain smoker, almost. So, what I did when I left government and went back to Columbia, was to expiate some guilt about not being able to really speak about the range of the addictions. I thought, you know, I'm going to study tobacco dependence. A lot more deaths are associated with chronic tobacco use than with opiate use, and I'd like to know more about it. How is it like the others? How is it different? And, at Columbia, we spent some time studying tobacco addiction, effectiveness of treatment, and I was

finally able to work with Bob Spitzer and we were the people who put, for the first time, tobacco dependence into DSM-3. Before that, the only mention of tobacco, if you really want to look at it, in all of the psychiatric textbooks, it was a psychosomatic disorder of the pulmonary tract. It was fascinating how little concern there was, in psychiatry, about tobacco as an addiction or nicotine as an addiction. So, having gotten that in, defending that for a while and studying that, I found that it was very difficult to set up programs in New York. Roger Meyer, another prominent member of ACNP, said, "Come up to Connecticut. We have all these big insurance companies. I'm sure they'll be happy to help you do this." That didn't quite work out like that. Roger had an alcohol center, and I was delighted to really get a chance to study that other addiction that I had not paid attention to. So, by that time, I had covered alcohol, tobacco, opiates, and the other stuff and I was feeling reasonably rounded, but not making very much progress in terms of publishing anything innovative. I think, to a certain extent, if you spend a lot of time in policy and government, you sort of lose those skills to work on the molecular level, or even the physiological level. And, I felt that way. I think we got a couple of things done, nothing remarkable, and then, when Bill Pollin called me to come and head the Addiction Research Center in Baltimore, I felt that was a nice closing of the circle. I mean, I started out as a medical student, I wanted to go to the Addiction Research Center, wrote to Wikler, never got there, wound up in the same building but working in something else, and here I'm asked to come back and head the Addiction Research Center. Now, it had moved to Baltimore from Lexington. But, could you want a more poetic circle than that? It was just irresistible. Bill was sort of grateful, because, I think, I might have persuaded him that tobacco dependence ought to be part of NIDA's portfolio, because I got interested in that in the early seventies. And so, he called me, I guess in '84, and that's where I went and spent some time. By that time, cocaine was the great threat to the national well-being, and we reintroduced studies of cocaine at the Addiction Research Center for the first time since Isbell gave them up. Isbell had given cocaine and why he thought it was so risky and deadly, I don't know, but he said, "That's a dangerous drug. You just don't want to do an experiment with that." I don't know what was behind that, but I didn't feel we had very many options. You know, we had millions of people using it. You'd better find out what you can about it. And we began that, but within a year of getting down there, Bill decided to retire. And I got persuaded by Ed McDonald and Bill, to take his place; a strange kind of funny coincidence. Ed McDonald, who then became a White House advisor on drug abuse, had been a classmate of mine at Temple, and

he wanted me to do it. I said, "Look, I want to stay at the Addiction Research Center." And he said, "Well, you can do both." And I said, "It's going to be very hard." And he said, "I want you to do it, anyway." And so, I agreed, and during that time we got a few things done. We got NIDA involved in AIDS, which people were reluctant to do. We got it involved in work place testing, so that all of this testing that is now done, in terms of employee programs and things, at least, is overseen by a scientific agency looking at the quality of laboratories. We, also, funded some of the first work on cocaine dependence, which was priority then. And then, I was delighted to return to the Addiction Research Center when Bob Schuster, whom I had brought to Chicago, took over as head of NIDA. So then, you know, I stayed there until about 1990. Bob wanted to make some changes, and then, somebody else from the past returned. Benny Primm was asked by Fred Goodwin to head up what was the equivalent of a whole group to expand treatment again. I mean, this thing waxes and wanes and there was this tremendous demand to expand treatment again. And so, he created something called the Office of Treatment and Proof, and he asked Benny Primm to head it up. Benny and I had been friends from way back in the early seventies. In fact, Benny had gone to Vietnam with me. Once we set those programs up in Vietnam, I was told, now you go to Vietnam and make sure they're working. So, immediately after I had taken on that job at the White House, I had to go to Vietnam and I took a group of people with me. Benny was one of them, and so, Benny and I were good friends. And when he was given the mission of expanding within government all the treatment, he had not very much experience, and he said, "Come work for me. Help me get this thing set up." So, I returned with the notion of expanding treatment, and I put up with that as long as I could, and I said, "It's time." I guess old fire horses have to retire to the pasture sometime. About a year ago, I said, I've had about enough of government and I've stopped and I guess that brings you up to date.

LH: Well, it's a remarkable career, Jerry, and I think you can be awfully proud of what you've accomplished. I'm just so happy that you did go to Lexington, Jerry, because, as we've talked about before, addiction was a kind of a dirty word in psychiatry and nobody wanted to touch it.

JJ: Well, I think maybe that is the major achievement. By putting that funding in, initially, by writing the legislation that enabled the creation of NIDA, and deliberately increasing its research base, over those two to three years, we escalated that research base for NIDA about as fast as I thought they could absorb it. What we've done, as you can see when you look at the posters here, is the addictive disorders now represent a major area of neuropsychopharmacology.

LH: Oh, yeah.

JJ: And, I think they've made their contribution to expanding the horizons of science. In that sense, it's sort of an indirect contribution that began a long time ago.

TB: What are you actually doing now?

JJ: A number of things. I think I'm trying to figure out what I want to do when I grow up. But, I'm a consultant to a small company. I'm a Professor at the University of Maryland. I teach, something I never thought would exist, people interested in Addiction Psychiatry, as a subspecialty. So, I do that and I'm also doing some work on tobacco, returning to an old interest. Can the product be made less hazardous? There can be some areas where that can be done. And so, I have sort of a mixed set of things that keep me busy, and I don't know which I'm going to concentrate on. I'm still writing some chapters for textbooks, trying to finish that off, and pretty much staying busy with too many different things to get any one of them done.

LH: Well, I think anybody, with your breadth of experience and energy and curiosity, is going to keep busy for the rest of their life, and I hope some bigger things are still to come in your life.

JJ: Thanks, Leo.

LH: Thank you, Jerry.

## 16. DAVID S. JANOWSKY

LH: Today is Friday, May 9, 1997. I'm Leo Hollister and we are videotaping one of the series of interviews of the people involved in the early development of the field of Psychopharmacology, a series sponsored by the American College of Neuropsychopharmacology. We are in Nashville today and talking to a wonderful person, who himself had some experience in Nashville; as well as in many other parts of the country. Welcome, David\*.

DJ: Thank you Leo. I'm very happy to be here.

LH: Let's see, David, I'm always interested in why people decided to go into medicine and, particularly, psychiatry. Can you tell us a little bit how that happened?

DJ: Well, I came from a background that had nothing to do with medicine. My father was a musician, a symphony violinist and a music teacher in the public schools, and my mother was an artist. I didn't know what I was going to be when I grew up. However, in the 9th grade I took the Kuder Interest Inventory and it showed that I was a social do-gooder type, and that I liked science. One of the options was to become a physician, so I sort of decided at that moment that I would become a physician. My grades until then had been adequate, not great, and in fact in the 7th grade my dad had to pull strings to keep me from being put in a vocational tract, something about my scoring poorly on some sort of selection test. I mostly got straight A's after that in high school. No one in my family had been a physician and my parents were not encouraging, at least to my face. I went on to college at San Diego State College. It wasn't a university then, and ultimately I went on to UCLA, and then on to medical school at UC San Francisco.

LH: You went to medical school at...?

DJ: At UC San Francisco.

LH: Good school.

DJ: A good school, right. I did that after 3 years of college. You could do that then. I went on to

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\*David S. Janowsky was born in San Diego, California in 1939. He received his MD in 1964 from the University of California San Francisco. He trained in psychiatry at the UCLA Neuropsychiatric Institute, and then served as a Clinical Associate in NIMH at the Clinical Research Center in Bethesda. After positions at UCLA, the Tennessee Neuropsychiatric Institute and Vanderbilt University, and the University of California San Diego, he became Chair of Psychiatry at University of North Carolina at Chapel Hill, in 1986. He was interviewed in Nashville, Tennessee on May 9, 1997.

medical school and enjoyed it relatively well, although I didn't really love it, especially the preclinical years. I liked the clinical years a lot better and always liked psychiatry. However, it was not particularly "in" to become a psychiatrist at that time. There were certain social pressures against being one by our classmates, such as the idea that all psychiatrists are "crazy and weird," and not "doctors."

LH: Anyway, so you got exposed to psychiatry there?

DJ: I was exposed to it in bits and pieces. There are two things that actually got me into psychiatry. Until my third year of medical school, I had no particular interest in psychiatry, but, in the third year, in our clinical psychiatry rotation, they sent you out to the San Francisco General Hospital and, basically, they threw you into the admitting wards, which were really quite wild.

LH: Front line battle.

DJ: Front line battle and you were supposed to see a patient each day, talk to them, get to know them and write them up and then you would talk to the attending psychiatrist and the course director, Dr. Jerome Motto who ran the service. And, I just loved it. I thought, "This is great." It was so interesting to learn about these strange people's lives, and, especially, amphetamine addicts, schizophrenics and suicidal people. It was very raw, and very exciting.

LH: It was the county hospital?

DJ: San Francisco General Hospital was the county hospital. But, I was good in pediatrics and while on the pediatrics clerkship at San Francisco General Hospital, I had written a think type of research project in pediatrics for Moses Grossman, who was the head of the Pediatric Department there. I got an A on my little research paper. I thought up a novel way to treat neonatal jaundice, which I later learned had actually been published by someone else and was ultimately applied to people. Of course, it wasn't my technique, but by logic, independently, I had figured out how to do it. It consisted of giving albumin to babies to bind the bilirubin. Dr. Grossman was impressed and he was very encouraging and treated me very well. Beyond that, I liked pediatrics. And, so, I was going to become a pediatrician, and indeed ultimately became a pediatric intern. But in our 4th year, as our psychiatry experience, we were assigned to one or two cases and told to follow them as outpatients for six or eight weeks. We'd see them once a week. My supervisor was Dr. Mardi Horowitz, who later went on to great fame as a psychotherapy researcher. One of the cases was a gay person, who was having tremendous conflicts in terms of his sexuality. I was working with him and I felt I did a good job. And, again, people's stories just interested me.

Another experience in my senior year, other than seeing the outpatients, was that I took an elective on one of the wards. The unit was a milieu therapy ward, a creative sort of situation. My job was just to hang out there, which I did. I even participated in some of the activities that the patients did, and I interviewed patients. I was there for about 4 weeks and again really enjoyed the experience. But it was very unacceptable in our class to be a psychiatrist. Those who liked psychiatry and planned it as a career were thought of as not very medically oriented, were not too practical and were thought to be strange, and not with it. I mean this was at least the image. So I just went on into what I thought I liked and what was "in," and I got a pediatric internship at UC San Francisco's Moffitt Hospital in San Francisco. I liked it okay, but after a while I found it kind of routine and/or sad when someone died. I kept thinking that I really did love psychiatry. I felt like it was a forefront area. I mean, the whole dynamic direction was very strong and intellectually stimulating, and drugs were just getting to be popular.

LH: And, this was what year?

DJ: I graduated medical school in '64, so I was a student from 1960 to 1964.

LH: So, that was the time when psychiatry was swinging from the dynamic to the pharmacologic?

DJ: Well, it hadn't yet swung, at least in most programs. At that time, it was very dynamically oriented, but with medications being given. It was almost like people would give medications apologetically and it was sort of an afterthought. And, I thought, well, you have these people's stories that are interesting, you have a whole world of dreams and dynamic psychiatry, and have this biologic thing, and especially this drug thing. I was very practically oriented and I believed that maybe we could combine all this. I felt the field of psychiatry would go the biologic direction and that it was a wide open field. I thought that Internal medicine or Pediatrics was more closed. And, so, anyway, at some time in my internship, I just said, "Well, I'm going to take a psych residency." So, I finished my Pediatric internship and, then, went down to UCLA and began my psychiatry residency. They started us off in the inpatient rotation and they assigned me to a fellow named Rod Gorney, who was a very interesting guy. He was very interested in philosophic things and he was a very good psychiatrist. He still is. He is there. And, he set up a ward as the therapeutic community, similar to the one I rotated on in San Francisco. He called it a milieu therapy community. You could treat patients and they might be on that ward for a year. This was at the UCLA Neuropsychiatric Institute and the whole program was extremely psychodynamically

oriented. And I found it very interesting. There were also a few biologic types there also, like Arnold Mandell and Bob Rubin.

LH: That was when Norm Brill was the Chairman.

DJ: At UCLA, the dynamically oriented types were the heroes. But, Bob Rubin was a young assistant professor and Arnold Mandell was there and they were very biologically oriented and I hooked up with both to some extent. And, Rod Gorney and I began to talk about doing some work in the area of premenstrual tension, because some of the patients would come in very psychotic, then they would have their menstrual period and get better. So I did some work looking at mineralocorticoids and menstrual cycles in one or two of these patients, and I published in Archives. And, Dr. Gorney, being a sort of big picture guy, had us do some work where we looked at premenstrual tension from an anthropologic point of view and even across species. And, I should go back one step. My interest in research came out of the research experience within pediatrics that I mentioned, thinking about albumin and neonatal jaundice. But it also came out of the fact that in my third year of medical school, just going into it, I had a summer clerkship with a fellow named Werner Rosenau. He was a pathologist. You know, it was a way to make money to start with. He asked me to try to isolate white cells from blood. We were trying different sugar solutions. We were trying different techniques. By accident, one night, I put my test tubes in water to let them soak and went home. When I came back there were only white cells in the bottom of the test tubes. We discovered that we actually had developed a technique for isolating living white cells. It was serendipity, but they were alive. The red cells had been lysed, and the white cells were happily there. So, we perfected that technique over the summer and published it in JPET. Werner Rosenau put me as first author on the paper and it got more reprint requests than I've ever gotten since.

LH: Was this Edward Rosenau?

DJ: No, his name was Werner Rosenau. He was a German guy. He was probably an associate professor of pathology at UCSF at the time. And, so, that whetted my taste for the glory of research. But, I didn't think I was going to be a researcher. I thought I'd be a clinician. So, anyway, when I got to UCLA, this fellow, Rod Gorney and I did do some research on premenstrual tension. I also was very interested in doing psychotherapy, which I did a lot of in treating these patients and I sort of liked them to be the sicker the better. I mean, I didn't want to treat healthy people.

For the second year of psychiatric residency, some of us went down to Harbor General Hospital, which is a big county hospital in LA. And, again, this was a real slam bam kind of place led by a famous psychiatrist whose name was Pietro Castelnuovo-Tedesco, a brilliant dynamic psychoanalyst. That year I had to make a choice about what to do next. One choice was to finish my residency, do a child fellowship, and go on to the Berry plan and be deferred into that and then spend 3 years in the air force. I thought I was going to be in the Air Force as a military child psychiatrist and I figured it would take quite a few years. The other choice was to apply to NIMH and go there to be a clinical associate at the Clinical Research Center in Bethesda. I had a very strong interest in milieu therapeutic communities, as opposed to pyramidally structured medical model wards. At NIMH a fellow named Jack Durell wanted to compare a therapeutic community oriented system with a regular system to see which worked better. I interviewed to come and run the therapeutic community ward and I was accepted. At that time, if you went to NIMH, you went after two years of residency. You were there two years, and you got credit for a third year residency. You also got your military obligation out of the way all at once. Basically, for putting in one extra year of my time, I would become a psychiatrist, be in the Public Health Service avoid the draft, and not have to go to Vietnam. And so I decided to go to NIMH.

LH: A good deal.

DJ: It was a wonderful deal. So, anyway, I was going to go and be with this therapeutic community oriented kind of guy, but when I got there Jack Durell must have had a political fight with somebody, and they'd stripped him of his unit, and they assigned me to Biff Bunney. So, I mean, I literally walked in the door thinking I was going to be with my boss, Durell, and they said, go see Dr. Bunney. And, so, I ended up on Bunney's unit. Everyone knew he was a famous and a very distinguished psychobiologist/psychopharmacologist. I was supposed to run his ward. There were a number of now very notable people in his group, in the group right next door, and on the floor above us. These included Herb Meltzer, John Davis, Will Carpenter, David Kupfer Richard Wyatt, Fred Goodwin, Dennis Murphy and Keith Brody at the least. I'm sure there were others. It was a very high powered clinical research group, but all of us were just getting started. We were all young punks right then. We were either clinical associates, like I was, which essentially was a Fellowship, or they were just a little beyond that. And, we were all crammed into a very small amount of space. My job was to run a bipolar ward. And, so, I did that for about a year. I wanted to convert it into an equalitarian therapeutic community kind of situation, but Bunney didn't like

that idea, because he felt that it would leave things too loose and not controlled enough. So, basically, I did my thing, did it as best I could in terms of setting up the ward the way I wanted to. I wrote a paper with a fellow named Richard Epstein, called "Playing the Manic Game." It actually ended up being a very popular paper that people have quoted ever since and used to train residents. It has to do with how manics interact with others. We had many manic depressives on this ward, three or four at a time, and they would all drive everybody up the wall. And, so, we wrote a paper about that, and it now is a classic.

LH: So far, you've been talking more about clinical activities. How did you ever get into biologic research?

DJ: Well, John Davis was there at NIMH and I think John and I probably both felt a bit alienated from the power structure. He was working with a guy named Bob Colburn, who was a pre-clinical person. For example, he was involved with the actions of drugs. John inspired me and invited me to work with John Colburn and him. I was very interested in premenstrual tension, which I have mentioned, and, as I said, had done some research on it before, and so, we did some work looking at monoamines and their release and uptake as affected by progesterone and estrogen, doing this in rat synaptomes. And, I was also involved at NIMH under Dr. Bunney's supervision in giving L-Dopa to depressives to see if we could turn off the depression. This was following the Bunney-Davis and Schildkraut catecholamine hypothesis. In fact, in the cases we did, L-Dopa seemed to actually convert them either into hypomania or help the depression. But, overall, it didn't really work over time, but we did have one of the first papers on that subject. In another paper a fellow named Mike Paul and I were the first to show increased urine cyclic AMP in manics. And, I wrote another paper, which, again, was sort of a semi-clinical one which involved looking at the dynamics of how people in a research system think they are helping the patient, but actually are doing it for research glory, and maybe to the patient's detriment. This was basically a paper about rationalization and self-deception, and you can imagine how popular that one was. At the end of that second year at NIMH in 1969, I had finished my military obligation, and I wasn't sure what to do next. Nobody was begging me to stay at NIMH, or even asking me to. I had been rejected by Stanford, so I found myself looking for another job. I went out to California and took a job at UCLA, again at Harbor General Hospital, setting up a crisis emergency service. I did no research for a year. This now was 1969. At the end of that year, John Davis called me and said that he had been asked to come and take over the clinical part of the Tennessee Neuropsychiatric Institute in

Nashville. A preclinical unit had been there, but the whole clinical research unit, maybe 10 beds, was to be developed at Central State Hospital. He asked if I would come and more or less run the ward for him. John and I had been good friends, and I was basically feeling okay about being in LA, but my wife didn't like LA at all, and Nashville sounded sort of exotic, so we thought why not give it a shot. So I went out to Nashville, interviewed, and became a member of the Psychiatry Department and the Pharmacology Department. I was paid by a Center grant run by John Oates, an internist and a clinical pharmacologist.

LH: Now you came to the Tennessee Neuropsychiatric Institute.

DJ: Right, in 1970, and we set up a research ward very quickly. I came in September, and by January, we had a research ward up and running and had hired people and so on. I should mention that we set it up to be extremely therapeutic, as well as research oriented, with many of the principles of a therapeutic community. That was quite unusual in that day and age. So we tried to help the patients clinically, but at the same time to do the research. It did work. We set up a system that was designed to interact with the preclinical people in terms of ideas, if not studies. A lot of the preclinical studies that were going on were involved with monoamines. For example, Fridolin Sulser and his group were looking at clomipramine and its effect on serotonin. There were other people working on drug interactions and there were people working on marijuana and how it affected cell biology and so on. All that inspired us. So our clinical unit looked at a lot of things, and I was the one who was clinically running it. But I was also one of the main investigators and contributors to the research directions it took. Several major findings came out of that unit. We were one of the first to show, in controlled studies, that methylphenidate activated pre-existing psychotic symptoms. Thus, we supported the dopamine hypothesis of schizophrenia. In addition, via a combination of luck and serendipity, we were giving physostigmine which is a cholinesterase inhibitor which causes central acetylcholine to increase. We were giving it to see if we could turn off antidepressant-induced confused states, thinking these could be an anticholinergic syndrome. I had the idea that maybe physostigmine could turn off mania. The concept was like that of the heart, i.e. there could be a balance between adrenergic and cholinergic factors in mania and depression, with mania being too little acetylcholine and too much norepinephrine or other monoamines and depression being the converse. Indeed, we found that the mania in several patients was turned off rapidly and dramatically by physostigmine. Over a period of minutes depression was induced. From that, I proposed the adrenergic-cholinergic hypothesis of mania and

depression, published first as a letter to the editor in Lancet and later as a hypothesis paper. It was probably the first, or at least one of the first multi-neurotransmitter hypotheses, and it set the tone for future ones.

LH: Well, that was a very novel hypothesis at the time. What ever happened to that?

DJ: Well, you know, that's an interesting question. I mean, I pursued it after I left the Tennessee Neuropsychiatric Institute. In 1973, I went to the University of California San Diego. I pursued our Ritalin schizophrenia work. We looked at Ritalin's effects on projective tests in schizophrenics and found that it increased the pathology as it increased growth hormone. We kept plugging away at that until I left San Diego in 1986. Craig Risch, Leighton Huey, Louis Judd and Chris Gillin, and I did a number of neuroendocrine studies looking at hypersensitivity to acetylcholine. Reactivity to physostigmine appeared to be more intense with respect to behavior in those with a history of depression. We then tried to look at mechanisms, such as what happens to neuroendocrines when all this is happening. We looked at cortisol, ACTH, prolactin, and epinephrine which all increased dramatically with physostigmine, and abstracted the neurochemistry from the neuroendocrinology. That also led us to propose an acetylcholine hypothesis of stress regulation. Acetylcholine was proposed to be a master neurochemical that turned on many others such as CRH, Beta Endorphin, cortisol, prolactin, epinephrine, etc. What has happened to the hypothesis and the work over time is interesting. It is still there. You don't hear as much about it. It is in most of the psychiatric textbooks, but the serotonergic hypothesis really has become the theory of the day.

LH: We always have to be suspicious of a fad.

DJ: Yeah, well, I don't know if it's a fad. I've been studying and thinking about how the cholinergic system might interact with the serotonergic system. In 1986 I left San Diego and became Chairman in the Department of Psychiatry at the University of North Carolina in Chapel Hill and more or less my life stopped as a scientist for the next 8 years.

LH: Do you have any regrets about taking on a chairmanship too early in your career?

DJ: Well, I was 46 at the time. I don't regret that I took it on too early in my career. I just regret that I took it on at all. I feel that I did an okay job as a chairman, maybe even a fine job, but it was at a price of, first of all, being focused so very much on the job and not doing too much research . It also took an emotional toll. I think my style was not to be a dictator. I did great in little groups. I think it was very hard for me to deal with large groups of people as a boss. So, I regret that I ever

bothered to do it, because I feel like I sort of went into something which had its positives, but, for the most part, was a negative.

LH: You know, when you become a chairman you have to look after your people and forego your own ambition.

DJ: That was part of it, but I think what was worse was that there are so many agendas when you're chairman you can't make everybody happy all the time. There's always somebody who isn't going to be happy and it's a very adversarial relationship at times, at least that was what I felt. When I came to UNC, even though this wasn't an area that I specialized in, I was assigned to be the head of a center for alcohol studies. It was sort of a package deal. So I was going to be the Chairman of Psychiatry and head of the Center for Alcohol studies. I mean alcoholism wasn't my area of research even though I had done some work in that area. But I figured, look, if they want to give me this as a way to keep my research going, why should I say, no. And, so, I took over the UNC Center for Alcohol Studies while trying to be effective as a Chairman. In that format I tried to do some research. Actually, it worked out fairly well. I was able to do research, at least indirectly through other people such as David Overstreet and Amir Rezvani. Do you know David?

LH: I've heard of him. I don't think I've met him.

DJ: Well, he came to San Diego for several months in the mid-1980s. This was a few years before I left for Chapel Hill. He developed a strain of hypercholinergic rats and I said, David, you know, these animals, if they're hypercholinergic, maybe they're also depressed. From that we spent the next 12 or 15 years working together on an animal depression model, using Flinders sensitive hypercholinergic rats. So he came to Chapel Hill in about 1990 and I put him in the Alcohol Center. We did some work with the rats with respect to alcohol, but especially we kept pursuing a pre-clinical mood/depression direction with these animals. Around this work and that of several others, we set up a fairly strong pre-clinical behavioral pharmacology section. Dr. Amir Rezvani was studying the ability of the calcium channel inhibitor, verapamil, to block alcohol induced hypothermia, a physical effect. This was something that was going on before I arrived. I said why don't we see if verapamil also blocks alcohol consumption? This was a very simple minded thing to do, but it actually changed Dr. Rezvani's research from a physiologic direction to a more clinically relevant behavioral direction. So I had a preclinical operation going in the alcohol center, done somewhat by remote control.

LH: Then, you lost track of the cholinergic hypothesis of depression.

DJ: Mostly, except for the Dr. Overstreet connection.

LH: Has anybody tried to use the cholinesterase inhibitors to actually treat mania or depression.

Has anybody tried Aricept in depression or mania?

DJ: Well, people haven't yet tried it for mania that I know of. But, what I was going to say is that you asked whatever happened to the hypothesis, and, actually, what's happened is interesting. Over the years people have given choline as a precursor to treat mania.

LH: We did that.

DJ: You did that? Did you do it for mania? I thought you did it for schizophrenia.

LH: No, we were interested in Huntington's and tardive dyskinesia.

DJ: That's right, I remember now. Very recently, there's been a pretty convincing paper that came out of the McLean group, done by Bruce Cohen and his collaborators. They gave choline to rapidly cycling bipolar patients who were on lithium and it seemed to really help. In fact, their paper just came out in the last few months. I was reading it, and it quotes our cholinergic hypothesis. Then, there has been some work using pupillometry to reflect cholinergic tone. The authors found that when you give a muscarinic agonist like pilocarpine you get greater constriction of the pupils of patients who have affective disorder. And, then, there's been some other work more recently with brain choline uptake, using NMR Spectroscopy, showing that depressives pick up more of it than non-depressives. This phenomenon goes away when you treat the patient with Prozac (fluoxetine). There's also been some work like we did that has now been done by Bob Rubin, showing hyper-reactivity of ACTH and cortisol when a low dose of physostigmine is given. Bob Rubin gave such a low dose that it didn't cause any behavioral effects or nausea, which is theoretically very important. Anyway, if you look at the data as it comes out, there is almost nothing that doesn't fit the cholinergic hypothesis. The only piece that really doesn't fit very well, and this is very important, is a lack of an antidepressant effect of anticholinergic agents such as scopolamine. For example, scopolamine really doesn't help depression and it should, but on the other side of it, if you give any of the centrally active cholinesterase inhibitors, you will increase depression, especially in depression prone people.

So, I think the hypothesis still is there, but it doesn't get much play at meetings and very few people are doing any research other than what I just described. It is gratifying to know that this cholinergic direction might even have a clinical application, such as using cholinesterase inhibitors

to turn off mania, etc. Indeed, you know, there has been some talk that you could give physostigmine in the Emergency Room to turn off mania, but I think that would be difficult in terms of side effects.

LH: Yes, it is tricky because it has a sort of biphasic action.

DJ: That, and then it has a very steep dose response curve.

By the way, I should mention that over the years I have kept up a general interest in the whole area of ovarian hormone linked psychiatric disorders. I think that some of the work that I did, where we were looking at serotonin and norepinephrine release with ovarian hormones, was quite groundbreaking. In 1972, we proposed that monoamine changes might be the cause of premenstrual syndrome and we predicted how drugs such as SSRIs, which at that point had not been used clinically, might be good treatments for premenstrual tension. People don't quote that paper. It was in the Archives of Sexual Behavior. In fact, with our pre-clinical work and hypothesizing, we preceded what actually has turned out to be the recent treatment for premenstrual tension and what is now the main direction of premenstrual tension research. We also put together an aldosterone-angiotension hypothesis of premenstrual tension, the concept being that angiotension and aldosterone stimulated by monoamines caused the dysphoria. In any case, when I stopped being Chair in '94, I decided, for many reasons, to stay where I was in Chapel Hill and not become a Chair or a faculty member somewhere else. Mostly this was due to family considerations. Since 1994, what I have done aside from seeing a lot of patients clinically is that I have developed an interest in the relationship of one's core personality to psychopathology. Around 1992, I took an American Association of Medical Colleges course on how to be a university medical school administrator. Part of it was to take a test called the Myers-Briggs Type Indicator. You may know that test. It is used a lot in the "real world." It divides people into extroverts or introverts, sensing or intuitive types, thinking or feeling types, and judging or perceiving types. This test is widely used in management circles and very little studied in formal psychiatry and psychology. So, anyway, I took this test as part of a management course. It said that I was not a "natural manager," which by then I had already figured out anyway. Managers have profiles, for example that are either extroverted or introverted, sensing, thinking, and judging. Mine was extroverted, intuitive, feeling, and perceiving. I got very interested in the test because I thought, here's a test that is uncanny in describing one's personality. It struck me as amazing that you could take this test and it really could tell what you are like, at least for me. At the course they

had us play some games in which we would, for example, take the three highest feeling people in the room and the three highest thinking people and the goal was to have them decide what to do if one has a Little League team and needs to send it to the finals, and there is only enough money for 15 of the 17 kids. The thinkers quickly said, "Let's get the best players", and the feelers said, "Everyone has to go, let's figure out a way to do it." I even said that I would write a check. The thinkers were quite judgmental and said that we would never succeed in getting any money. Well, anyway, I thought this was really an amazing kind of psychological thing, because it is talking about people's basic personalities and what they are like. So, I began to study the Myers Briggs Type Indicator. I've been giving the Myers Briggs Type Inventory and Cloninger's Tridimensional Personality Questionnaire, which measures harm avoidance, novelty seeking, reward dependence and persistence. I gave both to anybody I could find on the inpatient units as a starting point. And, I've discovered that the patients who have unipolar depression have certain profiles that are very distinctive. For example, one that shows up often in depressives is being introverted rather than extroverted, sensing rather than intuitive, feeling rather than thinking and perceiving rather than judging. Social phobia patients are extremely introverted, more so than the depressives. They are also highly judgmental. People who try to commit suicide are usually highly introverted, but I found that they are also highly feeling oriented, which means they care very much what people think of them and are subject to being crushed if people are down on them. They are also very judgmental, meaning they are likely to come to judgments or get things done, and may be hard on themselves and others. So, anyway, I've been pursuing this direction in some depth. I've given the tests to a number of alcoholic and other substance abusers in a community detoxification center, and followed them to see who relapsed who didn't, and who went to AA meetings, who didn't and so on. I actually found some results that have been very interesting. People with low persistence on the Cloninger TPQ scale relapsed much earlier than those who have high persistence. Introverts tended not to go to AA meetings. There is a study by a fellow named Fritzi in Germany who gave 10 normal doctors physostigmine and looked at their neuroendocrines and their personalities and their coping mechanisms. He showed that the ones who became withdrawn under stress or tended to give up when they were under stress or tended to not use denial were the ones that had the most physostigmine reactivity, both behaviorally and in terms of neuroendocrines. So, I've been thinking that the thing that I might want to do next is to go and get people who are not clinically ill and categorize them by personality profiles. For example, a combination of introverted, sensing,

feeling, judging, qualities could be those prone to depression if you give them physostigmine. So I want to begin to define the biology of personality as it underlies psychopathology.

LH: That's just what I was going to bring up. Now, the Millon test is geared to pick up personality disorders, isn't it?

DJ: I'm not sure I know that test.

LH: He's a psychologist who developed a widely used test. I think it was primarily for the purpose of making diagnoses of personality disorders. But, what you're talking about is normal personality, what is also called temperament, which we never hear much of now.

DJ: Right. I've never figured out how to tell the difference, but I'm making the assumption or hypothesis that these temperaments, under certain environmental conditions or stress conditions, are predisposing to depression and other related symptoms and illnesses. So, for example, who is to say that a gene for a depression, if it exists, isn't basically some combination of introversion, and basic temperament types? If you take bipolars and unipolars and give them this Myers-Briggs Test as I have, the bipolars are over-represented as being intuitive types, which, by the way, correlates with their being creative, as in being a dramatist or artist. If you take the unipolar depressives, they tend to be sensing types rather than intuitive types. They deal with the here and now and what is in front of them. They're not particularly open to new experiences, and they are not overly creative. I think that this test might be particularly good in differentiating pre-bipolars who have not become bipolar yet, from pre-unipolars. One of the most genetically determined Myers Briggs scales is the intuitive-sensing scale. It correlates very highly with the Neo-PI openness to experience scale which has been shown to be highly heritable in twin studies. So, it could be that someday we will find a gene that is actually an intuitive gene or genes which are highly prevalent in bipolar disorder patients. Similarly, depressed bipolars are more extroverted than equally depressed unipolars, and conversely, bipolars are less introverted. Extroversion is also a highly genetically determined personality characteristic. My hypothesis would be that a lot of things we are calling a disease, such as alcoholism or bipolar disorder for example, are actually a cluster of genes regulating temperament or personality. These, under the wrong conditions like stress or too much alcohol, could lead to a given pathologic outcome.

LH: Now, how stable are these profiles? You know if you do it today and, then, two years from now, are they stable?

DJ: They're pretty stable. Actually, I'm doing a study right now which is trying to do a follow up after patients leave the hospital. I was wondering if their profile changes when they get out of the hospital. At least for normal people, they're pretty stable, maybe a correlation of  $r = 0.7$ , after six months on the Myers-Briggs test for a given dichotomy like extroversion and introversion. My preliminary results suggest that there is quite a bit of stability in the personality profiles of psychiatric patients, even if their depression alleviates. There is also some evidence that temperament changes over the years. Older people, for example, become less extroverted and more introverted over time. And, there's, undoubtedly, an environmental part to all of this. So that is the study I'm doing now. I'm following people in the hospital and I'm trying to follow them at one month, three months, six months and a year to see what's happening to these personality variables, and see, too, if they can predict outcome.

LH: Well, it's an interesting approach to research. As you say, there are not very many people into the personality area with respect to diagnostic nosology. I think Larry Seiver has made a kind of a career out of it. I have the greatest trouble deciding which of the personality disorders to call somebody, because there's such a tremendous amount of overlap.

DJ: Well you know that's something I've been thinking about. I believe that there is a tremendous overlap between personality disorders and Axis I disorders, and what you are seeing is clusters of temperament. By the way, one of the interesting things, carrying me back to the cholinergic thing, is that Larry Seiver and his group have given physostigmine to borderline patients vs. other kinds of borderline personality disorder patients. The borderline patients show behavioral hyper-reactivity of the cholinergic system. They get more depressed than other people when receiving physostigmine, just like the depressives do.

LH: Now, I think the change to emphasize diagnoses came from the St. Louis group. I think the whole idea of DSM from I to IV has been kind of a medicalization of psychiatric disorders. It is nice in terms of defining to each other what we're talking about, but it doesn't help you a bit to understand it.

DJ: Right. Well, not only does it not help to understand disorders, but when you get right down to it, the question is why is it that Prozac works for obsessive-compulsive disorder, minor depression, anxiety, major depression, premenstrual tension, and who knows what else. I mean, you suddenly have to think to yourself, well, okay, isn't that kind of interesting, are we missing something here by splitting instead of lumping?

LH: Well, if they try to deduce what relationships are between psychiatric disorders, based on the specific drug, it gets pretty difficult with the DSM-III or IV model, but if you could identify the personality characteristics that are common to all of these, then, that would be a drastic change in our whole nosological approach.

DJ: That's right. In one study, Robert Cloninger and his group gave people clomipramine vs. desipramine, and also gave them the Tridimensional Personality Questionnaire. From the results of the Tridimensional Personality Questionnaire, one could determine who was going to be a clomipramine responder vs. a desipramine responder. So, all of this has fascinated me. In a related set of studies, one of the things we did in the 1980s was to give a variety of inpatients methylphenidate on one occasion and placebo on the other. We then gave a test called the Barrett Leonard Relationship Inventory. This test shows how you perceive a significant other, i.e. are they empathetic, accepting, unconditional, genuine, etc. We found that if you are depressed, you tend to perceive an interviewer as quite low in all of those therapeutic qualities. After a rapid infusion of methylphenidate, the individuals who were depressed then perceived their therapist as wonderful, warm, accepting and giving and so on. So, now, here you are dealing with, on the one hand, turning on dopamine or some system like that in the brain and in minutes changing the perception of a significant other. To me, that has to be important. So, I've had this ongoing interest in how people's personalities and their interactions work through the interaction of biology and personality.

LH: Well, it sounds like it will be enough to keep you rolling till retirement to follow this.

DJ: It could happen.

LH: But, it is, as you say, a frontier. Well, I don't know, but the book, *Listening to Prozac*, of course, has been the biggest hype for that drug that you could possibly imagine, but all the assertions about how it makes you a new person, in terms of your personality, that would be something to look at.

DJ: Well, it would be. To me the question is whether or not you can change these things that used to be thought fixed in stone. They probably aren't, you know.

LH: If you thought it was fixed in stone, then, psychotherapy would be totally useless, because I suspect that most of psychotherapy is given for personality change rather than anything else. Well, that's quite an interesting career you've had in a short time, David, and I want to thank you for

coming and sharing it with us. It will be interesting to see what you'll come up with in another 10 years from now.

DJ: Thank you so much.

## 17. DONALD R. JASINSKI

LH: It's Tuesday, April 15, 1997, and we're here in Washington, D.C., to continue a series of videotaped interviews with people who know something of the history of psychopharmacology. With us today is Don Jasinski,\* who has long been associated with the Addiction Research Center in Lexington, and more lately, in Baltimore, and who has probably the longest experience of anybody alive now, in studying drugs of abuse. Welcome to one of the series.

DJ: Thank you, my pleasure.

LH: Probably it is interesting to figure out what determined how people got into their career, first of all, into medicine and, secondly, into whatever field of psychopharmacology they got into. Can you give us a rundown on how you got to where you chose your career?

DJ: Well, I think I identified medicine as a career while I was in college. I entered college as a pre-medical student, which was in Chicago, at Loyola University. Coming from a relatively poor family, I wound up at the University of Illinois Medical School, which was the state subsidized school, which was a real bargain in education.

LH: It was not a bad school.

DJ: No. It was, actually, a very good school. It had a wonderful medical education. I entered medical school in 1959, and what was interesting, at the time, was the growth of research in science and the medical school faculty was proselytizing and talking up research and research activities. And there were a number of opportunities for medical students to do things during the summer or with fellowships. Originally, I worked in the biochemistry department, but I sort of found that boring. And then, I took pharmacology, and pharmacology at the University of Illinois was a wonderful course, because the Chairman was Klaus Una.

LH: He was a great man.

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\*Donald R. Jasinski was born in Chicago, Illinois in 1938. He received his MD, in 1963, from University of Illinois Medical School in Chicago, Illinois. Starting in 1965, he served in the Public Health Service and then section chief in the Addiction Research Center at Lexington, Kentucky. He became Professor of Medicine at the Johns Hopkins University School of Medicine when the Addiction Research Center was moved to Baltimore to become the intramural program of the National Institute on Drug Abuse and held the position of Chief of the Center for Chemical Dependence at Johns Hopkins Bayview Medical Center. He was interviewed in Washington, DC on April 15, 1997.

DJ: Klaus had trained so many of the people in neuropsychopharmacology. One of Klaus' claims to fame, as many of his people have described him, was that Klaus had this knack for convincing medical students that there was much more glory in pharmacology than to go out and become a practicing physician and become rich. Klaus had attracted a large number of people. In pharmacology, what I found fascinating was the lectures. It was a superb course but coming up once a year to give our lectures on addiction was Harris Isbell, and Harris gave "the lecture." So, I became interested in pharmacology and I had a summer fellowship in pharmacology, and then, all through medical school, I was taking graduate courses in pharmacology.

LH: You never did have a degree in pharmacology?

DJ: No, no. I graduated medical school. I did my internship at the University of Illinois. Just prior to this, at the University of Illinois, their claimed area of expertise was neuropharmacology, basically electrophysiology and pharmacology, applied to electrophysiology. I worked very closely with Sid Smith, but Sid went off to become Chairman, at the University at Buffalo. So, I worked with a number of people but I never really had the hands to be a good neurophysiologist and I decided that, perhaps, I should be a clinical pharmacologist. What was interesting was the atmosphere, and Klaus Una had talked up clinical pharmacology. So, he said, "Ah, go with the best. Go with Isbell." So, he wrote a letter to Harris Isbell but Isbell had retired in 1963.

LH: I didn't know that.

DJ: Yeah, in 1963, and Isbell and Wikler had gone over to the University of Kentucky, because there Isbell had started at the University of Kentucky Medical School. Harris went over as Professor of Medicine and Abe Wikler went over as Professor of Psychiatry. And so, the response I received was from Bill Martin, who had just taken over as Director of the Addiction Research Center. Bill had been in Chicago, had been one of Klaus' students; so Bill interviewed me and said, yes, there was a position, a two year position, because this was two years in the Public Health Service. But there was a delay, because the slot was already filled. So, after the internship, I spent a year as a trainee in neuropsychopharmacology at University of Illinois in the pharmacology department. And there, I worked with one of the faculty, a guy named Buz Sulafsky, who now, I think, is Dean at the University of Illinois at Rockford. I spent the year, then I went to Lexington in July of 1965, and I entered the Public Health Service and I helped Bill Martin run the Human Research Unit. And Bill was, I think, coming into his scientific stride

at the time, so, it was a wonderful opportunity, a learning opportunity. So, I had a one-on-one mentorship with Bill Martin. And, what had happened was that Abe Wikler had retired, Harris Isbell had retired, and Frank Frazer had retired, all from the Public Health Service; Frank had gone to work for Eli Lilly and Abe and Harris had gone to the University of Kentucky. So, Bill was rebuilding the staff. I had a wonderful opportunity because Bill was mainly interested in doing neurophysiology but wanted to keep the Human Research program going. So, after I had been there about fourteen months, Bill wanted to know whether I wanted a permanent position; I said, yes, so I had a permanent position. By the time I had been there two years, I was a Section Chief, and probably, by about three or four years, I was running Human Research. Now, I was twenty-nine or thirty years old and I had this huge inventory.

LH: My, that's a rapid ascent.

DJ: That's a rapid ascent, yes. It was a very interesting time because there was a growth in the studies of addiction. A number of people, who were leaders in the field, were interested in bringing people into the field and facilitating their growth. So, they did very nice things for me by helping to do certain things. I had a very interesting time, because I also worked fairly closely with Harris Isbell, because Harris was still coming out to do experiments, and he had experiments going. But, he had also been made Acting Chairman of Medicine at the University of Kentucky, so I got to do Harris' experiments. I ran them. And so, I had a very broad based sort of experience at the time. Probably, what happened from the period of about 1963 or '64 up until the mid '70s came out of that laboratory, under the leadership of Bill Martin, was really some of the most productive things we've had in this area of substance abuse and addiction, the idea of protracted abstinence, Wikler's ideas of conditioning and conditioned abstinence, and the idea of multiple opioid receptors.

LH: Yeah, Bill was impressive doing that wasn't he?

DJ: Yes, and Bill was doing this, but I was doing the human experiments to show that these concepts of multiple opioid receptors could be applied to human pharmacology. We had gone on to develop treatment drugs. We had re-studied methadone, naltrexone, naloxone, and amphetamines. We had just marvelous things.

LH: You studied cannabinoids, too.

DJ: Well, there was an interesting roundabout way to the cannabinoids. Harris had gotten interested in cannabinoids and had worked out a relationship with Professor Kortha in Germany.

Kortha was, I think, I've forgotten which university, was also principal chemist, may have been at Shell, and he was isolating active principals from cannabinoids, from hashish. And, they used to ship them to us in vials, which were freeze-dried. Since they were extracted from plants, and were considered biologics and not drugs, they were not subject to the IND Regulations. So, Harris had designed the experiment and I actually ran it; but we took the vials, added ethanol, put the substance in solution, and drew it up with a syringe. We had weighed it first, then put into solution in ethanol, and then injected it into a king size cigarette, let the alcohol evaporate, and then, we would let subjects smoke the cigarette.

LH: You made your own reefers.

DJ: Yes, and we had gone through cannabidiol, tetrahydrocannabinol,  $\delta$ -8,  $\delta$ -9-tetrahydrocannabinol, a whole series of these, and found that the one which was active was  $\delta$ -9tetrahydrocannabinol.

LH: Of course, this was before Raphael Mechoulam's synthesis.

DJ: Yes, yes.

LH: So, you did a natural exchange. How were you sure of the compounds?

DJ: It was Cort that had identified these. Cort was a very, very sophisticated organic chemist. And, he had got interested as a side project. This was 1968. I had been out of medical school four years. I'd been working there a little over two years, and I was running these experiments. And we were pushing the dose of tetrahydrocannabinol, and we had this hallucinogenic response from tetrahydrocannabinol, from the  $\delta$ -9-THC; and I can vividly remember writing it up as a case report. And then, the next experiment was one of the experiments that Isbell had designed in the late 1950s and '60s. We did the cross tolerance between LSD and tetrahydrocannabinol. So, we took in as subjects, volunteers, made them tolerant to LSD, and then gave them tetrahydrocannabinol, to show that they were not cross tolerant. So, it was two different mechanisms of action as the intoxication syndromes looked different. We did these studies and never thought anybody would be interested in them; at that time, there was not much interest in marijuana research. This was probably '68, '69, somewhere in that era.

LH: I think we got some of the synthetic stuff around 1965, and then I dug out some synhexyl from Abbott, which had been in the freezer up there for twenty-five years, and it came down in a vial, where it looked like a little tar at the bottom, and we reconstituted that and did a comparison between THC and synhexyl.

DJ: It was about 1969, right after we did these studies. We had published an abstract, the Illinois State Medical Society was going to have a symposium on hallucinogens, and somehow I got an invitation. I suspect Harris couldn't go, so he routed the invitation to me; and the meeting was in Chicago and I remember it was held at the Sherman House in Chicago, and I grew up in Chicago. So, being a government employee, while writing this up, I was strictly straightforward with the science that tetrahydrocannabinol was a hallucinogen with a mechanism of action that was different from LSD. I had written up the paper in abstract form and sent it ahead. I'd gotten a call that they wanted me to come up and attend a press conference. At that time, as a federal scientist, you had to have clearance, but there wasn't time to get clearance to do this. I said no, as I didn't particularly want to talk to the press. This was a very interesting conference, it was a pro vs. con conference because of the other attendees, one of whom was Timothy Leary and a number of other people who were pro-hallucinogen at the time. Here I was, this young sort of scientist, really straightforward about the science, and I find myself with all these...

LH: Mystics.

DJ: With all these mystics in this group. At that time, Chicago had three newspapers. One was the Chicago Daily News. They used to have a morning and an evening edition. The morning session was delayed, it was supposed to end at 11 and it ended about 11:45. Now, the morning edition came out about 11 o'clock. So, I came out of the meeting, walking through the lobby, and in the lobby are the newspapers. The Chicago Daily News, on the bottom half, has a headline, "MD Offers Proof, Pot Is Poison." They had taken my paper and made this press release, which was published even before I made the presentation. So, I heard about that one, and had calls from many people, calling me at the Sherman House. That must have been about 1968 or '69.

LH: Shows you the power of the press, doesn't it?

DJ: Yes.

LH: The news came out, as I recall, in a kind of tabloid format, whereas the Tribune was a more conventional newspaper.

DJ: So, this was an interesting period of time. I never thought that tetrahydrocannabinol and the marijuana issue, at that time, was anything but straightforward, as we had just done these experiments. But, a lot had been done back in the 1940's, and I, actually, went back and reviewed all of the studies which had been done at the ARC on marijuana and tetrahydrocannabinol. There were a fairly significant number of studies, which were done.

LH: Oh yes, and a lot of them involved synhexyl.

DJ: Synhexyl was the other one that was examined in the late 1940's. I wrote this up, and there was another symposium at the New York Academy of Sciences and my address was on the topic of "What we should do about marijuana and its addiction potential." And, I had looked at this, really in a relatively straightforward way, and pointed out that there were a number of things we didn't know because the experiments hadn't been done. And, that conference was in New York, hosted by Stan Yollis. This must have been in the seventies. Interestingly, we just had to revise this data, and people are now interested in this data, again. It's amazing, about a month ago, at the joint meeting of the American Society for Pharmacology and Therapeutics and American Society for Clinical Pharmacology, they had a symposium on the marijuana issue and drug control in marijuana, and I was one of the speakers. So, this has gotten to be very interesting again, this whole idea has gotten revisited and I'm thinking that we will see more. I think we'll get a revision of interest in marijuana and tetrahydrocannabinol.

LH: Now, you never ran the Marijuana Commission, as I recall?

DJ: No, no.

LH: Well, I guess your group down there continued to study hallucinogens.

DJ: Most of the hallucinogenic work occurred before I came to Lexington. Most of that ended when Harris retired. What was carried on was the tetrahydrocannabinol work. Harris did wonderful work with hallucinogens. He was a very fine scientist. Harris was a very careful clinical experimenter, very precise and really did very well-controlled studies.

LH: He was always a soft-spoken, unassuming man, but anything he said, you ought to pay attention to.

DJ: When I went into this, I was very young. I mean, I was thirtyish and I was interacting with people like Harris Isbell, Bill Martin, and Abe Wikler. I got to interact with Harris and Bill and I took over the role of the relationship to the National Academy of Sciences, the KM Programs of Drug Dependence, the Abuse Potential Studies, so I got to interact with Nathan Eddy, got to interact with Moe Sievers. Moe Sievers did some nice things for me.

LH: Moe Sievers was a Dean of Pharmacology.

DJ: Yes, and of all those people, I think the inherently smartest was probably Harris Isbell. We are talking about some very talented people and Harris was a very smart man. Now, he was very soft spoken, you wouldn't think about it when you'd look at him, but he had presence. That was

in the days when people used to smoke. He used to smoke a cigarette and he'd be very quiet. Everybody would be talking, but before you know it, Harris would be the center of the conversation. People would be relating to him. And Harris would do this, particularly with women, and it was interesting. Women would find Harris, this person who they would talk to; he would relate well to them, they would ask his opinion about things, and Harris had no trouble giving people opinions. He was a wonderful lab chief. He was a father figure. If you talk about people who were still there, they'd talk about how Harris took care of them and they'd talk about this fatherliness of Harris. He was superb.

LH: Well, I remember a few years back, when he died, I wrote his sister who survived him, and said he was a giant, a soft-spoken gentle giant.

DJ: He was a very nice man.

LH: In fact, a lot of the work I did over the years was kind of a derivative of what he had done and, in a way, even before I knew him, I was imitating his work, so to speak.

DJ: I had been at the University of Illinois, which was relatively sheltered, and then, I went down to Lexington and the people I interacted with there: Harris Isbell, Abe Wikler, Bill Martin, probably some of the smartest people I ever met in my life, the most creative people. So I thought all science was like that. With these people, you know, I used to feel inadequate.

LH: You just stepped in at the right time.

DJ: Oh, yeah, I was fortunate in this.

LH: Boy, you learned.

DJ: I was fortunate, yes. I had this wonderful opportunity. They were constantly looking for people to bring into the area, and one of the things about people in science is that when you see somebody who's talented, or you think they're talented, you facilitate their growth and you give them opportunities; we all want to be teachers and have people develop.

LH: Well, I remember that, almost simultaneously, when I published the first paper on THC and Synhexyl, Andy Weil published one in Science, which wasn't a very scientific paper, on account of how difficult it was to do the study. And then, later, Andy wanted to get away from military service, so he went to the Public Health Service and they offered him a chance to go to Lexington. And, I was dumbfounded to hear that he refused. He wasn't going to go down to Lexington. I said, "You're a perfect idiot. If you want to do anything in this field, you don't turn down a chance to go to Lexington."

DJ: Well, you know, there was a history to that, and that history went back to the 1920's.

LH: Cliff Himmelsbach in...

DJ: Well, Himmelsbach to Larry Kolb, Sr. Most of the people, whether they were Himmelsbach or Isbell, had great respect for Larry Kolb, Sr. And Kolb had a very interesting career. He'd been in the Bureau of Mental Hygiene and had done the first addiction studies in monkeys in the 1920's and got interested in the addiction problem and was really instrumental in getting the Lexington Hospital open and initiating the research. He became the first Director of Lexington. He facilitated the growth of research and the Lexington Hospital opened in 1935, which was the height of the Depression, but he recruited Himmelsbach, who was a young medical officer, sent him off for training, for a few years, before the hospital opened, and then they supported them very well. They were small, but a very well supported human research unit, and set their standards very high at the beginning because they were very good scientists. And, that carried over. Harris had been at Lexington in 1935, when it opened, as a young medical officer, and then, went away to NIH and came back again in 1946 or '47.

LH: Has the history of the Addiction Research Center in Lexington ever been written-up?

DJ: No. There had been one time when we came closest to doing this, in 1975, which was the fortieth anniversary of ARC. There was a fortieth anniversary symposium and a book was published in which a number of people reminisced about the earlier period. I mean, if you interweave these stories, and you look at the tradition, it was really the growth of psychopharmacology, strongly influenced by the government and by Lexington. Probably, the idea was that they demonstrated that you could do controlled experiments, and if you look at Himmelsbach's experiments from the late 1930's, they're beautiful. They could be published today. I mean, a reviewer would publish many of these today in a journal, because they're controlled; the measurements are there; the data is generated; the hypotheses tested; and it's just good science, has a life of its own.

LH: The government certainly got a good crew there. Were you ever involved in the studies of screening compounds for the CPDD?

DJ: Yes, that's what I inherited. That was my major job, to do the Human Abuse Potential Studies and the screening, and that was when Bill took over the lab in 1963. He thought that, from a public health viewpoint, the Human Abuse Potential Assessment was probably the most important function of Lexington, to generate this data and to allow decisions to be made about compounds.

I inherited that and there were really two motivations. First, the surgeon general had this responsibility that we were fulfilling. The other important reason was that we would get our compounds very early, and the pharmaceutical companies couldn't tell us no, because if they were working on making all of the drugs in this area, it was necessary to put these drugs through our system. So, we got our hands on all sorts of interesting drugs and got to do thorough pharmacology in humans with very interesting drugs. And people looked at this as applied research, but it gave us tools for many things, and it stimulated a large number of things. When Bill took over and he inherited this program, the first drug he assessed was cyclazocine, which was a potent antagonist to morphine; it didn't look like morphine but would produce some hallucinogenic activity and dysphoric responses in the addict population. And Bill gave it chronically, and showed that it produced a withdrawal syndrome, which was not like morphine. And, then, Bill asked a very simple question, which was, if they became tolerant to the agonist effects, did they become tolerant to the morphine antagonist effects. So, he gave it chronically and showed that, no, they did not become tolerant to the morphine antagonist effects. It was this that led Bill, then, to the multiple opioid receptors theory. The idea that there were receptors to explain the diverse effects, that with cyclazocine you'd have different ideas of intrinsic activity, and cyclazocine was an antagonist at mu and an agonist at what we now call Kappa receptors.

LH: Yeah, he gave them the original names, didn't he? Mu and Kappa?

DJ: Originally he called it nalorphine type and the morphine type, and then, it broadened. That's another story. And, that was a story because I should have listened to Bill. But, we had looked at these drugs and knew there were two receptors, and we could explain the action of opioids and the actual term, opioids, was coined by Bill in his Status of Opioids in Pharmacologic Review, to include all the compounds. But, Bill had come up to me and he said, you know, Arthur Keats has reported on this. He said, "It sounds different, why don't you go ahead and study it?" And, I said, "Bill, my plate's full. I'm trying to do this with the barbiturates. I've got some other interesting things I want to do." So, he said, "OK." We, also, would have a relationship at the University of Kentucky and we would train graduate students, and Bill would be the advisor for graduate students, who would work in the chronic spinal dog laboratory. And, Bill was always saying he wasn't taking any more graduate students, but he was always taking one more, one last graduate student. We had all these drugs in humans. We had all these agonists and antagonists. So, he put the young man to work, studying and comparing all of these agonists, antagonists in the chronic

spinal dog. And, he brought in the data and the drug that Bill had wanted me to study, SKF 10047, which was a sigma agonist. And, Bill saw the profiles and realized, right then and there, that there could be Mu, Kappa and Sigma receptors, and Bill, very quickly, put all of this together, which was a wonderful thing.

LH: A great synthesis.

DJ: A great synthesis, an intellectual synthesis.

LH: And, he, also, did some rather simple animal preparations, as well.

DJ: Animals, humans. It was really humans. It was human data, which we had generated and that was there to explain it. There was a very interesting story on this, of how much of this came about. Pharmaceutical companies were producing agonist/antagonists as substitutes for morphine, and we would assess those, which were promising, and one of these was naloxone or noroxymorphone. Now, this was assessed because it had been shown to have some analgesic effect in humans.

LH: Now, that was the famous study by Lasagna.

DJ: Well, not nalorphine; this was naloxone. Nalorphine preceded this. This was naloxone.

LH: Yes, but it is used now, and it turned out that it had somewhat of an analgesic effect.

DJ: I've heard stories about that, of whose idea that was, and that may have been Harris Isbell's idea, because Harris and Frank had written a review in Pharmacologic Reviews, and Harris had recognized that nalorphine, in the volunteers, produced some effects like morphine. And, also, Klaus Una, there was a tie in, this is such a small world, and Klaus Una had been the pharmacologist at Merck, who had done the work on nalorphine. He did the basic pharmacology, and Klaus wanted Merck to proceed to developing nalorphine as a morphine antagonist but they didn't want to do it, and that's when Klaus went to the university. But, that relationship between Klaus and Harris was through the study of nalorphine back in the late forties.

LH: And, that was the beginning, of course, of the whole concept of a mixed agonist antagonist.

DJ: Yeah, but now naloxone was fascinating because Lasagna had studied naloxone; he had studied it and found a weak analgesic action, and we gave it to volunteers, and we went up to huge doses and saw nothing, no changes. And, then, we gave very small doses to morphine dependent individuals, which would precipitate abstinence. So, my project with Bill, which I did, was working out how to measure the relative potency of the antagonist. We would assay for precipitated withdrawal, and then, we did these studies comparing agonist/antagonist effects, and

the naloxone had, virtually, no agonist effects in humans. And, this was interesting because this was really clear evidence that you had a competitive antagonist. And this, then, was recognized; that was probably the second paper I ever wrote in medicine, which is human pharmacology and abuse potential of a little-known oxymorphone, naloxone. But, there were huge implications to this finding, which we recognized because I also did a study where we gave naloxone around the clock in very large doses by injection for, I think it was three or four weeks, and showed no changes and no withdrawal. And, we were looking at this and realized that we had a competitive antagonist. We had a tool that could be used to explain a number of the effects of agonists/antagonists in terms of multiple receptors, in terms of intrinsic activity at these receptors. And here, we had to explain this compound with zero intrinsic activity. The next experiment we did was doing studies of the interaction of cyclazocine and naloxone; with cyclazocine, that we now call a Kappa agonist, we showed that larger doses of naloxone could antagonize cyclazocine. This was really what crystallized for us, these phenomena in humans with naloxone, which led to ideas of multiple opioid receptors. And, it was really much stronger evidence, once we were able to do these studies in humans. And, then, we found that a Parke- Davis compound called profadol was clearly a partial opioid agonist. And, this was a drug with which you could begin explaining these phenomena in terms of relatively simple receptor ideas. If you had the receptors fully occupied with morphine as occurs in dependence, where we give people large doses of morphine to make them dependent, and we gave a partial agonist, it wouldn't have sufficient activity to suppress withdrawal, but it would also be able to precipitate it. If you lowered the level of morphine dependence, the same drug could now have enough activity to suppress withdrawal and we showed this phenomenon with two drugs Profadol and B4507, I think was the other drug. And, so, this just laid this out that you could do human pharmacology, with these relatively simple receptor complexes and you could explain the actions of drugs.

LH: I always felt that naloxone, which proved to be such an interesting tool, was synthesized by Harold Blumberg, but I don't think he ever got much credit for it. And, he synthesized naltrexone, too.

DJ: There's an interesting part of this story. One of the experiments we did with naloxone, which was very expensive to synthesize, because it was the main derivative that was made by Endo Pharmaceuticals, which was making relatively small amounts. It was apparent that naloxone was not going to be an analgesic, so there was not much interest in this. Endo had no interest in

developing naloxone as an antagonist. When we did these studies, one of the conclusions was that this would be the drug of choice as a morphine antagonist. However, the reason they didn't want to produce naltrexone was they had done a marketing survey and found how much nalorphine was sold. And, it was only a hundred or two hundred thousand dollars of nalorphine sold, which was a small market, even then. But, we had looked at naloxone and, in those days, we were looking at structure activity relationships and there were a couple of things we became aware of. One was that most of the antagonists were related to standard opiates, as substituted groups of nitrogen, and Sid Archer, who was a leader in this, and a number of other people, began systematically making substitutions on the nitrogen of cyclazocine. And, cyclazocine had been a cyclopropylmethyl substitution, as opposed to the nalorphine, which had been the N-allyl substitution. And, in man, but not in animals, the cyclopropyl substitution in cyclazocine produced a compound, which lasted and produced effects for twenty-four to forty-eight hours, and it was very potent and well absorbed orally. We looked at naloxone, and there were two other ideas floating around at this time. One was, Abe Wikler had looked at conditioning in the Pavlovian response and found that the withdrawal syndrome and drug craving could be seen as a conditioned phenomena. And, the second was the idea of protracted abstinence, long lasting effects after drug discontinuation. If you looked at how you would treat withdrawal and who relapsed to addiction, the idea which scientifically made sense was extinction. With time, the conditioning would become less if you didn't reinforce it, and the protracted abstinence, hopefully, would resolve itself. The idea was to keep people abstinent, so the idea of the antagonist of cyclazocine was to produce a chemical blockade and then enforce abstinence, which would allow individuals to prevent relapse. And, that was the hypothesis underlying the work. So, we had looked at naloxone, which seemed to be ideal. And, naloxone was ideal because it produced no agonist effects by itself. But, if we gave naloxone orally, it was chewed up. It's got a very high first pass metabolism, and we would have to give huge amounts orally. And so, we injected it and measured the time course in antagonizing morphine; we looked at this and its effects were gone within about three to four hours. Even though you could give huge doses, because of the short half-life, we had the question of, what if you took the substitution from cyclazocine, the cyclopropyl-methyl substitution and replaced N-allyl substitution naloxone, the compound that had been made by Endo, but rejected because it was not a very good agonist or analgesic in their screens. So, Bill took a trip to Endo to meet Harold Blumberg and Alan Pater and received the toxicity findings on the drug, the animal pre-

clinicals, as soon as they could get an IND, we would do all of the Phase I studies, get all the human data. I gave the first dose of naltrexone by injection, which was 0.001 milligrams. OK, we are doing dose- raising studies. There's one thousandth of a milligram. Eventually, we wound up giving 50 milligrams, but we had done this very carefully. So, we looked at this, and I did the whole thing, compared its potency to naloxone in precipitating abstinence. We showed that, unlike naloxone, it was very effective orally. The cyclopropylmethyl moiety did protect the molecule against the first pass metabolism. It produced a very long lasting compound in man, which lasted twenty- four to forty-eight hours. So, we did the time course and the blockade. So then, we did the other experiment, which was to give naltrexone chronically, and then, give morphine chronically, on top of that and showed we did not get physical dependence and the withdrawal syndrome. So, we had to pick a dose. Bill said, "What dose should we give?" I said, "Well, maybe 25 milligrams." He said, "Let's be safe; let's double it." So, we picked a 50 milligram dose to do these studies. We did the experimental studies. We gave people 50 milligrams once a day chronically, and gave them morphine four times a day, and then, withdrew the morphine, showing really no withdrawal and they were exposed to large doses of morphine. So, it was an effective blockade. This was about 1969 or '70. I have memories of this, because we published this. Now, there's a very interesting thing; people keep coming back wanting to know how the dose of 50 milligram tablets was standardized, because when it went on to development, the 50 milligram dose became the dose. And, it was never standardized. It was decided one afternoon when we said, let's pick a dose and we'll do it.

LH: Lucky hunch.

DJ: Well, yeah, it probably could be the dose. But, that was a very interesting time in history because it opened up a lot of things.

LH: Of course, naltrexone has all the qualities of a perfect drug for treating opiate dependence, and yet, it had very little impact on the field, because people won't take it.

DJ: The other thing we worked on there, which we don't really get recognition for, was what we interpreted as our mandate, the relationship between addiction, the narcotics, and asocial criminal behavior. We were dealing with what we would, back in the old days, call psychopaths, but now, you call character disorders, or anti-social personality disorders; we were interested in their response to morphine. It was a very fascinating thing for people who are interested in psychopharmacology, and I think everybody who has given a drug and watched a complete

personality change as a result. What fascinates people is to take somebody who's depressed, give them an antidepressant and a month later, they're a different sort of individual; or take somebody who is psychotic, and you treat them with an antipsychotic; or somebody with free floating chronic anxiety that you treat and is now functioning and a different person. We found we could change the personalities of these people with morphine, make them feel much better, and be much nicer people. And, we were interested in a biologic approach to the concepts of addiction. We did interesting experiments, which never really got clear recognition. At that time, we hypothesized that there was, what you might call a state or a trait, which made these individuals much more susceptible, which made them much more susceptible to the morphine. That theme had been pursued for a long time, but this was in the 1970's, and it was not popular to talk about addicts having some sort of a disease process. Science is affected by society and it's just looking at this historically, I'm getting old enough to look at things historically now, how society has affected this field of addiction. We had, back into the last century, beginning in probably the 1860's, the 1870's, the growth of the Abstinence Movement, Prohibitionist Movement, and the Prohibitionist Movement hit its heyday in this country in 1900 to the 1920's. First, we prohibited alcohol. Then, the prohibition came for narcotics. We reversed the prohibition of alcohol but we didn't reverse the prohibition of narcotics. So, the prohibitionists found their home in the narcotics bureau, in my estimation. It's amazing that people espouse the philosophy of the abstinence movement without understanding it. I was struck by listening to General McCaffrey talking about marijuana, and the idea that the original marijuana laws and the prohibition of marijuana was really in many of the states used as an alternate to alcohol, it's very much the prohibitionists' type of thinking. But then, we had an outgrowth of this, which transcended everything, which was the idea of Marx's philosophy and that all evils of man are due to economic and social conditions, so that addiction was really a social problem, a social and economic problem. If you took people and put them into the right sort of job, sent them to school, they would change their behavioral response. Those of us, who looked at this, realized that psychopaths or sociopaths, these people suffered a great deal, but it was not entirely in response to their environment. Environment contributed, but there was probably something else. We're now ending an era. I think this era of Marx's philosophy is diminishing. Our friends in molecular biology, I think, are going to the opposite extreme where everything is genetic.

LH: Well, it's interesting that you bring up the Prohibition Movement. After alcohol was legalized, it still persisted in having an effect on the classification of other drugs. You think things would have been different if marijuana had never been declared illegal?

DJ: Marijuana? Yes. Well, I spent my career, I did this for the government and I've done this now in my academic career, to try to understand this issue. Again, this is relevant in, what we now call narcotics, and I called the opioids very early, because this is in what I was interested, in the human studies. I probably studied more opioids than anybody in the world in humans, different classes of these drugs. I was interested in the problems associated with their use: everything from inappropriate treatment of people with severe terminal cancer pain because of restrictions on narcotics, to inappropriate use of narcotics, to laws and lawyers dealing with these drugs in unprecedented ways. We, as scientists, know that science changes. Our concepts of today may not be our concepts of ten years ago or a year ago. So, what you wind up with as a scientist is arguing with people about decisions, which were made on the basis of existing scientific advice, which may have been wrong at the time or inappropriate, and not in light of current knowledge. So, this is really part of our conflict. I think that marijuana was controlled on the basis of two hours of hearings before Congress and was controlled because a number of states in the southwest and the northeast had already controlled it at a state level. In the southwest, it was controlled, primarily, as I understand it, because it was a habit used by the Mexican laborers.

LH: It was a low class drug.

DJ: Yes, a low class drug. In the northeast, it was used as a possible alternate to alcohol. These were very short hearings. The interesting part of it, historically, was that the AMA thought there was enough evidence to control it, but not to prohibit it, but they were shouted down and it was controlled as basically a prohibited drug. Now, we live with this, and people ask us, as scientists, to defend the decision which was made, in terms of science, and there's an inconsistency — you have to tell people there is inconsistency in the world. Life's not fair.

LH: Well, we get locked into a frame of thinking and it's hard to break out of it, and I suppose, that one of the best examples is the twenty-five year old war on drugs, which seems not to have been very effective.

DJ: Again, going through the 60s and 70s, I was convinced that there could be a social solution, but the problem was not only a social one. I think we now accept that we have people who are varied, in terms of brain chemistry and certain sorts of dysfunctions, and we accept that some of

us may be born with anxiety. Some of us may be born with a tendency toward depression, and that it's acceptable to correct nature's mistakes. But we don't believe the same can be true in terms of addiction. Many of us believe if you talk to people who are addicts, they have personality disorders. They have impulsivity. They have low mood states. They have poor self-image; and to develop an appropriate pharmacology for these people, I think, should be the mission, but we don't do it. That addiction is a social problem, is the idea with which the war on drugs was conceived.

LH: So, there is an addictive personality?

DJ: Yes. Well, I think there's a propensity towards addiction. I think that's just common sense. You take a number of people and you expose them to any sort of drug that's reinforcing: some get into trouble and other people are not going to get into trouble. What distinguishes these, who get into trouble from those who don't get into trouble? It's interesting, what is different about those that get them into trouble? If you look at those people, whom we used to see in prison, we see all sorts of differences. We see personality disorders, and we all know that the addict with an antisocial personality disorder is the one which causes havoc. And, we tend to separate that from the "recreational user." Or, the person who gets addicted in the course of treatment for pain; we tend to separate those, whether they should be separated or not, I don't know. Obviously, there's something about certain people, if they're exposed, they will get into trouble with the drugs. Looking at this, watching kids, my kids are now growing up and are doing fine, but you watch your kids go through college, and most kids drink and consume huge amounts of alcohol in college, and some probably do drugs, but then they reach maturity. When they get to be 23 or 24, they're out of college, stabilize and you watch them, all of a sudden most don't do it anymore because it makes them fat or they don't want to do it, because they've got to do something else. And, they change their drug taking behavior, and yet, some don't change and persist. What makes those different? Is it entirely environment? Is it genetic? Is it induced behavior? Is it learned behavior? I have no idea, but we speculate.

LH: Well, it's a tough problem, but I don't think anybody's had much more experience on the pharmacology of these drugs than you have. Do you think our search for drugs to prevent heroin abuse or prevent cocaine use is likely to be successful, and if so, which way should we go? Should we do the methadone route, a drug that substitutes, or should we go to naltrexone, a drug that blocks?

DJ: I think there are other alternates to this. But most of our current treatment drugs for heroin and opiates really emerged out of the research at Lexington. The study of various opioid drugs and their interactions, preferably these drugs would modify the opioid receptor. Now we either have drugs which act as an agonist or drugs which act as an antagonist at the opioid receptor, and then strictly a pharmacologic treatment with either agonism or blockade. An issue, which in my mind hasn't been clearly resolved is, if you take an individual, an addict sociopath, and give them opioids, are they better off on the opioids or off the opioids? The argument from the side of methadone programs, which administer a mu agonist, is that people are better off with methadone than on the illicit opioids. But we measure efficacy from methadone in terms of retention and treatment. We don't measure efficacy in terms of the changes we produce in the individuals. To me, one of the great shortcomings in our field, reflecting back on this, is evident from the distinction between pharmacologic opioid addiction and antidepressants, which both emerged about the same time, in the early-'60s. To get an antidepressant accepted by the FDA, you have to do a study and put in a placebo group, you need a placebo-controlled trial. We now have large numbers of antidepressants, and we have data showing they work. This did not happen with the treatment drugs for opiates, which came along at the same time. We realize that when we give antidepressants or placebo to depressed people during these clinical trials, some of them may commit suicide during the course study and we do the study, nevertheless. The idea of doing controlled studies was resisted in the substance abuse field. Methadone, you know the story as well as I do, was approved originally by the FDA on the basis of clinical experience, not controlled studies. I think this has hurt us in this area.

LH: Well, there are some things like historical controls, and I think the evidence for the historical control with methadone has been pretty good. Well, everybody's looking for the magic bullet for cocaine but, so far, no luck.

DJ: Well, I think we switched the way we look for treatment drugs. And, at least, with cocaine, we have a hypothesis that the reinforcing effects of cocaine are really dopamine related; the hypothesis is that cocaine is a dopamine reuptake inhibitor; therefore, the excess dopamine is what's responsible for its reinforcing effects. Therefore, to find a cocaine treatment drug, we look for a cocaine antagonist; we look for an antagonist to dopamine. So, we've been looking for dopamine antagonists, because, technologically, that's what we can do. Whether this will result in a cocaine treatment drug, I don't know. Whether you can simply explain all of the reinforcing

effects that we see in humans by dopamine is unclear, because with cocaine use in humans, you'll get a mixed bag of effects, including a lot of noradrenergic effects. And, whether you can find a drug, which is a selective dopamine reuptake inhibitor or blocker of dopamine reuptake, which will result in a cocaine treatment drug, I don't know. Can you find a safe agonist, which will be the methadone for cocaine? Yeah, I think so. I think we already have a couple of those, which are possible.

LH: You were one of the first people to study buprenorphine in humans. Where do you think that fits into the treatment schedule for opioid dependence?

DJ: Buprenorphine was a very interesting drug. We knew we had partial agonists and we knew we had competitive antagonists and the idea was, "Could you get a partial agonist to substitute for methadone?" I mean, it was just sort of a logical thing. Methadone, when you looked at it from a pharmacologist's viewpoint, was a strong agonist. Methadone does everything that heroin and morphine do, including producing respiratory depression. If you take all of what we now call mu agonists, when they're used from a public health viewpoint, people die. There are deaths, which are respiratory deaths. The second issue was that we knew that methadone was awfully hard to get off of, because the methadone withdrawal syndrome was much longer lasting than heroin. So, buprenorphine came along, really, as an analgesic to be assessed for abuse potential. And, I remember this very clearly, because it had, like naloxone, like naltrexone and cyclazocine, the cyclobutylmethyl substitution. I was doing the studies and we were doing dose ranging studies in our addict volunteers. Our addict volunteers used to have jobs, and I remember one individual very well, I even remember his name, but I won't tell you his name. But, he was a guy who used to work as a clerk, so we used him on the study. The next day after the study, it was about thirty-six hours later, he looked at me and he says, "You know, Doc, I still feel that drug." Right then and there, I changed the whole idea and went in and did the study, not from the vantage point of abuse potential, but also looked at it as a human pharmacology study and looked at its potential for addiction. This was, really, a very simple thesis, that methadone, a typical mu agonist, had all the properties of mu agonists; but we could also get partial agonists, and buprenorphine was a partial mu agonist, which was orally effective, which was also long lasting, and it could be used as an alternate to methadone. Because of its limited physical dependence capacity, and its lessened ability to produce respiratory depression as a partial agonist, its use, instead of methadone, would potentially reduce public health and social problems associated with methadone. If you

look at DAWN data, for example, the number one opiate is heroin, in terms of deaths and emergency room visits; number two, you will see is methadone. So, that idea was just simply to do this study, show it was feasible, and buprenorphine could substitute for methadone. My hope, really, at the time, and I didn't think it would take this long to do it, but I thought that the use of methadone, with the restrictions in methadone clinics, was the wrong way to go. I think that people who are addicts should be treated as anybody else who has a disease, any other sort of disorder. If methadone is useful, they cannot get treated by their doctor, as you can be treated for everything else, but you have to go to a methadone clinic to get treated. And, methadone clinics, usually, are outside the scope of medicine. Most of us in medicine have peer review about the way we practice and what we do. I think that the hope was that something like buprenorphine, which was a drug which clearly had lesser potential to create public health and social problems, might be a drug which was useful: to be used along with other psychotropic drugs, to treat people along with antidepressants and anti-anxiety agents, and could be an opioid agonist used to reduce addictive behavior, just as naltrexone was. That may come about, to move treatment of addiction back into the mainstream of medicine.

LH: Having been one of the first to study naltrexone, would you have ever predicted that it might become more sold for treating alcohol dependence rather than opioid dependence?

DJ: I missed that. No, no, I missed that because the observation which suggested this, which we ignored, and sometimes you know, in retrospect, you realize you're a dummy. The medical director of Endo, Ralph Jacobson, a very good guy, called me with a story. He told me that on a navy aircraft carrier out in the ocean, one of the corpsmen or pharmacist mates was found unconscious, and they injected him with naloxone, huge amounts of naloxone, and he woke up. He swore up and down that he hadn't done any drugs. All he had done was drink the medicinal store of alcohol. He had gotten into the alcohol and drunk himself silly. It was very early in the development of naltrexone. Bill had done a study of the interaction between naloxone and hypnotics in the chronic spinal dog, in which naloxone reduced some of the effects of barbiturates. What we published seemed a curiosity, and we never took this to the next step of a treatment drug. It's interesting now, in retrospect, how we overlooked this; and I guess, the geniuses made the jump from the data. I would have never made this jump from our data. I didn't make it, but in retrospect, once I heard this and saw this, yes, there were indications along the line that naltrexone might work in alcohol dependence. There were a number of people who had tried

naloxone, primarily, to antagonize alcohol and barbiturates, subsequently, in seemingly very vague experiments. The results weren't really clear, one way or the other. There was some suggestion of efficacy. The phenomena of the interaction of naloxone and opiates is really striking; because you have somebody who's experiencing opioid agonist effects and you give them a dose of naloxone and it just reverses it. Well, you did this against the barbiturates; you would have a subtle effect only. You could never get a complete reversal, as you did with the opiates. And, that's what turned us off from looking at this, and we never thought that it was there. And, also, we had our own philosophy of drug binding. A drug worked by activating this receptor and another drug worked at this other receptor, and we were not changing our ideas about what drugs were about.

LH: Well, Don, you've always seemed like a veteran in this field, and yet, you're still a fairly young man. I expect you have many more years of productive life.

DJ: It's been interesting and I have been a beneficiary of changes. And the changes, what I see is that we have stopped, as a group, training clinical investigators. In my day, to be a clinical investigator was a marvelous thing. It was the epitome of a scientist; it was the area to go into in science. Now, it's molecular biology. The problem is that molecular biology, which does wonderful things, doesn't necessarily work on a disease state or address a clinical situation. So, I'm still active as a clinical investigator, my services are in demand, and I'm beginning to see they're even in more demand than ever before. And, I'm beginning to see certain interesting things happening, that most drugs and medicines came about from somebody fooling with the drug, and trying it in some disease state. Chlorpromazine, your claim to fame, is a classic example. If you look at the history of benzodiazepines and many of the other psychoactive drugs, their application in therapeutics came about because somebody saw it and tried it in a disease state. It's been fascinating to watch people develop these drugs, e.g., the serotonergic drugs, which have effects as serotonergic agonists and antagonists. To develop these selective ligands for receptors, requires running a dozen or two dozen clinical trials in different sort of disease states, e.g., schizophrenia, types of schizophrenics, antidepressives, appetite suppressives, or whatever you want to name. They may or may not work in these areas, but they require a very extensive development program. I think we're in the very early stages of seeing more people becoming clinical investigators again, to begin trying to work with a unique drug in small scale studies rather than these big pharmaceutical development programs, getting back into clinical investigations at the human level. That's my view of much of this, and I think it's going to start changing. And,

there aren't many of us left, who do these human sorts of pharmacologic experiments, enough to keep me in business.

LH: You don't have to convince me. I'm a human pharmacologist, myself. Well, anyway, among all of your other credits is the fact that when Lexington had to close and move to Baltimore, it was you who shepherded the Addiction Research Center from one location to the other, and did it with enormous success, far more than some of us would have predicted.

DJ: I moved up there in 1979. The justification for Lexington was that you could do human experiments and have resources and facilities to do human experiments that other people couldn't do. Not that they weren't capable of doing it, but just because at Lexington you had the experience; you had the history; and you had the resources. So, I rebuilt the human research unit, and felt that this should be the flagship. This was another interesting part of history, if you like stories. Bill Martin, once it was clear that Lexington was closing, Bill did not want to leave. So, Bill became Chairman of Pharmacology at the University of Kentucky; I was made Director in about '76 or '77. And, then, I spent the next two years organizing a move from Lexington, and finding a home, which is another story. I became a bureaucrat, an administrative bureaucrat. But, there was one interesting thing, which happened at the time. Another thing that I never thought would have the profound effect on society that it did, which I thought, at the time, was really a straightforward, trivial experiment. I had a memo from Bill Pollin as I was then, Director of Intramural Research. One of the things you do as a director is you write lots of memos, you respond to memos, you know that if you have this amount of money what you can do with it; how're you going to solve this problem; what sort of size of a science experiment can you afford? So, you had to be very adroit at writing memos and responding. At that time, the NIDA Council was pounding on Bill Pollin about the very simple idea that heroin affected less than one percent of the population, while cigarette smoking affected fifty percent of the adult population. And, the Institute wasn't doing anything about smoking. I think Avram Goldstein was on the council then and wanted them to do more about smoking in terms of the Institute's research activities. The idea was that this could be done at the Center, instead of the Cancer Institute getting all of the money for cigarette smoking. So, Bill Pollin, as the institute director of NIDA, wanted to get some of the money to solve the problem of smoking. So, he sent a memo, and I responded that there were a couple of things, which occurred to me, that we could do to look at cigarettes and tobacco. We were looking at opium, which had morphine; we had fermented beverages, which had alcohol; we

had cannabis, which had tetrahydrocannabinol; we had mushrooms, which has mescaline. Each of these had an active ingredient, which was responsible for the pharmacology. And, it would seem to me that it was hard to argue that God would make tobacco different from these other plant products. You could hypothesize that nicotine would have the properties of a reinforcing drug, which was similar to these other drugs of abuse, which we have shown shared some reinforcing properties. And then, I thought that the way to do this, was to determine the abuse potential of nicotine as a lead compound and then to define addiction in terms of a behavior, as was the commonly used approach for all drugs of abuse. It was quite obvious that there were certain people who compulsively used tobacco, who couldn't stop, and by that definition, by the compulsive use and inability to stop, they were addicted to tobacco smoking. The question was, whether the mechanisms of that behavior was similar to the mechanisms, which we felt underlie the behavior observed with opiates and other drugs. So, I started this out as a process, and at that time, most people didn't think nicotine was an addictive drug. Smoking was a habit. The first thing I did was to recruit Steve Goldberg, who had been a pharmacologist up at Harvard, and Steve was expert on monkey self-administration. And I said, "Steve, people have showed that the monkey and other animals don't self-administer nicotine." I said, "This is the project. I have a job for you. Okay, this is what the money comes for. They gave us the money. They gave me permission to do this. This is what you have to work on to justify your coming into Intramural Research." So, Steve did this and really showed that by doing the experiment the right way, nicotine was highly reinforcing, and self-administered when given with limited access.

LH: Were these the first self-administration experiments with nicotine?

DJ: Yeah. There have been others, but these were the first to show that nicotine had a reinforcing property. When we moved up to Baltimore and I had rebuilt the lab, the first experiment up in Baltimore was in response to a request from Bill Pollin and Bill, "We've got all this stuff about clonidine in opiate withdrawal from Herb Kleber's Yale group and a lot of people don't think it's real." So, I set up and did the experiments in the controlled study of clonidine vs. placebo in opioid withdrawal. And then, my friends down the hall, George Bigelow, Roland Griffiths, and Maxine Stitzer had been doing some stuff on cigarette smoking with a guy named Jack Henningfield. So, I said, "Jack, you want to come and have a Fellowship with me in Intramural Research?" And he said, "Sure." So, I said, "We really should do something about nicotine, study its reinforcing effects." I said, "We're going to do the classic abuse potential

studies.” The first thing he did was review the literature, and he wrote a paper showing how nicotine and heroin were similar in what they did. We got some nicotine, pure nicotine, from a reference lab, some place. And, we put nicotine in a solution and we did a rising dose response curve. We gave them an injection, nicotine in the vein; gave placebo, and then, three doses of nicotine. And, what we discovered was, if you just listened to them, it was a very short acting drug, but you asked them what it felt like, they said, cocaine or heroin. Now, these were addicts, who’d had intravenous experience, and we’re giving them nicotine. We must have done a hundred people, this way, over the years. The next experiment we did was with phenylamine, I had bought some infusion pumps, because I had a hypothesis, and it’s still a good hypothesis, that perhaps, one of the trace amines was the pathway for amphetamines. And, we had done phenethylamine in the dogs at Lexington and showed they were reinforcing, very short acting, and I had gotten a study and a protocol and IND to do phenethylamine infusions in humans. It never came about, but I had the infusion pumps. And, as it happened, we moved up from Lexington and brought the infusion pumps with us. So, I said, “Jack, as an experiment, let’s take people and let’s see if people will self-administer nicotine.” So, we took people who were smokers with quite a history of intravenous drug abuse and we sat them in a room. I think the experiment was for two or three hours; we put the catheter in the vein, hooked up to a syringe, and we hooked it up to a lever. We had a computer monitor and we had them on cardiac monitors and told them, in order to get paid, all they had to do was sit there. If they sat there, they could smoke, but if they pressed this lever, it was hooked up to a pump, which gave nicotine. So, we did that with these people and it was amazing. Almost all of them started testing the lever, and pretty soon, they were injecting nicotine; when we’d look at lever presses, it was very regular, just like puffing on cigarettes. So, we clearly produced results that showed nicotine was reinforcing. Then, we measured this with both the smoking and the nicotine. We had a scientist from Japan, my friend, Tomogi Onagida, and he arranged for a young man to be trained in clinical research, a Japanese fellow. The wonderful thing about the Japanese, they’re very stoic and very patient. So, we were measuring the effects of nicotine, in terms of its clinical pharmacology, what it does to the blood pressure, what it does to the heart rate, what it does to the pupils, and subjective effects. The problem is, if you give a dose of nicotine, the central effects are gone within two minutes. The blood pressure effects will last longer and the plasma levels last even longer, but the central effects of nicotine are very short acting. So, it’s a very hard thing to measure these effects, which last one minute, but we completed

this project and published the paper showing that nicotine was typically reinforcing. It raised the same subjective liking scales that heroin raised, the MBG. And then, we did combinations of self-administration and of subjective effects. This, we did out of curiosity, as I thought this was really quite obvious in what it showed and we published the findings. And, to his credit, the individual, who's really to be credited, was Bill Pollin, who was Institute Director. Bill saw these data and saw that we had the scientific basis for saying that cigarettes are addicting. I don't know why Bill had such an interest in smoking, but he did take this as his life's work. Bill was the one, who took this as an institute responsibility, on the basis of our data; once we had the data, he took as our mission to eventually get on the cigarette package that cigarettes are addicting. He really led this battle up through the Public Health Service and HHS and to Congress about the addiction potential of nicotine. I thought these were really relatively straightforward experiments, which had been modeled on classic abuse potential studies we had done with dozens of drugs, but I never thought, in retrospect, that they would have the impact that they had.

LH: Well, it's too bad your message didn't get across to some high ranking politician, but that's another matter. Anyway, it's been great talking to you, Don, and I'm sure you've got, as I said at the beginning, you've got more experience with studies of humans in taking substances that 283 could be abused, than almost anybody alive, now. And, I hope you continue your great work for a long while. Thank you.

DJ: Thank you. It's been a pleasure.



## 18. SAMUEL C. KAIM

LH: It's Monday, April 14, 1997, and we're in Washington to continue videotaping the History of Psychopharmacology, sponsored by the ACNP. My name is Leo Hollister and I'm pleased to welcome, today, my old friend and colleague, Sam Kaim.<sup>5</sup> Welcome, Sam.

SK: Thank you.

LH: I guess we've known each other for longer than we care to remember, what is it, 1960 to 1997?

SK: 1960 to 1997.

LH: Thirty-six years.

SK: Thirty-seven.

LH: That's a long time. Tell me, Sam, how did you get started in medicine and in psychiatry and, eventually, in psychopharmacology? You can break that up.

SK: Well, I went to medical school in Zurich, Switzerland and the teacher, who impressed me most, was Hans Maier, the Chairman of Psychiatry at the Burghölzli. He was a dynamic man, had had five wives and many kids. He was a successor to Eugen Bleuler and I had occasion, during my stint there as a resident after graduation, to translate Bleuler's last paper into English for an American journal. That's a paper on The Biological Memory of All Cells. This is way before anyone knew about DNA. Bleuler was really a wonderful, gifted man. He was a little fellow with a long beard, a lot of stories about him. After he retired and when Maier succeeded him, there's a story about Bleuler standing on a street corner in downtown Zurich and he kept trying to get across the street. He'd put one foot down, then retreat, did this for about thirty minutes. A policeman came over and said to him, "Old man, you look like I ought to take you to the Burghölzli" and Bleuler said, "No, don't do that. I spent thirty years there. I've had enough of that place."

LH: Of course, he was the director of it for many years.

SK: He had been the director for many years.

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<sup>5</sup> Samuel C. Kaim was born in New York City, New York in 1911. His undergraduate training was in Cleveland at Western Reserve (Case Western) and his medical training in Switzerland, at the University of Zurich, with a psychiatry residency there at the Burghölzli Clinic. He spent much of his research career at the Veterans Administration and became the first director of an Alcoholism Service in the VA which after Vietnam expanded to Alcohol and Drug Dependence Services. In 1975, he became a director of staff of the National Academy of Sciences that coordinated one of the pilot studies of naltrexone in the treatment of heroin dependence. He served as a consultant to NIDA until his retirement in 1993. He died on 24 March 2012 in Washington, D.C. He was interviewed in Washington, D.C. on April 14, 1997.

LH: He was a kind of charismatic teacher that got you interested in psychiatry.

SK: Right.

LH: You, eventually, trained there, didn't you?

SK: Yes, I trained there after graduation. I spent a couple of years at Burghölzli, stayed there for two years, and it was during that period that I got involved with psychopharmacology of the time.

LH: We're talking about what date now?

SK: 1937 and '38. Well, I'm a pre-historian. Anyway, I was in charge of the insulin shock and Metrazol convulsive therapies at the Burghölzli and, at one time, I used it in combination, so, they were my first two psychopharmacologic agents that I worked with. Adolph Meyer used to visit there, periodically, and I remember visiting his clinic in Baltimore, the Phipps at Hopkins, and it was the mirror image of the Burghölzli. I felt like I'd stepped back in time to my own time at the Burghölzli. Burghölzli was quite a place, still is. Manfred Bleuler, Eugen's son, I shared the podium with at the University of Louisville on two occasions when they had their international psychopharmacology seminars.

LH: That was one of John Schwab's.

SK: Schwab's, yes. One of our patients was Einstein's son, who was a schizophrenic. I saw a piece in the paper, recently, it was quite interesting, that Einstein never visited him. He did send a hundred dollar check every month for his keep. We had a private wing and the son was in this private wing. Imagine a hundred dollars a month at the Burghölzli, to have a private room and great therapists.

LH: You can't even get a glass of beer in a hospital these days for that.

SK: You could get a breakfast, maybe. Anyway, it was quite a place.

LH: Do you think that Einstein just couldn't deal with his son's mental illness?

SK: I don't know. He was an interesting man, apparently. I never met Einstein, but the son was interesting. Every time we gave him ground privileges, we'd have to revoke them. He had a habit of going behind the women patients and goosing them.

LH: Well, he wasn't totally crazy, was he?

SK: In 1938, after the Anschluss, and the Nazis takeover of Austria, the New York Times correspondent in Berlin had his wife as a patient at the Burghölzli. She had broken down on the trip to Europe and he decided Europe was getting too hot for him and his family, so he asked me to accompany him on the boat from Paris to get back to the states.

LH: That must have been a nice assignment.

SK: Yes, except she was a violent, unpredictable patient and she had a heart condition, so we couldn't sedate her very heavily. And, she tried to jump overboard a couple of times. At one point, I was holding her ankles while she was trying to get through the porthole of one of our cabins. I earned the five hundred dollars and our first class passage. But, that's how I got back to the states. It was a question of getting out of Europe in time. In fact, Maier, who was half Jewish, told me how lucky I was to be an American getting out of Europe in 1938.

LH: This was in 1938.

SK: Right. We brought her to the Hartford Retreat for treatment, which is now The Institute of Living.

LH: Now, who was in charge of The Institute of Living then?

SK: I think it was a man named Burlingame. I'm not sure. I've forgotten now. I think that was his name. This goes back sixty years. Anyway, I spent four years in military service during World War II and, then, I went to private practice in Illinois. Then, after a short period, I went to the VA Hospital in Coral Gables.

LH: That would have been in 1950.

SK: 1950, right. And, it was there that I got involved with the EEG. I took training at the Medical College of Virginia in 1951 and, subsequently, a refresher course at the Boston VA. With the experience I had with Metrazol, I had a tool to use, the EEG, activated by Metrazol, to assess patient's threshold to convulsions and this was my chief tool in psychopharmacology at the time.

LH: So, you used a Metrazol activated EEG to predict how much shock to give them to induce convulsion?

SK: I used the EEG, first, to assess the effect of various psychopharmacologic agents on the EEG. That interested me at the time. I, also, used these agents to allow us to do an EEG on patients who were restless, a little violent, and in some neurological cases. I was in charge of both psychiatry and neurology at the VA, there. So, I had lots of patients. I had sixty-eight patients under my care. I was usually the only psychiatrist there. I used these drugs to quiet patients down, so I could do an EEG. Well, two men from Roche approached me, I think in 1958, with four drugs, four numbered drugs.

LH: Hoffman-La Roche?

SK: Yes. I found one of the drugs of interest. It was RO5069, which at the time was called methaminodiazepoxide, and later chlordiazepoxide, familiarly known as Librium. It was the first of the benzodiazepines, which were brought over from Europe by Leo Sternbach, who had these drugs on his shelf for a long time. When he immigrated to the states, he got a job at Roche and the Roche people were looking for something in the way of CNS activity.

LH: Had methaminodiazepoxide ever been tried in man before?

SK: No, I was one of the first twelve clinical investigators of the drug.

LH: And, you were trying it in epileptics?

SK: I was mostly involved with epileptics and was trying it in patients who had seizures. The interesting part of it was that some of these patients were alcoholics. Actually, a lot of my patients were alcoholics, and I found that during withdrawal from alcohol, patients did very well with Librium; it prevented seizures and DT's. Roche and the University of Texas, then, sponsored the first symposium on psychoactive drugs, including the anxiolytic Librium, and a drug called, Nitoman, which I had rejected, among the four drugs that I had studied.

LH: Was that also benzodiazepine?

SK: No, it was a tetrabenazine.

LH: Oh, a tetrabenazine.

SK: Yes. I didn't think much of it, but, anyway, the twelve of us had a very good symposium. It was published in the Diseases of the Nervous System.

LH: And, that meeting was sponsored by Earl Cohen, wasn't it?

SK: Yes, he was one of the sponsors.

LH: He's still practicing in Houston.

SK: Is that right? You can tell him my "Regards."

LH: I will.

SK: The meeting was at Galveston. My good friend, Red Tyler, was down there. He had been my Chief during my service at Brooke Army Medical Center. He is a great guy. He's now dead. Anyway, the...

LH: So, your paper in Galveston was on the use of Librium for alcoholics and in epilepsy?

SK: Yes, in epilepsy, not in alcoholics, actually in anyone with seizures. I think eight of them were epileptics and several were alcoholics. That's where I got into alcohol withdrawal and using Metrazol activation. In epileptics, who had been on Dilantin and other anticonvulsants, I did a

base EEG, than Metrazol activation to see what their seizure threshold was, before I would gradually taper them off Dilantin and start increasing the dose of Librium. And, then, I would do the same, do an EEG, followed by Metrazol activation. I found that in most cases the threshold increased so, that patients were doing better with Librium than they had with their previous anticonvulsant medication. And, also, their seizures were decreasing, especially of those involved with alcohol. So, we thought we had a good anticonvulsant, as well as an anxiolytic in Librium. We had a patient in status epilepticus and I found that an intravenous dose or two of Librium would stop the status. This was before Valium, which is now the drug of choice for status epilepticus.

LH: But, didn't we use intravenous sodium pentothal for status at the time?

SK: Yes, but it didn't really do a lot, and Dilantin intravenously wasn't nearly as good as Librium. And, then, Valium was even better. Valium is now the drug of choice. As Librium was the first of benzodiazepines, a new class of psychoactive drugs, there was a lot of interest in this symposium. It was picked up as an interesting and provocative new idea in psychopharmacology, and in 1960, I was called up to Central Office in Washington to present my findings to the Research Service at the Central Office. Ivan Bennett had just left. He had been the Chief of Research in Psychiatry at the Central Office. He had just left to become the clinical research director at Lilly. After my presentation, I was offered his job. I took it, reluctantly, because I'd been in Florida ten years.

LH: And you had to leave Coral Gables.

SK: Yes and I came in time for the blizzard of the Kennedy inauguration. My then wife, Polly, was a hostess for the inaugural committee, and I had to chauffeur her around in all those snow drifts. We had about three feet of snow and Washington doesn't do well in snow. I think we were the last car on the road. We were escorting governors around to hotels where they were supposed to stay.

LH: Polly was from Iowa and you went to college in Cleveland, so you knew something about snow.

SK: Yes, a little bit, and I had a little Thunderbird, which did very well in snow. Anyway, I became involved in the big research the VA had, the pioneering cooperative study, which NIMH and many other organizations subsequently followed, carrying out multi-sited studies with various new drugs as they came along. Now, I had never been in any of their studies when I was at Coral

Gables. I had always been involved in my own work, with the EEG mostly. I'd done a study, back in 1953, on the EEG and multiple sclerosis and had done a number of studies, which I'd presented at Harvard, at MIT, and at other places. But, I'd never done any study with the cooperative study group. When I came to Central Office, it occurred to me this would be a great vehicle to study alcohol withdrawal, which I had pioneered with Librium. I thought let's see if Librium will stand up to the older methods of treatment. So, we tried four drugs, including Librium in 537 cases in 23 of the VA Hospitals. And, the patients on Librium had a total incidence of two percent of seizures and DT's, compared with over ten percent in each of the other groups. Librium, now, has become the drug of choice in the treatment of alcohol withdrawal. Two psychiatrists at the University of Missouri wrote a very nice paper on the use of benzodiazepines in alcohol withdrawal. They had sent questionnaires to 101 hospitals inquiring about the drugs they used for alcohol withdrawal and eighty-two percent were using one of two benzodiazepines, Librium or Valium. And, when questioned why they had switched from the older drugs to the benzodiazepines, thirty-six of them said, due to my paper. So, I feel that I did contribute something to American medicine, which has lasted and I am eternally grateful for, at least, bringing one standard medication to the scene.

LH: Well, Librium detox is still a favorite method by a lot of people.

SK: Right. I think Librium is still used more often than Valium, which is second best, I would say. I was, at one time, offered the job of clinical research director at a pharmaceutical company back in 1967. When I told the Chief Medical Director, at the time, that I was leaving, he said, "Oh, you can't do that, Sam. What can we do for you to keep you here?"

LH: Was this Bill Middleton?

SK: No, this was Hal Engle. So, I told him, "Look, Hal, I've been shuffled around about alcoholism all these years. A third of my patients have been alcoholics, yet, the VA and the military keep denying alcoholism as a disease. I think it's about time we faced up to it. I'd be interested in staying if we could have an alcoholism service." We'd never had one in the VA. In fact, there were all kinds of rules against admitting alcoholics, in the first place. They had to have cirrhosis of the liver or some severe complication before they could be admitted. So, Engle said, "Okay, you are now the Director of the Alcoholics Service of the VA." I got an office and a secretary.

LH: That was a fortunate stroke, because you became the person, who made being an alcoholic acceptable. How many psychiatrists would treat alcoholics in those days? None!

SK: That's right. In 1962, I had come to your hospital in Palo Alto and set up a conference to bring together fifty scientists from various disciplines to plan a program of research on alcoholism. This was back in '62. I used your offices, your secretary. You were very kind to me and we gathered fifty eminent scientists who came up with all kinds of ideas for alcohol research. Making alcohol research respectable finally opened the doors for alcoholic patients; who didn't have cirrhosis of the liver and that, in turn, made it a little easier for the VA to accept my idea of having an alcoholism service. Subsequently, with the Vietnam War, we were getting reports of opium addiction among our troops in Vietnam. I was encouraged to add drug addiction to the alcohol service and we, then, had an Alcohol and Drug Dependence Service in the VA, starting about 1970. I was on a task force at the Pentagon and, also, on one at the White House about what to do about all these drug problems. The Admiral, in charge of the Pentagon's task force, kept denying it was a problem. He said, "There are only 69 cases of heroin addiction worldwide among all American troops." I said, "Bill, how did you arrive at that?" He said, "Well, let me call the office." He calls his office at the Pentagon and comes back, "69 cases, that's all we have." I said, "Would you define those cases"? "Well, those are the only objective cases, the overdose ones. Nothing else is objective." We already had 2,000 cases at the time in the VA system.

LH: How could somebody be so blind?

SK: I had to go to meetings at the Pentagon. We had meetings almost every week, trying to decide what else to do. We had an edict from Nixon, "Cure these patients within one week." I laughed. All the Admirals and Generals in the office at this meeting kept their heads down. No one dared to look up to laugh. I was home free. I could laugh, because I wasn't in the military. However, this reminds me of another problem I had. In 1966, there was an annual meeting of the American Association of Medical Surgeons of the US in Washington and I was asked to Chair a program on Alcoholism. And, I ventured a theory that military service contributed to alcoholism. The soldier drinks after duty, the loneliness of being away from home and so on. Well, the AP picked that up. I got "holy hell" from the legal department and, also, from the Chief Medical Director. "How can you do this in the middle of the Vietnam War? What American mother now wants her son to go into service? This will destroy the war effort." Although, it nearly did; we did not win that war.

LH: No.

SK: Anyway, the alcohol was my lead into all kinds of things, but, also, it led me into lots of trouble. On the drug side, the VA had started a study on LAAM, a long acting substitute for methadone, and I took it on. After the VA study, the Special Action Office on Drug Abuse headed by Jerry Jaffe and I plotted what next to do with the drug problems. I took him and his lieutenant, Jeff Donfelt, to dinner at my country club and we came up with three research projects for the drug problem in the country. One was to find an effective but non-addicting narcotic as an analgesic. Well, the National Academy of Sciences Committee on Drug Dependence had been looking for that drug for fifty years without any success. So, we bypassed that idea. It's still on the books, but that one, luckily, we let go. The second one was to find a long acting substitute for methadone and that was the LAAM project, which I pursued for twenty years. The head of the neuropharmacology section at FDA didn't like addicts. He wouldn't review LAAM. So, I would see him every year, sit down with him; the White House encouraged him, also, to review LAAM. But, he wouldn't budge. Finally, the FDA started a new program on orphan drugs and their first project was LAAM. At the same time, NIDA had started a new program on new drug development. Also, they picked up LAAM, so LAAM finally became converged between the FDA and NIDA. I was brought on as a consultant, as they called me the Grandfather of LAAM.

LH: Well, it took long enough for it to reach maturity. It was almost twenty years from first studies to its final approval, two or three years ago, wasn't it?

SK: It was twenty years, from 1972 to 1993, twenty-one years. Bill Martin was on the panel. Luckily, the FDA panel had some good people on it, including Bill Martin. Anyway, they finally approved it. One of the questions about LAAM was its long lasting effect. So, in 1981, Don Jasinski, who headed up the Addiction Research Center for NIDA, sent me on a fourteen clinic visit. These were fourteen clinics still using LAAM after many years. And I found that no one had died from LAAM, no serious complications, no serious adverse events. The patients liked it; the staff liked it. I brought that report back to Don Jasinski, and still, the FDA wouldn't look at it. Naltrexone had appeared on the scene. Dick Resnick had been doing some work with it. It was synthesized at Endo, which, subsequently, became a part of DuPont. It was really in the public domain. It had been around.

LH: Who was the chemist that developed both nalorphine and naltrexone?

SK: Bloomberg.

LH: Harold Bloomberg. I've been trying to think of his name.

SK: My memory isn't great, but, occasionally, a name comes back.

LH: You've got a few years on me, but I'm getting old, too. I've always thought that he didn't get as much recognition as he should have, because they were very important drugs. And, of course, about naltrexone, we still don't know the whole story.

SK: That's right. The Academy took it on, reluctantly, as a small multi-sited project. You were the Chairman of that committee to evaluate narcotic antagonists. The National Academy of Sciences never had done this before. This is the first time they had taken on a study; usually, they just review other peoples' studies. This is the first study that they took on. You were the Chairman of the committee, and I was the Director of the Staff doing it. We recruited five clinics. We found retention of patients in the study very difficult, because this is a drug without any positive reinforcement. The patients found no pleasure from it.

LH: Say your excuses and leave, but you can't do that with methadone.

SK: Yes, right. But, anyway, the retention rate was not great, but we had no serious problems with the drug. And, one of our criteria for success was decrease of craving. We had a craving scale and it did show that craving lessened while patients were on naltrexone. Also, it reduced appetite. Some drug companies got interested in possibly using it as an appetite suppressant, but I don't think that went anywhere. It's a nasty drug to take, very bitter.

LH: Have you tried it?

SK: Oh, yes, sure.

LH: I wrote a paper some years ago about Adverse Effects of Naltrexone and, I think, before that, Lew Judd had published one on naloxone. But, you know, if you block the endorphin systems life isn't the same.

SK: You know, I asked that question of Hans Kosterlitz once. I said, "What happens to the endorphins when we use naltrexone?" He said, "Oh, endorphins, you know, they're so ephemeral, they last only for a few seconds. Naltrexone is a long acting drug. It isn't going to do much one way or the other." He didn't think it would do anything.

LH: Well, we tried to measure dinorphine in using Albert Goldstein's lab, but the data was so fragmentary, that we couldn't make much sense out of it. But, nonetheless, you succeeded.

SK: We did get the project finished and, now, the people, who are highly motivated, can kick their opiate habit with naltrexone, people like doctors, lawyers, executives.

LH: If you've got a lot on the table to lose, you're going to.

SK: That's right, that's right. And, naltrexone is, also now, being tried on alcoholics with some success.

LH: That one puzzles me.

SK: Yes, me too.

LH: You remember Virginia Davis at the VA in Houston?

SK: Yes, I remember her talking about tetrahydropapaverine....

LH: That's right. She thought that alcohol dependence was opiate dependence in disguise, but nobody else really believed that and Sievers took off on her in the worst sort of way. But, I don't know how to explain how naltrexone works.

SK: Yes, that's one of the evolving mysteries of psychopharmacology. Apparently, in some peoples' hands, it works. Be that as it may, I still am hopeful that narcotic antagonists will have a place in our armamentarium.

LH: Well, which way do you think we should go about cocaine dependence? Should we go for substitutive route like methadone or the antagonistic route like naltrexone?

SK: I would go for the antagonistic route. I think it's preferable, theoretically. Whether it will work is another question. You know, methadone and LAAM do work; naltrexone is an iffy thing yet.

LH: You know, theoretically, it should be perfect.

SK: Yes.

LH: Like we said, it's perfect but you can't give it away.

SK: Yes, right. Now, there's a question about where do I think we're going in psychopharmacology. You did a good paper on that, I recall. At an ACNP meeting, you gave a paper on "The Future of Psychopharmacology."

LH: I did?

SK: Yes, you did. It's published somewhere. If you look in your files, you may find it. It was a good paper. I enjoyed it. I would say, judging from my own limited experience with the benzodiazepines, that they are going to play an expanded role in seizure control, either alone or aligned with other anticonvulsants. I think this is one area, which I'm almost sure that there will be a very good addition to our therapeutic armamentarium.

LH: Why do you think that Roche never picked that up though?

SK: Well, I was at a meeting in San Francisco once, early on, at the time when Valium was first used for status epilepticus, and when I saw that in the insert from Roche, no mention was made of this, I got up and, rashly, said, I was very upset that Roche hadn't included status epilepticus as an indication for Valium.

LH: Well, you see they can't do that unless they've produced data to the FDA.

SK: Yes. Roche, apparently, didn't want to open the whole subject up because to prove that Valium is good for that indication they would have to do more studies. They felt that physicians have great leeway in using drugs that are proven.

LH: Off label use.

SK: Yes and they didn't want to go through all the problems that I had with LAAM.

LH: You're not going to sell a hell of a lot of drugs to treat status epilepticus.

SK: No, that's right. There wasn't a great sales pitch. I don't know if they have it in there now; I haven't seen a PDR lately. But it is a great drug for status and I'm sure it saves many lives and Librium, which I did even before Valium, also, could be used the same way. So, that was about what I see in the future.

LH: Well, I'm still trying to follow up why you think that benzodiazepines still have a future, because there're a lot of people ready to write them off.

SK: Well, I think that would be very wrong. I know when I first presented papers at meetings about Librium's use in alcohol withdrawal, I had people, eminent alcohol specialists, so called, who shouted me down, "You're going to get these people hooked on benzodiazepines, on Librium or whatever will follow. These are addicting drugs." A drug that is used for, perhaps, ten days for an indication like alcohol withdrawal is not going to lead to addiction and, as far as I know, there is no case that has become addicted after treatment for alcohol withdrawal. It's like someone getting morphine after surgery. He gets morphine for two or three days, maybe, for the post-operative pain. He is not going to get hooked on morphine. If a doctor, incautiously, uses it for several weeks, sure, but I don't know of cases, after two or three days of legitimate analgesic use.

LH: Medical use of these drugs very rarely is followed by abuse. The Committee on Problems of Drug Dependence is one that I probably feel best about my participation in and that Committee had begun to question whether the search for the non-addicting analgesic was worthwhile. How many people get addicted to the addicting analgesic, in medical use? None!

SK: You are right, I think....

LH: And, God knows how many potentially good drugs we kept from going on the market by being concerned about addiction.

SK: Right. I spoke to Nathan Eddy, at one point, about the quest for a non-addicting perfect narcotic. Even he had started to question this whole thing. I remember I was at one of the early meetings of a committee at the Academy that consisted of about a dozen people. And we sat around a conference table and Vince Dole was sitting outside waiting to present his first talk about methadone. We had him come in. He spoke to us and we all thought it was a very good talk and he had a very good idea. Addiction at the time was treated as a criminal offense, not as a medical problem. And, here we had the first medical treatment for addicts. Henry Giordano was a liaison member of our committee, from the Bureau of Narcotics and Dangerous Drugs. Giordano asked Dole to leave the room and he said, "I'm going to call the police and have that man arrested. He's breaking the law", which he really was, because, until that time, doctors were not allowed to prescribe addictive drugs to non-addicts. I know; I was in practice and that's one of the things I knew about. And, we had to talk him out of it. We said, "Look, Henry, this guy has a treatment, finally, for this problem. The jails have not cured them. Let's give him a chance." And, we, finally, talked him out of arresting poor Vince Dole and his wife, Marie Nyswander. That's a marvelous thing they did, with methadone.

LH: Oh, yes.

SK: Mary Lasker invited me and Dole to her apartment, at one point, to make some plans for the future of the drug problem. She was very supportive and Vince and I went over all the possibilities, as I had done with Jerry Jaffe. I'm afraid we didn't come up with any new solutions though. It's a tough problem, still, and it's at a plateau. We have about half a million heroin addicts in the country. We'd probably have more than that in the way of cocaine addicts and multiply that figure if marijuana is included. So, it's still big problem; new psychotherapeutic agents probably will help us solve some of the problem. What they will be, I don't know.

LH: Well, now that you have brought it up, what do you think of the current efforts to solve the drug problems? We've been going on a war against drugs, now, for over twenty years. It doesn't look like we've won very many battles.

SK: It's very disappointing. The anti-addiction program hasn't worked. Jail hasn't worked. The limited presidential programs have been of limited value. The drug therapies, also, have had some effect, except that we perhaps reach only twenty percent of addicts, at any one time, with a drug

program like methadone. So, we are not winning this battle. It isn't getting much worse. It's on a plateau. I got into it in 1970, so, it's twenty-seven years ago. I would say we are about where we were then, in the way of population of addicts.

LH: We are with heroin and, possibly, with marijuana, but I think cocaine has increased quite a bit.

SK: That's correct. Cocaine is now the drug of choice.

LH: And, of course, another local specter is ICE; methamphetamine is back again.

SK: The ecstasy drugs, is a dangerous area. And prescription drugs are, also, being abused. So, we're in a very precarious situation where we don't have any definitive answers. We're groping, yes. And, it's a long time to grope. I remember when I was at the Burghölzli; Maier presented a couple who were addicted. And this was a wealthy couple, who had spent all their money on drugs; they had sold their house in order to get drugs, the wife had even sold her clothes. She came to our meeting in a fur coat and that's all she was wearing. That was my first introduction to addiction. I was very impressed by this as a problem and felt we need to do something about it.

LH: Didn't you mention that part of your training was at the Institute of Living later on.

SK: I didn't train there, no. I just took that woman patient there. I didn't train there.

LH: For a long many years, that was the place to go if you were famous or a very rich alcoholic, before the Betty Ford Clinic took over all the business.

SK: And Burghölzli used to get their share of kings, princes and merchant princes. I had many famous patients while I was there.

LH: I think your campaign, first of all, to make the VA recognize the alcohol problem and, secondly, to make it legitimate as an illness to be treated by the VA, was a major step forward and I think you, eventually, brought the treatment of alcoholism back into the domain of psychiatry, where before it was sort of an orphan, with either general practitioners or internists taking care of the consequences. You know, when you had cirrhosis of the liver, you went to the internist, but nobody was much interested in trying to prevent that.

SK: I did have one-recognition about my role in alcoholism. The NIAAA had its twenty-fifth anniversary meeting last year; they picked sixteen studies, the seminal studies in alcoholism, and one of them was the one I did on alcohol withdrawal. So, I felt I had achieved something in that field, being selected as one of the sixteen seminal reports. I got one commendation from NIDA for my role with LAAM. It was an interesting commendation recognizing my historical knowledge

of LAAM and my help in furthering it to approval. I feel I have accomplished a little bit of something and I feel gratified with what I've done.

LH: That's what you need when you get to be our age, some sort of accomplishment before we turn in our chips.

SK: I was thinking this video may prove of some help to my son, Eddy, who is working in the pharmaceutical field, in planning my obit. So, I will let him see the video and he can write my obit from it. So, it will have some use.

LH: I remember Nathan Eddy used to be notorious for drowsing off during lectures and, yet, he could pop up with the most salient question afterwards.

SK: Sounds like you.

LH: I could never pop up with a question. I said to him, "Nathan, rumor has it that you aren't really sleeping, that you're just intently listening." And, he said, "Don't you believe it."

SK: You also always knew when the question arose, and the answer.

LH: Well, anyway.

SK: I enjoyed my contacts and friendship with you and Klett, and Walter Ling and Jim Musser, and so many others in the VA.

LH: That's one of the other satisfying parts in one's career, the people you meet, the friends you make, and the really bright people you run into. I can't think of any other career more satisfying. Would you change it?

SK: No, no. I met Bleuler, Adolph Meyer, Kosterlitz, Goldstein, Jonathan Cole, all the greats in the field. Bleuler was especially a marvelous man.

LH: Well, I've always thought we've been extraordinarily fortunate in medicine and in science, in general, to be doing work we enjoy. I always say, rather than being a member of the "Thank God, It's Friday" club, it's better to be a member of the, "My God, It's Friday" club. A week goes by so fast and you haven't got as much done as you hoped, it's nice to be in that position. Well, thank you for sharing your thoughts with us. It's awfully good to see you.

SK: Well, thanks for having me and I wish you well. You're still in use.

LH: Off the record, how old are you now?

SK: Eighty-Five.

LH: Oh, my goodness!

## 19. DONALD F. KLEIN

LH: I am Leo Hollister and I am interviewing Donald Klein.\* He has been president of this great organization and he's been Mr. Panic Disorder for the last 30 years. In fact, I'm normally against new diseases, syndromes and signs, but if somebody came up with the idea of a Klein Syndrome for Panic, I would be perfectly agreeable to it. But, how did this all get started, Don? What made you go into medicine, in general, and psychiatry, in particular?

DK: I wanted to be a scientist since childhood. No one in my family was a scientist, but my father fostered this by regular trips to the museum of Natural History and Planetarium. Actually, when I was in high school at the Bronx High School of Science, a great experience, I wanted to go into Chemistry as a research scientist. I had been fooling with chemistry sets since I was a kid. I loved it and did well in Chemistry. And, then, when I got to college, I stumbled onto Freud. I got to college young; about 15 when I started. And I was wandering around the stacks of books in the library one day and found Freud's books; he was talking about all the things I was interested in. It was mostly sex and I figured this guy must have something going for him. So, I really got interested and read a great deal of what he wrote; my desire at the time was to be a research psychoanalyst. And I understood that to be a psychoanalyst you have to be an MD. It struck me that was pretty foolish, but I didn't mind becoming an MD, so...

LH: So, you choose to become a psychiatrist before you actually entered medical school. You were going into psychiatry to be an analyst.

DK: Right, exactly, psychiatry was sort of a steppingstone to become an analyst. Anyway, in 1948 I graduated from college, top of my class. I was 18, then. I couldn't get into medical school, probably because the vets had all come back then, but also anti-Semitism for medical school admission was very real then. So, I spent a year in NYU graduate school in Biochemistry and Physiology, which was actually not a lost year, as I basically learned how to use a library and some fundamentals of physiology and endocrinology. And, then, finally I got admitted to Long

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\*Donald F. Klein was born in New York City, New York in 1928. He received his MD in 1952 from SUNY Downstate Medical Center in Brooklyn, New York. He completed his psychiatry residency at Creedmoor State Hospital in Queens, New York. He has focused his work on clinical psychopharmacology, anxiety disorders, and depressive disorders. At the time of the interview, Klein was professor of psychiatry at Columbia University, and scientific director of the New York State Psychiatric Institute. He was interviewed in San Juan, Puerto Rico on December 13, 1994.

Island College of Medicine (LICM.) The only other acceptance was from Howard. LICM was extremely clinical, generally considered a baby catching trainee school. However, the clinicians were astute and critical, and the training to deal with patients has stood me in very good stead. In my senior year it became Downstate University. Downstate made a budding hematologist out of me, because psychiatry was so lousy and hematology, as taught by Janet Watson, was really engaging. She was a pioneer in hemoglobin molecular structure and Sickle Cell anemia. I worked as a laboratory assistant to Norman Kretchmer who had his PhD and was in my MD class. We did paper chromatography when there were only two papers, winging it with Pyrex pie-plates. Norm went on to be the head of NICHD and remained a good friend, although he consistently referred to me as a "spook." The psychoanalysts were terrible; they spent all their time reading to us from their textbooks, although we all knew how to read, and telling us if we had a question about anything that was our resistance or counter-transference. But, it didn't turn me off, completely. Anyway, I interned in the Public Health Service. It was in the days of the Korean War and I hoped to spend two more years with the Public Health Service, taking care of tubercular Eskimos, rather than go to Korea. But, then, I got fired at the end of my intern year, because Eisenhower had a reduction in force and the bottom half of the intern class was dropped. I was squarely in the bottom half, because I didn't get along with them very well at all. I asked too many questions. However, their psychiatry rotations were mentored by two very bright psychoanalysts, Richard Silberstein and Milton Horowitz, who also thought questions were resistance, but who were personally engaging and intellectually alive. This revived my psychoanalytic interests and I re-developed the misguided goal of being a research psychoanalyst. So, I was scurrying around. I had a wife and a kid at the time and felt lucky when I got a job as a first year resident at the Creedmoor State Hospital, where they gave me a house and a gardener, a maid and, probably, a chauffeur.

LH: Who was in charge of psychiatry there at the time?

DK: Nobody, when I was a first year resident, in 1953. Creedmoor was a 6,000-bed locked hospital and after I was given a book on the mental status, I was told that I should take care of my 300 patients upstairs. They also told me that the nurses would teach me how to do ECT, but fortunately, I knew that from my internship. That was all the training I got. It was a great experience, but also a great responsibility all of a sudden. The patients were fantastic. We had no psychotropic drugs at all in 1953, except paraldehyde and amyta; all we had was ECT and nursing care. And, then,

primarily because the draft was after me, I went back into the Public Health Service and spent two years at the Narcotic Hospital in Lexington, KY. That was a wonderful experience; that's what's turned me onto Psychopharmacology.

LH: Now, you jumped out of the Public Health Service earlier, but, then, you went back into it?

DK: I called them up and I said, "Look, I've got a whole year of psychiatric residency, don't you need me?" And, they said, certainly, with a whole year of psychiatric residency, my goodness we certainly need you down in Lexington, KY to run the Admission and Withdrawal Service. I didn't know much about admission or withdrawal or narcotic addictions or anything at the time, but I went down there and the guy in charge took me on rounds once. And from the next day I was on my own. I had 70 beds to take care of using methadone withdrawal. It was a terrific place and I liked it a great deal. I had complete misconceptions about what addiction and addicts were like.

LH: There were some giants working there at the time.

DK: Well, I met Abe Wikler who was probably the smartest guy I ever met, thinking deeply about psychiatry and pharmacology. He wrote a book called *The Relationship of Pharmacology to Psychiatry*. During the period I was down there, I actually had the opportunity to discuss with him what the contents of the book and its layout should be.

LH: It's a classic text.

DK: A classic book, which fell like a lead balloon, because it just came out after imipramine was introduced, so it had nothing about the antidepressants. And he missed the boat on lithium. He felt that lithium was having its effects by toxicity. Yet because of the thinking and the whole discussion of how you go about experimentally studying drugs and relating them to psychiatry, the book may still be the best single volume in the field. The book has disappeared, so, I don't know anybody that knows that book any more.

LH: Heavily underused, right?

DK: Well, I tell people about it, and especially my juniors. Anyway, I got involved while I was in Lexington with studies on reserpine, chlorpromazine, and LSD for a two-year period. The LSD studies were being financed by a mysterious foundation. As we found out later, they were funded by the CIA. The criteria for selecting subjects and the requirements for inclusion in the LSD studies were pretty clear. The people selected were from those with two or five year federal prison terms, who considered themselves "stoned junkies" and were never going to recover.

LH: A CIA front?

DK: The whole thing was due to brainwashing concerns, which was the glib explanation of the time. The Koreans had those American pilots, who had been shot down, getting up on TV and saying they were capitalist stooges. You didn't see the rifle pointing at them off screen, so it was assumed they had been brainwashed and LSD was the obvious culprit. Anyway, I made good friends with Wikler at that time, although he was really put off when he understood that I wanted to be a psychoanalyst. He thought that was not too smart.

LH: Heresy.

DK: But Lexington was actually an analytic hospital. It was run just like Chestnut Lodge. The head of the hospital was a training analyst and 50 patients were in intensive psychotherapy. They had a psychotherapist and an administrative therapist, who took care of all the grimy details like parole. In retrospect, it was a completely bizarre setting. I remember seeing at least one authentic miracle. I was in charge of a ward with 100 World War I veterans who had been hospitalized continuously since World War I. They weren't in the VA, because there wasn't any VA for World War I veterans. They were under a thing called Executive Order and had gotten bounced to Lexington from the psychiatric unit at St. Elizabeth's Hospital.

LH: But weren't they drug-users?

DK: No, they were just plain army folks who had gone psychotic during, or just following, World War I. Most of them just sort of sat around on the benches and looked at the wall. And they had gotten excellent nursing care and all sorts of interesting things with occupational therapy and psychotherapy. But whatever they got had not done any good to anyone. So, I decided to give them all Thorazine (chlorpromazine.). I gave them 200 milligrams a day, which was a big dose then. And I remember one of them came up to me, after about six weeks, and said, hey, Doc, when am I getting out of here? I never thought that could happen. It was really remarkable and made a big impression. I left shortly after and went back to Creedmoor, finished my residency and got into research. I was working first with a group of psychoanalysts, who were running an intensive psychoanalytic clinic devoted to six families with autistic children. These identical autistic twins walked around on their toes. I asked the supervising psychoanalyst how the mother had done that but was told this was resistance. That was somewhat disillusioning. When that boondoggle was shut down, I worked for John Whittier who was unusual, an MD, PhD, psychoanalyst and veterinarian. We did one of the first controlled studies on mepazine, a drug that everyone said was terrific because it didn't cause all those terrible side effects and mental confusion like other

phenothiazines. The only trouble with it was that it didn't work. It was the only phenothiazine taken off the market. That experience reaffirmed that double blind, randomized, controlled studies were a pretty good thing to do. I went to the New York Psychoanalytic Institute about 1957, and that's a long sad story, in itself. Essentially, I burned out two analysts and they got rid of me. I ended up in 1959 at Hillside, working for Max Fink. Hillside was a psychoanalytic hospital but Max Fink was a whole different character. He was a neurologist and psychiatrist who had psychoanalytic training and worked with Morris Bender. He was studying ECT and used it as an experimental treatment to be studied for its effects on brain function, rather than just as some sort of punishment. Also, he wanted to get involved in studying the new psychotropic drugs. And that's how I got going. Max was a complete nihilist. He did not believe in diagnosis. He thought that they had no evidence for any of the diagnoses because people in reliability studies, making independent diagnoses, did a very bad job of it.

LH: Still do.

DK: Probably. At least, we have some inclusion/exclusion criteria, now, but, then, we didn't have anything. So to study the new drugs, Max and I went to the head of the hospital, Lew Robbins. Lew Robbins was an analyst, but very broadminded. He wanted to understand things. And, we said, look, we've got to, somehow or the other, collect data on what these drugs do to people. And Lew agreed that we should do it and that I was the only person in the hospital, who could write orders for medication. I would write orders for anybody but the residents had to first call me up. And right then, I was able to ask why they were putting the patient on medication. I also interviewed the ward staff, resident and supervisor, as well as the patient. Then I would see the patients every week until they were discharged. Anytime the residents wanted to change the dose or the drug, they had to call me up and tell me why. That was the best learning experience I ever had, because I saw all sorts of things done that I never would have done, and some worked and vice versa. I did that for almost two years. During that period, I evolved this notion of pharmacological dissection. The idea came from the observation that there were distinct patterns of response to Tofranil (imipramine) and Thorazine (chlorpromazine). One of the patterns that I came upon early was that there were patients who had, what we now call panic disorder with agoraphobia. In those days, they called them schizophrenic, although not delusional or hallucinated. But when patients with this pattern went on Thorazine, that we thought was an anti-anxiety drug, they got much worse. That was very disappointing because at the time Menninger

believed that anxiety caused everything. Thorazine was good for schizophrenia that goes with very bad anxiety, and so, it should have been good for lesser anxieties. But it wasn't. And, then, when we got them, as a last resort, on Tofranil, it stopped their spontaneous panic attacks. So, I published that back in the early 1960s, but nobody believed it. They thought it was just some sort of crazy idea. First of all, Tofranil was an antidepressant and these people weren't depressed. And, besides, Thorazine was not an anti-anxiety drug, so why did it not work on them? And, it struck everyone very strange that you would have an antidepressant drug that would knock out panic, the worst form of anxiety, and make it possible for patients who were afraid to leave a room, go out by themselves. I did a long series of double blind placebo controlled studies, thereafter, which showed that I was, essentially, right, that imipramine stopped the panic attack. And developed a theory that agoraphobia was secondary to panic inciting anticipatory anxiety, followed by avoiding situations where you might get a panic attack and couldn't get to help or get out of there.

LH: Did you try any MAO inhibitors at that time?

DK: Yes, I did. As a matter of fact, in our second paper, we reported on 4 patients who responded positively with MAO inhibitors. But, I was able to point out that what we had wasn't a general antidepressant effect. These patients responded badly to ECT. So it wasn't that they were just depressed in some peculiar way. For many years, it was thought that all the antidepressants worked to block panic. Now, we know there are antidepressants that don't work. And I came up with this idea of pharmacological dissection, putting people together with a similar pattern of response to medication and, then see if there was something about them in their baseline state that you can use diagnostically. And that's the way I've been thinking about refining diagnosis.

LH: It is a rather unusual way of making diagnosis; choosing a drug that you think is good for that diagnosis, you would give them a drug and make the diagnosis after the fact, so to speak?

DK: Exactly. The first big study we did in this area of research is still one of the biggest studies ever done in a single place. We took 300 patients as they came along and randomly assigned them to placebo, Thorazine or imipramine and, then, we tried to figure it out as to what they responded. And that, actually, took me out of my antidiagnostic phase, because the best way I could make sense out of the various drug response patterns was to recognize that there were relevant diagnoses. But they weren't the diagnoses like schizophrenia that everyone was using loosely. They had been described a long time ago as agoraphobics and even before that as secondary to panic attacks by

Freud. But, then, there were depressed people, who responded poorly to imipramine and I recognized that those were the ones the English had described before as atypical depressions.

LH: That was Will Sargent?

DK: Sargent, Dally, West, and a whole group of English psychiatrists, who were very good observers, and recognized that there were peculiar depressions, who did not respond to ECT and tricyclic antidepressants but responded to monoamine oxidase inhibitors. I followed that up, years later, with Fred Quitkin, when I got to Columbia in 1976. It became the largest series of randomized placebo-controlled trials contrasting imipramine, phenelzine and placebo. Phenelzine worked by far the best. In the new DSM-IV, atypical depression is included as a parenthetical modifier.

LH: Now, as I understand it, in those days, you were trying barbiturates first in the treatment of panic on the assumption that those were considered the antianxiety drugs, but that these patients didn't respond to barbiturates. Is that correct?

DK: What happened was that panics wouldn't respond, but between panic attacks on barbiturates they would feel better. But, then, a panic attack would come along and, then, they'd start taking more barbiturates. What they thought was that a panic attack was the outgrowth of their chronic anticipatory anxiety. If anything, it was the other way around it was the panic attack that was promoting the chronic anxiety. So, a fair number of people who had a panic disorder ended up getting hooked on barbiturates and alcohol, which both actually helped anticipatory anxiety but not panic attacks.

LH: Now, in retrospect, of course, in the 1980's, alprazolam came along and that seemed also to work in panic.

DK: There's no question that alprazolam works in panic. You see, first, what I said was that panic had to differ from anxiety because imipramine knocked the panic out, and the person was left with the chronic anxiety and their phobic avoidance. I didn't say, although a lot of people thought I had said, that generalized anxiety disorder would not respond to imipramine. I just simply said that chronic anxiety would take a long time to go away. We then showed that for people who only had specific phobia and anticipatory anxiety, but not agoraphobia, imipramine was no better than placebo. Now, the question was whether imipramine works in panic disorder and alprazolam in generalized anxiety disorder? And, the answer seems to be that imipramine as well as alprazolam works in both. So that does confuse the issues, in terms of trying to get a neat

dissection. There were some interesting findings regarding this in the Upjohn study in which they compared imipramine and alprazolam. Two British psychiatrists did a cluster analysis of the patients' description of their panic attacks, and found that for those patients, who had a lot of dyspnea, shortness of breath, imipramine actually worked better than alprazolam, and for those, who didn't have a lot of shortness of breath alprazolam actually worked better than imipramine. So, it struck me that maybe there are different sorts of panic attacks. That is, another type of pharmacological dissection. In generalized anxiety disorder, it takes 4 to 6 weeks for imipramine to work, and it works in doses of 80 or 90 mgs a day that aren't really good enough for panic disorder; patients with panic disorders need more than that. It's still not clear to me whether the very high potency benzodiazepines, such as alprazolam, clonazepam and bromazepam, which are effective in panic disorders, are doing something different than the lower potency benzodiazepines. There's only one study on diazepam in panic disorder, but in that study they ran the dose up to about 45 milligrams a day. The patients got somewhat better, but the panic measures were quite unclear. So, I think it's still moot.

LH: 40 milligrams of diazepam would get you in the ballpark, on the basis of the comparative potency of diazepam and alprazolam.

DK: That's true.

LH: So, your kind of pharmacological dissection in psychopathology led to a new formulation for panic attack?

DK: Yes. And, then, when I got to Columbia, we started studying the psychophysiology of panic attacks. Now back in the 1960s, Pete Pitts discovered that by giving intravenous lactate to patients he called anxiety neurosis, they got a panic attack. But he got into a fight because it was argued that the tremor and feeling of paresthesias the patients got from lactate frightened them into a panic attack. So, it was argued that non-specific stress produced the panic. What Pitt then did was to give these patients EDTA, a powerful calcium-chelating agent, which threw some into tetany but the patients didn't panic. But that got ignored. And, the general consensus was that lactate was doing nothing specific. Then, an English psychiatrist, Desmond Kelly reported on 8 agoraphobics who panicked after lactate. But, when he gave a MAO inhibitor to these patients 5 out of the 8 got better. Then he gave lactate again and the 5 patients, who had gotten better on the MAO inhibitor, didn't panic anymore. So, I said, you know, that's more than conditioning. So, when I got to Columbia, I set up an experiment with lactate and imipramine, showing that imipramine blocked

the panic and even after the patients were taken off imipramine for a month they did not get panic if you gave them lactate again.

LH: So, it's kind of desensitization.

DK: It pushed the switches around. I wasn't quite sure how, because we brought back a number of them six months later. They were panic free for six months and they have not expected to again get a panic attack at all. But what we found was that about 40 percent of them panicked. So, whatever imipramine does, I think it downregulates the suffocation alarm, it goes away eventually.

LH: How did you get to this "suffocation alarm" hypothesis?

DK: Well, a couple of things. First of all, everyone assumed that panic is a sort of fear, which, you know, makes sense. But actually it doesn't look like fear, because the outstanding feature of the panic attack is dyspnea that depending on the seriousness of the attack occurs in 70 to 90 percent of the patients. The person says I can't get a deep breath; I'll run to the window; I'll throw it open; I just can't get a deep breath. And, that's not part of fear. There have been seven good studies now of people who have been shot at in combat or jumping out of airplanes and they all report palpitations, trembling and sweating, but they don't report dyspnea. And, the other thing that tipped us off that panic wasn't fear was that when we took the blood levels of epinephrine, norepinephrine, cortisol, and ACTH, of panicking patients it was flat. There was no surge of these substances in panic attacks as you have with fear. Now, we reported that somehow lactate was suppressing the hypothalamic pituitary adrenal system, but got the same effects with inhaled carbon dioxide, which doesn't give you an osmotic load. Scott Woods, at Yale, took patients, wired them up, put cannulas in, walked them into situations where they likely get a panic attack, like a supermarket, and again found no cortisol surge during clinical panic. And, then, I started to think, well, isn't it peculiar that the two powerful panicogens that don't produce any increase in cortisol and so far are lactate and carbon dioxide, substances which are intimately tied in with what happens to you if your respiration is compromised. The surest sign that you're not breathing enough is that your blood carbon dioxide is going up. And lactate is a remarkable substance that only comes from one place and it only goes to one place. When glucose is being burned, it goes through pyruvate on its' way out as carbon dioxide but if you don't have enough oxygen it gets shunted into lactate. So you have two sure signs there that there's something wrong with your respiration: carbon dioxide or lactate is going up. And those two things induce panic. So, that's what got us going to develop the idea of the suffocation alarm system. And we've been pursuing that idea and written

about it extensively. We've got a lot of good circumstantial evidence that those situations where carbon dioxide is likely to increase are those situations where the amount of panic increases. In those situations in which carbon dioxide is low, or kept low, panic is unlikely to happen. Childbirth is a situation which according to all the psychological theories should be very panicogenic. There are many internal sensations signaling danger. You are actually in danger. There is uncertainty, because you don't know what's going to happen next. In fact, patients with panic disorder never panic during childbirth, perhaps because people have the lowest blood carbon dioxide levels during childbirth.

LH: Because they are hyperventilating.

DK: Hyperventilating at a furious rate. I want to tell you one more story. If this works out, I will be very pleased. What an experimenter ought to do when he or she develops a theory is to look for a place where the theory doesn't stand up, because that's a way to enrich the theory. So my theory implies that anytime somebody is suffocating, asphyxiating, they ought to panic. And, in general, that's true, but there's one big exception, which nobody had ever pointed out and this is carbon monoxide intoxication. When people asphyxiate with carbon monoxide, they just fade away. If brought back before they die, they don't tell you that they had a panic reaction. They just fade away. People have been found in their cars in their garage. Nobody ever jumps out of the car and runs out of the garage, panicking. So, that seems to be a hole in the theory.

LH: Carbon monoxide intoxication would be primarily oxygen.

DK: It has been shown, by the way, that the carotid body is measuring both oxygen levels and carbon dioxide levels and if the oxygen level goes down, or the carbon dioxide level goes up, that stimulates the brain respiratory centers by the 9th and 10th nerve. So I think the carotid body is a suffocation monitor. I knew that Sol Snyder had found that carbon monoxide was a neurotransmitter, so, maybe, it's screwing up the alarm system and I let it go at that. And, I got a letter from Sol, in which he says that they have just shown that carbon monoxide is an inhibitory neurotransmitter in the carotid body. It gave me a terrific study to do, which I was trying, unsuccessfully, to get through the IRB. The idea was to produce panic attacks with 7 percent carbon dioxide in panic patients and by mixing small amounts of carbon monoxide with carbon dioxide, the alarm system should be sabotaged and stop them from panicking. I think this would really be a conclusive evidence for the theory. So I thought we'll find out, but never did.

LH: It would be an important study. It's very interesting that you mentioned that shortness of breath signifies panic. I remember talking with Mandel Cohen a few years back and we recognized that some of the patients, who had nocturnal panic attacks, one would have thought that they had paroxysmal nocturnal dyspnea. They would wake up in the middle of the night, gasping for breath and fool you. But, of course, they didn't have a large heart or wet lungs. So that is an aspect of fear and anxiety, certainly.

DK: Mandel Cohen was 40 years ahead of everybody. He showed that carbon dioxide was a panicogen, but nobody picked up on it. He was the one who went to World War II veterans and showed that they did not have dyspnea when they had fear on the battlefield. He said it very loud and clear, back in the 1950s, that whatever that peculiar thing was that happened in "neurocirculatory asthenia" was not fear. He was very, very clear about that. We invited him to give a lecture at Columbia, where he did not endear himself by comparing the influx of European analysts to a swarm of locusts. He was a real pioneer.

LH: He certainly was. From now on, I suppose you are going to develop and test this hypothesis in every way you can think of.

DK: Right. We have also another hypothesis that we're working on. The other thing that we pointed out a long time ago was that half the patients with panic disorder have a history of separation anxiety as kids; they remember that they didn't want to go to camp; they fought going to school; they resisted school; they stayed out of school; they wouldn't go to sleepovers. And with my wife, Rachel Klein, we have done a 20 year follow up on school phobic kids that we treated, and the only thing that developed, in excess, was panic disorder in later life. So how do you bring together the two hypotheses, suffocation alarm and separation anxiety? Well, it has been shown in animals that endorphins decreased both separation anxiety and carbon dioxide sensitivity. So it's conceivable that there is some link there. If you had a situation like periodic endorphinergic deficit, that, in my opinion, would increase both separation anxiety and suffocation sensitivity.

LH: I was just wondering, has anybody ever looked at submarine crews? Here, you have a situation where people are threatened with suffocation or drowning.

DK: Actually, I went back to the work by Haldane, which was done in 1918, on submarine crews. What essentially came out of that study is that carbon dioxide levels in the subs are 2% and you can become a submariner only if you can adjust to that. We're trying to experiment on the endorphin line and find out if you give lactate to normal subjects what happens. We already know

that if you give naloxone to normals, very little happens. Pickar gave a whacking dose of naloxone to normals and they got nervous and anxious, but that was about it, nothing terrible happened. But, I wonder what would happen if you gave lactate to subjects pre-treated with naloxone, whether normal subjects given an endorphinergic deficit are lactate sensitive. We'll do that to see how that works out.

LH: I don't recall anybody placed on naltrexone to develop panic.

DK: No, there is no report on any patient who developed panic after being put on naltrexone. There are reports on some peculiar episodic dysphorias with naltrexone but they are not well documented.

LH: Well, obviously, if you muck up a system as important as we think the endorphinergic system is, it is likely that something will happen. We reported a number of years ago dysphoria produced by naltrexone that for me would probably explain why it's been so hard to get it accepted into clinical practice. People don't feel particularly good on it. Well, that's quite a career of taking pharmacological dissection and developing a systematic description of agoraphobia, that wasn't so well described before and then testing its' pathophysiology. It will keep you busy for a while I reckon.

DK: I hope so.

LH: Now, since 1976, your whole career has been at New York Psychiatric Institute.

DK: Right. I'm Director of Research at the Psychiatric Institute, which is a pretty nominal title. I don't have any real power as Director of Research. It's just one of those titles. I do have a very big department in Therapeutics that has an anxiety clinic, a depression service, a family study group, and a biological studies group. They do a lot of work.

LH: That has been very productive in terms of publications. Well, that's an interesting career you've had and more to come, I think.

DK: I certainly hope so. It was also fun being involved with ACNP; it's a very elite organization. People, who are in it, are very smart successful people. One of the problems, I believe, with being successful is that it makes you somewhat conservative; you don't want to rock the boat too much, because, after all, you've done all right. But there have been a number of developments recently that I think should shake us up, in terms of how psychopharmacology is going to go research wise in ensuing years, both, from the point of federal support and from the

point of view of pharmaceutical industry support. I think the ACNP could play some proactive roles there. I hope it will do.

LH: Well, you've been a creative thinker in this line, on the more general political line, too. What do you think the ACNP should do?

DK: Well, I think, for one thing, the ACNP ought to try to formalize a relationship with the various heads of the federal agencies, including the FDA and NIH and so forth, and to meet with them regarding their agendas. Like, for instance, I'm the head of a mental health clinical research center and I'm not at all certain as to whether mental health clinical research centers are viewed favorably as being a sensible way to spend money. I personally think that psychiatry is in a relatively primitive state as compared to, say, internal medicine. They're way ahead of us in objective measurements and physiological understanding. Are RO1s by independent investigators a really good sensible way of funding research?

LH: That's sort of Rosalyn Yalow's idea. You provide support to individuals rather than huge amounts of money to centers.

DK: I think for Rosalyn that makes great sense, but I think for psychiatry, we still need to get critical masses together who can collaborate as experts in a variety of fields, because we're nowhere near Rosalyn Yalow. And, for that reason, centers make sense in psychiatry. It would be interesting to have a discussion about that with someone like, Dr. Harold Varmus.

LH: Well, what do you think of the future of psychiatry, with everybody nipping on our heels and trying to get a piece of the turf? You know, psychologists, will soon prescribe drugs.

DK: I'd be surprised, very frankly surprised, if that happens in the near future, simply because, they're not qualified; they don't have any knowledge of medicine and drug interactions. The training they get doesn't qualify them for it and malpractice lawyers would have a field day. So I don't think that's going to happen. But I think the psychotherapy area will change. Psychiatrists who solely practice psychotherapy, will be people dedicated to surviving on low incomes, because the psychologists will undercut the psychiatrists, and the social workers will undercut the psychologists, and the psychiatric nurses will undercut the social workers, so, in no time at all, you won't be able to make a living by doing solely psychotherapy as an M.D. I think psychotherapy has a place in treatment, but I also think that it's a function that can be delegated, so it ought to be supervised, following proper diagnosis. In my own practice we have psychotherapists, but they don't work up the patient. The psychiatrist does that and dispenses the medication. Psychiatrists

collaborate with them and do whatever else is needed, internal medicine with a psychosocial backup. It makes sense to me.

LH: Well, undoubtedly, there's going to be some big changes in the not too distant future.

DK: Right.

LH: Well, I'm sure, as they come along, you'll be part of the thinking about it. You have always applied your agile mind to many issues and I look forward to seeing what you do in the future.

DK: Well, thank you, Leo. I appreciate it.

## 20. JAMES C. KLETT

LH: We're here in Washington to continue the series of interviews on the history of psychopharmacology sponsored by the ACNP. I'm Leo Hollister and my guest today is Jim Klett.\* Jim is an old friend and colleague and co-author. Jim, you're still out in Maryland?

JK: Bel Air, Maryland.

LH: That's a wonderful spot.

JK: Yes, it is.

LH: And, you still have that magnificent kitchen?

JK: Yes, but it's not as active as it used to be.

LH: Well, by golly, if I had a wife who cooked like Shirley does I'd be looking like a balloon, but you look pretty good.

JK: I'll have to tell her that you said that.

LH: Tell me, how did you get started in your career?

JK: I did my undergraduate work at a small Liberal Arts College in Jamestown, North Dakota where I was born and raised. I intended to major in mathematics, but as sometimes happen, I encountered an inspirational teacher who captured my imagination. So, I ended up with a major in psychology and went on to graduate school, first at Washington State College in Pullman, then onward to the University of Washington in Seattle. I was majoring in clinical psychology, but still felt attracted to mathematics. I had some good teachers at both schools. At the University of Washington, there were two very well-known quantitative psychologists: Allen Edwards, who wrote many of the statistics text books of that day, and Paul Horst, who was one of the founders of the Psychometric Society and editor of *Psychometrika* for many years. Those two people contributed to my continued interest in statistics, but I had committed myself to a career in clinical psychology by that time. The Veterans Administration (VA) had gotten an

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\* James C. Klett was born in Jamestown, Dakota in 1926. He received his PhD from the University of Washington, Seattle, Washington. He worked at the VA Hospital in Northampton, Massachusetts and then at Perry Point, Maryland where he became involved in the VA Cooperative Studies of Chemotherapy in Psychiatry throughout his career. He was interviewed in Washington, DC on April 12, 1997.

early involvement in controlled clinical trials with a study of prefrontal lobotomy conducted in six VA hospitals, and as a VA trainee in clinical psychology, I ended up doing some of my early work testing these patients before and after their surgery. That was my first taste of clinical trials.

LH: No wonder you dropped out of clinical psychology after dealing with prefrontal lobotomy.

JK: Right. Cecil Peck, who was Chief Psychologist in the VA central office (VACO) at that time, knew I had a research interest, and so my first job was at a VA Hospital in Northampton, Massachusetts. This had been one of the hospitals that had participated in the lobotomy trial, but also there was an interest there in doing some early psychopharmacologic research. I spent a couple of years there, partially involved in the ongoing lobotomy study. Finally, I was recruited for the staff of the Central NP Research Laboratory (CNPRL) at Perry Point by Ivan Bennett, who was at that time in VACO, before he went off to Eli Lilly, never to be heard from again. My initial assignment was to write up the results of the lobotomy study or help write it up. The Cooperative Studies of Chemotherapy in Psychiatry was just starting. Incidentally, the VA was also involved in multi-center studies of chemotherapy in tuberculosis.

LH: Really, the Armed Forces and the VA. That was in the 1940's.

JK: Yes. I was trying to make the point that the VA had a considerable involvement in large-scale multi-center clinical trials and was organizing the first cooperative study of chemotherapy in psychiatry at the time that I came to Perry Point. Incidentally, there were some very good investigators, like you, who were doing single investigator studies in the VA at that time. There was already quite a culture of research in the VA when I joined. Of course, I stayed at Perry Point for the next 35 years or so.

LH: Well, it's not a bad place to be.

JK: I was attracted to it because my main interest was in statistics and clinical trials methodology, and here was a program in which we could have large patient samples and do some definitive work on comparisons of treatments. That added up to be a very satisfactory career from my point of view. Another aspect was the many people with whom I was able to collaborate over the years, people whom I admired a great deal through our cooperative studies program. We had an Executive Committee, of which you were a member for many years and we had a lot of very fine people from within and outside the VA who served as members of that committee. I don't see the VA as currently playing as prominent a role in neuropsychopharmacology as they did at that time.

There are some excellent investigators here and there, but it doesn't seem to be a coordinated effort as it was in those days.

LH: Well, the VA is being swept up in this revolution of medical care delivery and nobody knows what their fate is going to be, especially as the large echelon of World War II veterans dies off. What are we going to do with all these magnificent hospitals?

JK: But, I think we need to pay some attention or respect to the people who played a role in the early days. I mentioned Ivan Bennett. He had brought a lot of energy to that job before he joined Lilly. Clyde Lindley, whose name you might not find by a computer search of the psychopharmacology literature, was the sparkplug who helped to organize and keep going this program of multi-centered trials in psychiatry.

LH: Clyde had a wonderful knack of being able to pull people together and get them to work together. I think it was his specialty. He took some psychology but he never got an advanced degree, but I think his specialty was personnel management and he did an admirable job. So, you were pulled in then just as the VA cooperative studies were really getting under way.

JK: The first multi-center study had passed the planning stages and was at the stage of distributing the drugs, blinded drugs. Perhaps I should give a capsule history of the CNPRL. At this time, there wasn't a separate Research Service in VACO. There was a small group within the Psychiatric Service: Richard Jenkins, a psychiatrist, Quinter Holsopple and Maurice Lorr, both psychologists who had been involved in the design and coordination of the multi-site study of prefrontal lobotomy. Lorr was well known in neuropsychopharmacology circles for the development of some of the rating scales that we used for many years.

LH: Oh, yes, the IMPS was the standard scale.

JK: The Multi-dimensional Scale for Rating Psychiatric Patients (MSRPP) was the earlier one. Later on, several of us (Jack Lasky, Doug McNair and I) collaborated with Lorr on the development of the IMPS. In any event, Quinter convinced VACO to open a laboratory at VAH Perry Point to have access to patients for pilot testing and to develop rating scales. I think he really wanted to get out of the city of D.C. and to Perry Point, which, as you say, was a nice place to live. He was joined by Mordecai Gordon, another psychologist. That was the nucleus but Quinter died and they recruited Jack Lasky to replace him as Chief of that Center. Jack and I arrived at about the same time.

LH: I wonder what ever happened to these people. I haven't heard about Lasky.

JK: Well, Maury Gordon left the VA and went over to the National Institutes of Health.

LH: He was on some neonatal study there.

JK: Right. I used to run into him occasionally before his death.

LH: And, Jack?

JK: During the Kennedy years, Jack was seduced by his old professor from Michigan to join the Peace Corps, to help run the Peace Corps. He had left me as Acting Chief of the CNPRL and after leaving the Peace Corps, rather than come back and displace me, he was good enough to go to the National Institutes of Health. Jack was always a good guy.

LH: He became a Study Section Chairman.

JK: Executive Secretary, right.

LH: But, that was the last I heard of him.

JK: Well, he stayed there until retirement, now, some 10 or 12 years ago, and he's now up in New England. He taught at a small college for many years after he retired. At one time or another, at the CNPRL, our staff also included such distinguished colleagues as John Overall, who one would have no trouble at all identifying by a computer search.

LH: No, no, John's been very active, and, of course, right now we're colleagues again. He was the main reason I went from California to Texas. Well, Maury Lorr sort of got lost in the shuffle after John and Don Gorham came up with the Brief Psychiatric Rating Scale; a very useful instrument, wasn't it?

JK: Yes, I found it to be so. But, I could also understand why in the competition among scales that the Overall Gorham BPRS won out, because it was a brief scale.

LH: It wasn't as atomistic as the LORR scale.

JK: That's right, and that was an issue where one could argue whether it would be best to have longer scales with certain redundancy or to have these brief judgmental scales. But, in reality, what happened is that the BPRS is still in wide use today and the MSRPP or the IMPS is rarely, if ever, used any more.

LH: You and Maury did a lot of early work on identifying the factors.

JK: Maury became Chief of the Outpatient Psychiatry Research in VACO while the CNPRL focused on inpatient research, but Maury and I collaborated a lot and we were interested in the typology of the psychosis for a while. That had been a long interest of Maury's, anyway, and we wrote a couple of books together on typologies. I finally lost interest in it, but Maury has pursued

it beyond that. Gil Honigfeld spent about five years with us before he went off on his own and then reemerged at Sandoz.

LH: As the developer of clozapine.

JK: As the Project Leader for the clozapine research, but I would say he did his internship at Perry Point.

LH: I don't know what his reaction might have been when they told him, "Take this drug and see what you can do with it," because it didn't look very promising at first, but Gil saw it through.

JK: I agree.

LH: And, now, clozapine is considered to be the most revolutionary development in antipsychotic drugs in the last twenty years. There were a lot of interesting people then. Now, you were one of the co-authors of the very first report on Project #1.

JK: No, that's not the case. I think there were six authors including Maury Gordon, Dr. Frank Casey, the Director of the Psychiatry Service in VACO and I believe you were also an author on that paper.

LH: Yeah.

JK: I wasn't involved in that study. I came in on the second or third major study. Another person I'd like to mention with some special emphasis is Gene Caffey. I've always collaborated with somebody or as a member of a team, and for many years I worked with Gene Caffey. Caffey was a member of the Executive Committee. He was also the Chief of Staff at the VA Hospital at Perry Point, so it was convenient to work with him but he's also one of the most congenial people I've ever known, and when I think of the hundreds of hours I spent on airplanes with Caffey sitting in the next seat, believe me that was fortunate!

LH: Well, Gene was sort of a wise old hand, you know, he didn't say a whole lot, but when he said something it meant something.

JK: Well, those were exciting days, in fact, the VA studies I think preceded ones that occurred in several state systems, one in California, another one in Delaware with Fritz Freyhan, and a few of them scattered around the country. And, of course, it also preceded the Psychopharmacology Service Center. JK: Right. There's another study, by the way that occurred about that same time. It was by Al Kurland and Tom Hanlon out here at Spring Grove, Maryland and it was a large study comparable to ours, in many ways, to our Project #1 or #2.

LH: Did that precede or follow?

JK: I believe that it was at about the same time. But, of course, the ones that were done at the NIMH got all the attention, for obvious reasons. The VA wasn't getting enough money, and NIMH had a much better PR system than we ever did.

LH: Well, I think that study has been misinterpreted because it's said that it shows that there's a placebo effect in schizophrenia, and if you look at a thing carefully, there were just as many people who got worse as got better on the placebo; and, secondly, I think the diagnosis in those days was not very good. They probably had a lot of hypomanics and manics who spontaneously remitted, but in any case it got the publicity. I don't understand why because the VA studies were published in good journals.

JK: Oh, yes. That reminds me of another thing. You know, in those days, there wasn't a single book on how to do a controlled trial or a multi-center trial. And, now, of course, you could have a five-foot shelf, easily, of books on how to do them.

LH: Well, you were the co-author of one of the first.

JK: Another figure, who was very helpful at that time and in that context, was Tom Andrews, the Chairman of the Psychology Department at the University of Maryland, who participated in the development of that first protocol.

LH: Oh, yes, he was the prime mover as far as statistics were concerned.

JK: Yes, right, he and Maury Gordon. So, it was very helpful to have Tom Andrews available, but he was in his 40's, I think, when he died.

LH: I think so, very early.

JK: He played an important role at that time. I can only think of one professional statistician active in the field at that time and that was Sam Greenhouse, who by the way has a son by the name of Joel Greenhouse, who's also a statistician, a very nice fellow. That particular function was filled by quantitatively trained psychologists, like John, myself, Doug McNair and some few others, and it was almost always characterized by some collaboration between a psychiatrist and a quantitatively trained psychologist. That was a very productive kind of arrangement. Now, of course, we've moved into a different era. There are still a lot of good psychologists around that I used to run into in my site visiting, but we now also have a lot of very good statistically trained people, like Phil Lavori and others that are active in the field.

LH: Now back in those days how to handle all those data fields was not at all clear.

JK: Right. These were early days for computers and data processing.

LH: You were using punch cards in those days.

JK: Yes, and now many people don't know what an IBM punch card looks like. But, we had made arrangements with the statisticians at the Bureau of Standards to analyze the data from that first study. They didn't have canned programs to do it. They had to write the programs to do the analysis of multiple covariance. And, it took months to get this program ready, so much so that we were worried for a time that it might hold us up. In those days we would have to take a couple of boxes of IBM cards, get in the car, drive down to Washington and leave them with somebody, and, then, come back the next day, or a week later to pick up the results.

LH: Bring out a box of punch cards.

JK: Right, boxes of IBM cards, punch cards. So, it was a whole different era.

LH: Now, I suppose almost every pharmaceutical company has in-house statisticians who design protocols. In fact, the fun has gone out of it. They write the protocol and you give them the data and they analyze it and you never see it, yourself. They hire some flack to write up the results. It's not the same way it used to be.

JK: Sad but true. I think it was better when we had control of the process.

LH: Because, in those days there was still dispute as to which way to go on handling the data and exploiting more sophisticated statistical techniques than usual.

JK: I thought of something that in retrospect is kind of amusing. In our trials, to provide for a double blind control, one company like SKF would provide their drug and another company would provide their drug. We would specify that they had to be in a canister, so that would be standard. When the drugs arrived at Perry Point, we'd pack them up and send them to the participating centers. In this instance, when these drugs came in, we noticed that the labels from one company were an inch higher than the labels on the canisters from the other. Obviously, if you had these on the shelf, you could immediately see there were two different kinds of drugs. In order for this to be a double blind study, we had to repackage all that stuff to make it uniform. Those were kind of interesting days.

LH: A lot of chores besides grinding out numbers.

JK: Right.

LH: Well, what do you think? Sometimes I wonder whether we didn't do a case of massive scientific overkill, because these drugs were so effective compared to what we had before and so altered the natural history that it hardly seemed necessary to do these elegant trials.

JK: That's true in a couple of respects, but not so much in others. You may remember that shortly after I arrived, I used the data from Project # 1 in a sequential analysis program using patient pairs and, with eight patient pairs reached a statistically valid decision on the relative efficacy of Thorazine vs. phenobarbital. That study went on for another year and we ended up with 600 patients, but for good reason, we needed to have data on side effects and other stuff, as well. But, in another case our large sample sizes haven't really helped us all that much in the search for "the right drug for the right patient" which, of course, is still a very clinically important question. NIAAA just did a huge \$27 million study called "Patient Match" directed at that question.

LH: To find the right treatment for the right alcoholic?

JK: They didn't have much better success than we did. Even with these large samples, we could not detect differences easily between many of these new compounds.

LH: I think you were working on your side and John and I were working on ours, so I don't know who thought up the title of the paper, maybe it was one of yours, "The Right Drug for the Right Patient." It was an elusive search.

JK: Yes, that was my paper and I thought it was a catchy title.

LH: It expressed the whole search so well. Well, I suppose in those days that was sort of the beginning of a growing echelon of people who were applying advanced statistical methods to psychiatric and psychological problems, which probably spread out into other fields. I'm sure one of the large studies on anti-hypertension drugs and coronary surgery and so on have used a lot of the same techniques.

JK: Yes, I didn't mention the hypertension trials, but probably about the time that we got started, the first VA hypertension trials were on the drawing boards. There were a whole series of those, and I don't think anyone has questioned that they were valuable and important studies in identifying a variety of drugs useful for that purpose. But, interestingly enough, while we were going along in doing our thing in psychiatry, there was another group of people just 30 miles from where I worked, in Baltimore, that is, who were doing multi-center trials in diabetes.

LH: That was the University Diabetes Group. Boy that was a controversial group.

JK: It sure was, but mostly drawing from that nucleus of people, they finally founded the Society for Clinical Trials and the Journal of Clinical Trials, which is a first-class journal; I mean a really good journal and a first-class organization that attracted a lot of the bio- statistician types. One time, Jerry Levine, Gerry Klerman and I participated in one of their annual meetings. Nobody in

that organization had ever gotten into the mental health area at that time, and I don't know that they have since, because they had their own focus, diabetes and other disorders. But the statistical methodology papers were interesting and important.

LH: Eventually the laboratory at Perry Point dealt with all sorts of trials, wasn't it, until they made several other laboratories?

JK: For the first 15 or 20 years, we focused exclusively on mental health, psychiatry, neuropharmacology trials. But, the VACO Research Service was reorganized and we got pulled into a different orbit, and, then, we began to do trials in a lot of different areas. When Dr. Baker, Chief of Psychiatry, died, the commitment of Central Office Psychiatry diminished. There wasn't that kind of interest centrally in the program. We missed some good opportunities then. I think the VA could have done some good epidemiological work on tardive dyskinesia, issues like that, but they were done by others.

LH: But, it wasn't all drugs either. There was that study that Margaret Lynn honchoed on sociological aspects.

JK: Yes, Margaret used to be my neighbor before they moved down to Florida. I expect that you'll be talking to Sam Kaim sometime soon. It was through Sam that we got involved in research on substance abuse. Sam had been recruited by VACO in a research role. Sam's main interest had been primarily in alcoholism and shortly after he joined us, we did a study of alcohol withdrawal and DT's. By the way, this study of alcohol withdrawal was picked recently by NIAAA as one of the seminal articles on alcohol research in the last 25 years. I think it's a nice compliment to Sam. But, we were also ready to move into the area of drug abuse. Jerry Jaffe had been picked by President Nixon to head the Special Action Office for Drug Abuse Prevention. One of his jobs was to try to pull together all of the research that was being done in various agencies, including the VA, and to kind of centralize it. A couple of his main interests were to develop a long acting maintenance medication for heroin addicts, a long acting methadone, if you wish, and another one was naltrexone, a narcotic antagonist. These two pharmacological approaches were part of his goal in this role. Well, we did organize a trial of LAAM, but before it actually started, Sam Kaim retired from the VA and went over to the National Research Council. We needed a Study Chairman to replace Sam. I had been working with Walter Ling and found him to be a person of great energy and I felt he was ideal for this job, so I held out to have Walter take over. I believe that decision has paid off immensely since.

LH: That first study of LAAM was in the middle of the 70's, wasn't it?

JK: Yes, and eventually that study turned out to be the pivotal study for the approval of LAAM. It took years for the FDA and NIDA to get that done.

LH: I think it took about 18 years.

JK: Yes. That's another story, which we don't have time to talk about. But, it is important that that study provided the data on which the FDA based their approval of LAAM, and it is now available as one of the treatment options. At the moment, Walter and I have been working for some years on buprenorphine, another maintenance medication for heroin addicts, and I think the data we've generated is going to serve as pivotal work that will result in the approval of the new drug application for buprenorphine. That area of research has been very interesting and I think productive and it has always been a joy to work with Walter. I'm still working with him.

LH: I know. Well.

JK: Oh, yes, I have to close that loop. Sam Kaim went over to the National Research Council and headed up a committee on the development of the heroin antagonist, naltrexone, and he chose you and me and Danny Freedman and others to serve on that committee. We managed to do our job and put naltrexone, I think, in the proper perspective at that time, and it was shortly thereafter approved by the FDA. So, we played a role in that, as well.

LH: Yes, I remember I honchoed a committee to study that, and we did the first controlled trial, but we had to sweat it to show a difference.

JK: Yes, that study focused on street addicts, patients already in methadone maintenance, and also people in work release programs, I think. The problem we had, as I recall, was we had to get people clean before they could be switched to naltrexone, so we'd start off with hundreds of patients and we'd end up with a very low yield. And, then, they'd get on naltrexone and would drop out within the first six weeks, so it was very discouraging.

LH: It was not like methadone where you're hooked. However, even now, naltrexone has resurfaced as a treatment, apparently a very effective treatment, for alcoholism. I expect it is being used more now for alcoholism than for heroin addicts. Well, when did you retire?

JK: January 1988. So, I've been retired from the VA for almost 10 years.

LH: Did you still act as a consultant for a NIDA committee?

JK: Oh, yes. There were times when I wasn't sure if I worked for the VA or if I worked for the National Institutes of Health. I was on one committee or another for 20 years. A lot of us made

that kind of a commitment. I was on the NIMH Clinical Research Centers Committee and I spent 4 or 5 years on that after I retired, a very interesting assignment. And then, I had some other commitments. I was on some data monitoring boards, such as the VA clozapine study, and on the NIAAA Patient Match Study, and one thing and another. At some point shortly after I retired, Walter Ling said, "Let's put in a grant to NIDA for one of these Clinical Centers in Drug Abuse." By then, Walter was in private practice and I was retired.

LH: What a way to start a grant!

JK: Initially we got a large 5-year grant. I don't think NIDA has ever given a grant to two people whose credentials were as thin at that point in time. But, Walter is now a full professor at UCLA. He's certainly done very well.

LH: Now, ever since you began, and even earlier, the randomized parallel group double blind design has been the gold standard of assessing drugs, and, of course, these studies can be expensive and laborious. Do you foresee any development of techniques that might be less laborious, less expensive?

JK: Well, I've read some things that Don Klein has written about doing clinical trials, and although I can't repeat all of the lessons that he pointed out, I agree that it would help to strengthen the Phase 1 and Phase 2 part of drug development. But eventually there is the need to do the large Phase 3 definitive studies. Those clinical trials will pretty much remain the same, with maybe some statistical and methodological improvements. I also think we need to go back to the time in which the people who designed the trials spent a lot of time with patients instead of being on committees and flying around the country or to Nepal or someplace. For instance, NIDA now has been supporting screening, all kinds of drugs, trying to find something for cocaine. I think good clinicians have to sit down and talk to patients, ask them, "How does it make you feel?" You know what I'm saying? I think sometimes clinical trials have become kind of personal. You have a research assistant who recruits the patient and they fill out some forms but you don't have a wise sensitive clinician who talks to the patients. So, that would be one lesson that I think could be paid more attention to. I think you will still have to do large, probably multi-center trials.

LH: They were, in a way, victims of their own success, because they have been very effective in sorting drugs out, but by the same token, nobody wants to risk trying anything new, so you get locked into a system.

JK: Yes, there is that. I was reminded that you and John Overall did relatively small but quick studies, drug screening, to try to find rewarding compounds. I've been reminded of that many times since, because people ask me, "Is there some way that we can do this quicker, easier? How about sequential analysis?" You might think that's a very appealing technique to use, but there are some drawbacks with applying it to studies in which the duration of treatment has to be fairly extensive before you know if you've got a winner. It hasn't really worked out very well in clinical practice, for that reason and, also, because many of these Phase 3 trials have more than one objective, they need to generate a big enough database for adverse reactions, and so on, for the FDA. Anyway, in response to these kinds of questions about more efficient designs, I refer to your approach. If you want to screen a lot of compounds and be as efficient as you can, where you really lose time is getting geared up and, then, getting drug supplies, all of this stuff that you have to do in order to do a six or eight week trial. You may spend a year getting organized, but you and John and the rest of your group did these small studies very efficiently. You were able to get one study started, and while that one was being completed, you got another one organized, and so you really did a lot of work in a relatively brief period of time. So, I think that kind of efficiency, if you're in the business of screening compounds for activity, is the way you have to go.

LH: Well, of course, right now there's a huge controversy about the medical uses of smoked marijuana and oddly enough there are no controlled trials on that. But, I was thinking, you know, it's so simple to devise a new kind of approach, because you could have a placebo for the cigarette and a placebo for the oral capsule, both of which have been available for years, set them up in groups of four and randomize within the groups and, then, do a retrial of chemotherapy. And, of course, you have to have a rescue for, say with ondansetron or some very effective anti-emetic, in case it failed, so it wouldn't put the patient at too much trouble. Now, I think you could settle that issue very quickly and clearly.

JK: Well, that's true but, first of all, who would fund it? I'm not sure that the authorities are very anxious to approve marijuana for medical use.

LH: No, but I think the political pressure is going to get so great that they are going to have to fund it. With states taking action in their own hands, as I recently put it, they are making decisions about admitting drugs as therapeutic agents based on clever insight, rather than science. What doesn't make sense is when simply a group of voters say, "You know, it's O.K."

JK: What's the active ingredient of marijuana?

LH: THC.

JK: Now, that's available in a pill, isn't it?

LH: It's already approved.

JK: Sure, but the consumer isn't interested in taking a pill. Don't they want to smoke?

LH: There are some disadvantages to the pill, even if you're going through chemotherapy. First of all, the capsule may dissolve at different rates, and so, you have to time it so you are going to get the effect when you get the chemotherapy. The second thing is, you may need more than one, and that creates a problem, when do you put the second one in? But, the pharmacokinetics when you smoke marijuana, are just like you got an I.V. shot, you got it right in there, so that makes it different. But, people are not going to rest on the availability of the oral drug. You know, it's evident that a lot of people want to try to smoke the drug. And, I think there are ways to test it without using the conventional design.

JK: Well, you would want it blind, wouldn't you?

LH: You could make a blind trial, but it wouldn't be a parallel group design within patient, that's because you would have to assume that every dose of Cisplatin is going to cause the same amount of trouble for the patient. You do get into the problem of, so called, conditioned nausea and vomiting, but if you started off before they ever got that conditioning, I think you could avoid that.

JK: Sure, that kind of design might work for that application or in the case of pain, analgesics and pain tolerance, where you get a quick answer. There you might use a Latin square or repeated measures trial for crossover trials very efficiently, but not in the usual application with depressed patients or schizophrenics where the response time is much longer. There, I think, we're stuck with the parallel groups design.

LH: Well, would you have done the same career all over again?

JK: Absolutely! I've really enjoyed the intellectual challenges and the people that I have worked with. There are a lot of people I haven't mentioned that have been important to me in my career. You didn't ask me how I got into ACNP. Jon Cole told me that I ought to be a member of ACNP and that's how I came to join the organization. Also, Jon Cole was at the Psychopharmacology Service Center at that time and asked me to be a member of his committee for grant reviews. So, Jon Cole gave me a first step up in several ways, and there are others like that, as well.

LH: Well, I was going to ask you, what do you see the chances of replacing people like you and John Overall, the pivotal pioneers in the field of statistics applied to psychopharmacology? Are

we getting enough new people in the field to keep it alive and flourishing, or should the ACNP take a little more liberal policy toward admitting people in this discipline?

JK: Well, yes. I think it is important to have people represented in the membership and it doesn't always work out that way. I sponsored Phil Lavori on two occasions.

LH: He's good.

JK: Oh, he's outstanding.

LH: But, he is a member now.

JK: I'm not sure of that.

LH: Didn't he get accepted?

JK: My two attempts to get him failed. I don't know if he is a member, currently.

LH: Oh, that's a pity. He's a solid citizen.

JK: First rate! So, there ought to be an attempt to recruit people like Phil and some others because the organization needs it. Remember, these teams that we used to have, with you and John and Gene Caffey and myself. Phil is working with Klerman and others on the depression studies. ACNP needs those people who can work together with clinicians, but bring together a lot of expertise in quantitative work, and there should be some outreach to get them in. Now, they're not replacing people like John Overall. These positions are now, I think, being filled by biostatisticians, PhDs in statistics, and that's alright. That's fine. They don't come with the background in psychopathology that the psychologists tended to have or as much of an interest in the subject matter, per se.

LH: But, people cross disciplines all the time, as you did, so I think that even if they came from a purely statistical background you could give them enough know how in time.

JK: Oh sure, in time, especially if they make a commitment to working on psychopharmacology problems. Who's the woman at Palo Alto?

LH: She's doing the history of the VA?

JK: Oh, no, that's Margarita Hayes. There's a woman statistician at Palo Alto, Stanford, Helena Kramer. She's now a member of ACNP, I believe.

LH: Well, some of us feel, in that field, that there is a gap in the membership developing where it's not representative enough. You know, these guys doing basic work grind out references, you know, by the dozens. They'll come in with 36 published papers. That drives all the rest of the people for cover, because you can't do that as a statistician. You can't do that as a clinician.

JK: But, Leo, another thing has happened in the past 30 years or so. When I first arrived on the scene, wet behind the ears, if I described how you could do a chi-square test, people would oooh and aaah, you know. The clinicians really needed help in those days.

LH: That's right. I remember one time, ask Tom Andrews.

JK: But, the clinician of today, the investigators of today, are a lot more sophisticated than that, and so they don't have quite the same needs for quantitative back up. And, look what's happened to the computer field. All of this statistical stuff is in packages.

LH: Program in a package.

JK: If you know how to punch a couple of buttons, you can get your statistics done.

LH: You may not know what you put in, though.

JK: Yeah, you certainly do need to have a statistician involved in the planning and conduct of the trial. But, there have been some important changes of the kind that I just mentioned.

LH: Even so, you know, you can always get these program statistics. There are underlying assumptions on each one of these that I think are very often neglected, and the people use the statistics without meeting the underlying assumptions of it. So, you need somebody who knows a little more than how to push buttons.

JK: Well, John Overall is a good example of a person who knows how to use statistics creatively. John would always come up with interesting twists on looking at numbers. That's always been one of his strong points.

LH: I've called John a national treasure, in the same way that they have national treasures in Japan. You know people who are artists in different fields, because he's an artist in that it's been a great privilege to know him. I guess, one of the things I can say for myself is I've had sense enough to know before I needed help and John's been an enormous help. Well, nice going over all the trials with you, Jim, and what's the old Pennsylvania Dutch saying, "We go all too soon and smart too late."

JK: Something like that.

LH: I felt sort of stupid throughout most of my life. Now, that it's beginning to get to the end, I feel a little better about it.

JK: Well, you and I share a lot of things, a lot of memories, but, obviously, one thing that we share is that we were part of the VA involvement in the early days. I think that era has passed and I

think that the people, who are newer to the field, may not recognize the important role that the VA played in those years. And, so, it's good to get that on the record.

LH: That's why I wanted to have you and Clyde and Sam and some of the other people, who were in that position, go on record, because I just think that, in terms of the pioneering effort that the VA has made, it never got as much credit as it should have, and it's a pity. Well, happy retirement. I'm going to join you soon. Well, so nice to talk to you, Jim, and see you looking so well.

## 21. ALBERT A. KURLAND

LH: It is Tuesday, April 15, 1997, and we're in Washington, D.C. continuing a series of interviews on the early history of psychopharmacology, sponsored by the American College of Neuropsychopharmacology (ACNP). Today's guest is one of the pioneers in the field of clinical psychopharmacology, Dr. Al Kurland,<sup>6</sup> who lives nearby in Baltimore, and we welcome Al to this series.

AK: Thank you.

LH: We're always interested in how people decided to go into psychiatry, and how they ever decided to go into psychopharmacology. Can you tell us how you got started?

AK: It may sound like ancient history, but I have to go back to the year 1941. I had just completed a year's internship at the Sinai Hospital in Baltimore, and I decided to get my selective service out of the way before I continued with my education. So in July 1941, I was in the armed services and was assigned to an infantry unit of some type and shipped off to maneuvers in the Carolinas. On December 7, late in the evening, I discovered that Pearl Harbor had happened and when I heard that, my immediate reaction was how did I ever get in this mess and how will I ever get out? And events followed very quickly thereafter. I was only recently married. Then, in a few months I was on a ship bound for overseas. I didn't get back for a couple of years, and during my service, I discovered many things. First of all I discovered that I didn't like ships. I got sick on whatever kind of ship they put me on, whether it was a big ship or a small ship or a landing craft or whatever. And on many of these occasions, I was not certain that I was concerned about which side won. But, anyway I managed to survive a couple of years of that, and in the course of my activities, I was promoted to being in charge of a battalion.

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<sup>6</sup> Albert Kurland was born in Wilkes-Barre, Pennsylvania, in 1914, and graduated in medicine in 1940 from the University of Maryland. After training in Army facilities during the war, in 1949 he became a staff psychiatrist at Maryland's Spring Grove State Hospital. He became director of research in 1953 and in 1969 was appointed director of the Maryland Psychiatric Research Center. In 1979, he was appointed research professor of psychiatry at the University of Maryland School of Medicine. He died in 2008. He was interviewed at Washington, DC on April 15, 1997.

LH: You were a medical officer?

AK: I was a medical officer at that time, and I saw an extensive amount of combat. Apparently, my activities were recognized to a certain extent. After a while, they thought that maybe I had enough of it and decided to rotate me back to the States. That was after a couple of years. And they asked me, what I would like to do when I went back. I hadn't thought about it very much, but when they said, "we're going to send you to Carlisle to get some combat training," I said, "Hey, you guys pulled the wrong switch."

LH: You'd already had that.

AK: I said, "I already had that. I don't need a post-graduate training, can you think of something else that might be more appealing to me?" So, they said, "well, what would you like to do?" I said, "Well, I saw in combat an awful lot of stress. I saw a lot of stress reactions. I saw troops killed by friendly fire, and, then the troopers shoot themselves. I saw all kinds of dreadful things." I said, "Look, I'd like to go to a neuropsychiatric unit, if possible to learn something about this situation, and, maybe, I might be able to find ways and means of being helpful in this area." Anyway, I was assigned to the Army General Hospital at Valley Forge to a neuropsychiatric service. It was a very awakening experience. It also brought to my attention a number of issues that had to be addressed, at least, from my standpoint, and learning more about.

LH: Now, was this one of the 90 Day Wonder training groups?

AK: Well, I don't know what you would call it, because wherever I seemed to go, I always seemed to be learning something. They sent me up to a general hospital on Long Island. I guess it was Mason General Hospital. The Army had a course for training people in neuropsychiatry. I went up there, and then, got to the hospital. And they came along one day and said, "Hey, you've been in the armed service for a couple of years now. You're due to get out. Would you like to stay in and get promoted?" I said, "I'd like to get out and not be promoted, because I've got a lot of things to catch up." Four years in the service put me pretty far behind in keeping up with the work I wanted to do. I arranged to get a Fellowship in Neuropsychiatric Research at the Sinai Hospital when I came out. So I started on that. Then, as I was working, I also got a part time job in an outpatient Veterans Administration (VA) psychiatric clinic. At that time, there was considerable interest in psychiatric circles in psychoanalysis, so I thought, well, maybe I'd go and learn something about

this. I exposed myself for a couple of years to analysis, and as I went along, I discovered that I was not considered a suitable candidate for psychoanalysis.

LH: Too analytical.

AK: Too analytical, all right. So, then, a couple of years had gone by, and I wanted to get myself certified in psychiatry. They said, "Well, you've never had any experience in a psychiatric hospital, you ought to go there for maybe a year or two." I had heard all kinds of dreadful stories about psychiatric hospitals. Remember, this is before the chemotherapy revolution took place. This is prior to 1951.

LH: In the 1940s.

AK: I went into the Army when the war started. It was 1941, right?

LH: Yes.

AK: I came out in 1945, 1946, and then I started getting back into training again. I had the Fellowship, I went to work in the clinic, I went into psychoanalysis, and then, I needed to get this hospital training. So it was about 1949 or '50 that I got out to the State Hospital at Spring Grove. My assumption was that I was only going to spend a year to get my training there, and then move on. I go out to Spring Grove, and I go to the Superintendent, and he says, "I'm going to give you an assignment." I said, "Well, all right." The hospital at that time had over 2,700 patients. It had about 23 psychiatrists, and they had a budget for medication of about ten thousand dollars.

LH: A year?

AK: A year. That was for 2,700 patients. So, the Superintendent says to me, "You're going to be assigned to the unit for the criminally insane, there's 65 beds and you take care of them." So I say, "Well, I don't know anything about the criminally insane." He says, "Don't worry. If you need any consultation you can go to any one of our psychiatrists and ask them." I do the mathematics in my mind very quickly: there are 23 psychiatrists and 2,700 patients. I've got 65 patients and if I try to get a consultation, the chances are they won't have much time for me, because they've other things to worry about. So I go to work and realize that I will be able to learn only by doing things. To do the best I could, I figured, "I've got to find something to activate myself." I started thinking of things I'd like to do, and I went to the Superintendent and said, "Look, I'd like to do some investigational work." He listens very quietly, very politely, and he says, "You can do this under three conditions." I say, "What are the conditions?" "First of all, you

do this in your extracurricular time, okay ? Secondly, you don't get the administration involved in any problems; and, thirdly, you don't ask for any funds."

LH: That's a good auspicious start!

AK: I figured, well, this is ground zero. But, anyway I went to work and started to study whatever I could latch onto. And then, I heard a rumor that a drug had appeared on the scene, Thorazine (chlorpromazine). It had taken about two years to cross the Atlantic. This was about 1954. Heinz Lehmann up in Canada had been working with it and just published a report on it. Have you ever heard the story about how Heinz Lehmann got involved with Thorazine? Are you familiar with that story?

LH: No.

AK: It's an interesting story. They had a detail man from Rhône Poulen come over to Canada, and Heinz Lehmann was working in a Canadian psychiatric hospital. So, they tried to have an interview with him and tell him about this medication but he was too busy to see them. He says, "Leave the papers on my desk and I'll read them at my leisure." So, he picks it up Saturday, takes it home. Now, Saturday was his day for reading; he always did that in his tub. While he was relaxing and reading the article about Thorazine he said, "Well, that sounds like an interesting idea. I'm going to check it out." He goes to his wards, selects 50 patients and he gives 25 of them Nembutal (pentobarbital), one of the barbiturates, and, then, he gives another 25 patients the Thorazine. He immediately realizes that there's a very important difference in what he's observing, because the effects of Thorazine are quite obvious. It brings a tranquilization, but it doesn't do anything to the consciousness in contrast to the barbiturate. Within three weeks, he carries out the study, gets a publication, and the dawn begins to break. Can you imagine trying to do a study today, getting something like that set up, underway, and finished in three weeks? Impossible!

LH: You'd have to have a year of lead-time.

AK: All right. So people start hearing about this new drug, and the superintendent says to me one day, "Look, you know, I heard about this Thorazine. Someone has told me that they gave it to a patient in one of the hospitals here and it seems pretty good." So, I said, "Well, I'll go ahead and try to get some." I get hold of somebody at Smith Kline & French (SK&F) and say, "Could I have some of this to try it on a patient?" "We don't have any more supplies, but if you want to buy it, we'll sell it to you." So what am I going to do? I go back to the Superintendent and say, "Look, they'll sell it to us, but where are we going to get the money"? He says, "Well, I don't have

anything in my budget." So I say, "Well, look, will you let me go to the relatives and see if I can solicit some funds from them to pay for it?" He says, "Sure, go ahead. I have no objection to that." I went to relatives and solicited funds from them, and got the Thorazine, and when I got the Thorazine, and started to use it, I began to see that we've got something dramatic happening. So, I went home to my wife and said, "Hey, look, there's an amazing drug coming along. Maybe we ought to buy some stock in this company." She says to me, "You're crazy. We just moved into this house. We've got a big mortgage, and we can hardly make the payments on it and you want to buy stock. Forget it." So I said, "All right, I forget it." But I began to get involved with Thorazine in my patients. This was very early. I built up a series. I went through all the rigmarole. Even in those days, to get informed consent and clear it with the administration it took some time. It wasn't as elaborate as later, but, anyway, I got underway with my studies and while I was working in this area, we got a call at the hospital from the National Institute of Mental Health (NIMH). You know, the NIMH had just been established about 1956 or 1957, somewhere around that time. I don't know the exact time. But, anyway, there was a chap there by the name of Savage. You probably know Charlie Savage. He was working at the NIMH, and there was a chap by the name of Lou Cholden, who was also at the NIMH. Cholden had come from the Menninger Clinic, and Charles had also been involved in analysis. And he'd been out in California, somewhere. They had heard about lysergic acid diethylamide (LSD) and they wanted to see just exactly what this drug was doing. Now, Charles Savage had done some earlier work with LSD. This was in 1947; remember Hofmann came out with LSD in 1943. Savage tried to give it to depressed individuals, on a chemotherapeutic basis but it didn't work. They were studying to see if they could give it to chronically ill psychotic patients and found out if it did anything to them, the individuals developed a tolerance. The superintendent calls me and says, "Hey, you're interested in research. I've got these two people from the NIMH. Would you like to show them around, sort of be their guide in the setting, help them find the patients, help them in whatever way you can?" I said, "Sure." I became an understudy to them. I saw what was going on with the patients and I went along with them. They discovered Nembutal (pentobarbital) tolerance, and that did not seem to be anything dramatic for them, so they went back to Washington. In the meantime, with all this happening, Thorazine, and then the other compounds began to appear on the scene. I got very caught up in them, because of my interest. One of the first grants I got from the National Institutes of Health (NIH), from the Psychopharmacology Section was ten thousand dollars. Jonathan Cole gave me

that grant. But I ran into a problem. If he gave me the grant, how was I going to administer it? I'd have to go through the whole state machinery and the bureaucracy. I said, "That is going to take too long and I'll never get started." So I set up a non-profit foundation called Friends of Psychiatric Research that was where the money was going to go.

LH: And it still exists, doesn't it?

AK: Still exists, and right now, they've got a multimillion dollar program, and a lot of investigators. I started that. And then, I got involved in doing more and more studies of one kind or another. They finally said to me one day, "look, we want to make it a little bit easier for you." I immediately became suspicious. "What are you going to do for me now?" "We're going to make you Director of Research here, because, after all, you know the impact of the drugs and what's going on in the literature and the excitement that's building up." Here I was, saying we should have research, and they say, "all right, you want research, we're going to let you do it. We're going to make you a director; we're going to give you a department." So, I said, "Well, who's going to be in my department?" "It's going to be yourself; you're going to have a secretary and you're going to have a budget." I thought it was, maybe, my salary and, maybe something for a secretary. That was my budget. Well, anyway, you know about the early days. There's no point in going over ancient history. But I was vigorous. I was youthful and I began to attend the meetings in psychopharmacology. You know how it was at those meetings in those early days. Everybody was excited about things and you got into discussions. You forgot what time of night it was, and it was a very exciting time, at least for me. So, as I got all these things going, I began to realize I needed logistical support. So I went to the Superintendent at that time, who became later the commissioner of mental health in the State. It was a guy by the name of Isadore Turk. I said, "Look, things are happening, and I don't have a thing. Let's set up some kind of a research facility." He says, "What do you want to do?" "Let's set up a research facility where we'll have a number of resources available." He says, "Well, okay, maybe you could put something on paper." At that time, the NIMH began to solicit proposals for setting up research facilities. So, he says, "Well, see if you can do anything." So I said, "Sure, I'll try." I start writing and filling out these forms, and getting some ideas of what I would need, and then, I contacted Gene Brody who was head of the Department of Psychiatry at the University of Maryland. Remember, I'm doing this in a state hospital, without the University of Maryland, without Hopkins. I'm doing this from ground zero without their involvement.

LH: I remember the story of all the studies of chlorpromazine. They were all done in public hospitals.

AK: Right and you know most of the work will continue to be done in public hospitals. I had a rather interesting and frustrating experience recently about this. I wanted to get involved with one of the newer atypical compounds, quetiapine or Seroquel, and I contacted the company, but I had to tell them, "Well, I won't have access to some of the state hospital patients because of the criteria in the protocol." They look over the protocol and they say, "Well, we can't give it to you then." I say, "why not?" "Well, we can't because if the patients are not competent enough to give you informed consent, we don't think we can go along with that." I began to remember the early days. Here's a state hospital with thousands of patients, including outpatients, I'm coming to them, knowing what I have to do and how to do it, and they get caught up in the nuances of a study which is complicated but which could be done. So, I got shot down.

LH: Well, I hope at the time you started your research, SK&F was eventually giving you the drug.

AK: Well, they eventually reached that stage. They reached that stage because they became aware that maybe I knew what I was talking about and I'd started to become productive, started to write papers. And what happened was that I went to Brody, who was the chief of psychiatry at the University of Maryland, and said, "Look, I want to write this grant. Are you guys going to support me on this?" He said, "Yes." Then, I went to Elkes at Johns Hopkins and I said, "Elkes, are you going to help me on this?" He said, "Yes."

LH: Was Elkes chairman of the department of psychiatry at Hopkins then?

AK: He was over at Hopkins at the time. So I put it all together, and then, when I looked at the bottom line, I figured it was going to cost a couple of million dollars. I submitted my grant application and in Washington, the NIMH, says, "We shall give you some money, but we aren't going to give you all you're asking for." "So, how much am I going to be short?" "You're going to be short about a million dollars." I'm thinking to myself, where do I get a million dollars? As I was meditating about that, my wife got a ticket for going through a red light, so I had to speak to one of the local politicians about it. When I was talking to him I asked whether he could help in any way in getting some money to ameliorate my situation. So he referred me to somebody in the legislature to discuss it with them. As I discussed it with them, we got into other things, and they said, "Look, you need some money for that?" "Yeah, I need a million dollars." Now, remember, at the time the legislature was almost out of session. They've only got seven days left, but the guy

thought maybe I was doing a meaningful thing, and he put himself to work and in seven days he got a bill put through. We got that million dollars, and we built the Maryland Psychiatric Research Center.

LH: Incredible, he must have been a wonderful legislator.

AK: He was. He was a judge at one time, and he became a legislator. So we have a friendship now that has existed over the years. At the same time, I built up the Friends of Psychiatric Research, and we began to get grants. We also had a lot of problems, because everybody was suspicious. They wanted to see whether the funds were being raked off into somebody else's pocket. You know how the public gets suspicious. Then, one day the Board of Directors said, "Look, you're entitled to some compensation for what you're doing, because you don't do it on hospital time," I said, "I never did anything on hospital time." So they went ahead and said, "We are going to give you a gratuity or something." And I said, "I think it's all right, the record is clear." Some enterprising newspaper character gets hold of this and it makes me look like I'm walking off with the state treasury. Of course, this was very shattering as far as my wife was concerned. Remember, I was only going to spend a year at the state hospital and here it is, fifteen years later, twelve years later, I don't know. I lost track of time. But in the meantime I was busy; I was working. And, then, I got into another area of exploration. I mentioned that Charles Savage and Louis Cholden (who eventually was killed in an accident), had introduced me to LSD. About the same time, up in Canada, Humphry Osmond and Abram Hoffer had gotten interested in treating alcoholics with LSD. They thought that was a good idea. There was another outfit up in Canada headed by a man by the name of MacLean, who had heard about the way some of the North American Indian cultures had treated their alcoholics with peyote and was doing research on that up there.

LH: And, a guy named Hubbard.

AK: Hubbard was working with MacLean up there. He was one of their research assistants.

LH: He was an engineer by profession.

AK: Well, anyway, he went to the Indians and observed it, and then he went back and persuaded MacLean to go ahead and try to incorporate what he observed in their treatment structure. Well, they did that and it seemed to be very helpful. Osmond and Hoffer heard about it, because they were working almost on a parallel track. They went and observed what MacLean was doing, then they brought Hubbard there to treat a couple of patients with LSD, and then a guy by the name

of Smith took over the project from Osmond and Hoffer and wrote the first extended series on it, indicating, "hey, it's getting some good results."

LH: Now, wait a minute, you're getting way ahead.

AK: Yeah.

LH: When did you first publish your observations on chlorpromazine?

AK: It was around 1954, somewhere around that.

LH: So that was one of your first papers?

AK: Yes. Well, there was an earlier paper that related to what you had done with reserpine. We started off with reserpine, and then you had come out with a very important presentation summarizing it at that time and pointing out that it wasn't doing very much or words to that effect. I think that preceded the work with Thorazine. Because Nathan Kline was very much involved with the reserpine study. I had spoken to him and tried to see what I could do there. I was relatively unimpressed by it; but then when Thorazine came out, it was much less of a problem in terms of possible side effects, the depression and the apathy. So I got sidetracked and went off onto Thorazine, and then when the other compounds started coming along, we started looking at them, too. Tofranil (imipramine) came along and then the monoamine oxidase (MAO) inhibitors. While Nathan Kline got involved with the MAO inhibitors earlier, there was a guy by the name of George Crane, who had been working with Nathan Kline at that time, and maybe even preceded Nathan in terms of becoming aware that this was doing something to tuberculosis patients in terms of their moods. Anyway, George came down to Spring Grove and did a lot of that work on tardive dyskinesia. He went through thousands of records on patients and began to provide some definitive evidence indicating that in some patients extended use produces this complication. In the meantime, this chap from the NIMH, Unger, comes over and says, "Hey, there's all this work with LSD in alcoholics happening up in Canada," and asked, "Could we do this at Spring Grove?" I said, "Well, no, you've got the whole NIMH." He says, "I can't have any beds for alcoholics over there, but you've got a couple of wards filled with them." At that time, in about the early 1960s, the state hospitals were admitting alcoholics and treating them for a couple of weeks or longer, depending upon what they felt their needs were. That was the era that preceded managed "mangled" care. We could keep the patients there for as long as we wanted to, and I convinced the Superintendent that we ought to try to replicate this work. He was interested in alcoholism, and he said. "Sure, go ahead and do it." So, we went ahead. We set up an experiment

to replicate exactly what they were doing up in Hoffer's and Osmond's place and we did it. We began to see that there was something there that we couldn't discount. As you know, it's very, very difficult to quantitate in any way, but, on the other hand, the feeling was that we did see some dramatic changes in some of these patients. We became aware that there was something in their reactivity that seemed to be the critical factor, and we began to focus on what we called the Peak Experience. At that time, my other difficulties began to pursue me, namely, in terms of getting the Research Center on stream. I built up a research unit, and was really looking at those possibilities very carefully, and I had good people working with me at that time. There was a chap by the name of Stan Grof, who came over from Czechoslovakia, and had a Fellowship with Hopkins. Elkes directed him to us because of his interest, and he worked with us. Savage came back. He had gone to the Institute for Advanced Studies or Training or something like that, and when he heard about what we were doing, he came and joined us. Then there was another chap by the name of Pahnke, who was getting his PhD. He had an MD already. He was getting his PhD in theology and he got involved in, what was identified at the time as the Good Friday Experiment. I don't know whether you remember that or not, where they took a group of seminarians and some of them got a hallucinogen and some of them didn't, and then they followed these people, some of them for twenty years. There was a recent review of those studies in one of the papers I get.

LH: You mentioned Charlie Savage; he came out to that Institute for Advanced Studies at Stanford, I guess, around 1963, wasn't it?

AK: Somewhere around that time.

LH: And, while he was there, I got him involved in a study we were doing on hallucinogens in psychotherapy. He'd give them four or five different treatments, three of which were hallucinogens, taped what happened, and then edited the tapes. It was a difficult job to listen to those damn tapes and evaluate the psychotherapy. But, then, he went back to Baltimore after that.

AK: Well, he heard about our work and I knew about his interest.

LH: Didn't you organize a fairly large control study with Thorazine in the early 1960s?

AK: Yes, we did a big control study. Everybody had some awareness of what the neuroleptics can do by themselves, but we became interested in what happened when you added an antidepressant or you added another type of compound to it. So we set up a big study, and we were trying to factor out whether the add-on drugs influenced the course of the activity. The bottom line in all that, in spite of the magnitude of the study, was that we didn't feel it did anything one way or

another. It didn't influence the course of events. And then, we also got involved with the antidepressants and did a lot of stuff in that area. And, then, another thing, which was very, very fortunate, was that the organization of the ACNP got started somewhere around that time.

LH: Around 1960.

AK: 1960. I learned about it from Frank Ayd. Frank Ayd was one of the original members who had been involved with some of the others and got the ACNP started. And when I heard about it, I said, "Hey, I want to come to your meetings." So he says, "You're welcome." I think I attended the second meeting, and then others began to join, too, because in those very heady days at the ACNP meetings, everybody was on the verge of a major discovery of one kind or another. But the interesting thing is, over the years that we carried on our research, and everything we were involved in – and we were involved in some very tenuous and sensitive areas – we never got in any trouble. Everything went along in a very carefully calculated way. And, even with the LSD research, some of my associates wanted to be exposed to the LSD, and said, "Well, maybe that will enhance our capacity for interacting." I said, "Before anybody gets involved, we're going to have some rules. The rules are you have to go through a procedure just like the patient. You have to be interviewed by a number of psychiatrists; and, the other thing is, to keep the thing on a level playing field, we're never going to tell anybody who was treated and who wasn't." I wanted to make sure that the thing was balanced, so that the people who had been exposed and the people who weren't would be equal, so that we couldn't feel it was biased. And even as that got shot down, when they finally said, "You are not handling this so well administratively," I didn't feel very badly about it. I felt disappointed. I felt that, all right, maybe I could have done a lot of other things, but I say, "Well, maybe somebody can do a better job." They put Will Carpenter in there (in charge of the Maryland Psychiatric Research Center) and Will Carpenter, you know, is focused on schizophrenia. But I see in the *American Journal of Psychiatry*, the 1995 issue, there was an article by him on clozapine in schizophrenia recently, and Meltzer took him to task. He wrote an editorial about it and, so, the ball started going back and forth. I read this, and then Carpenter sent a big letter to the editor of the *American Journal*, it came out twelve months later, but I read each of these documents very carefully, and while they accused each other of misinforming, misinterpreting, misconceiving certain concepts, I came to the bottom line: They were both right. LH: Well, that whole issue of the specific action on negative symptoms has been somewhat iffy all along.

AK: It's iffy, because even the rating scales, the criteria that they're using to identify and to grade them, were iffy. The companies seized upon avidly to promote negative symptoms with Compound A vs. Compound B.

LH: Quicker action and negative symptoms were the gimmicks they all used.

AK: I don't fault them for that, because they've got to have some way of promoting their compounds, plus the money goes back into research, a lot of it, anyway. I've never gotten involved with the drug companies or given anybody a hard time about it. I've always been sympathetic to what they're doing. If they want to make a few extra dollars, that's their problem, not mine.

LH: Now, are Will Carpenter and Carol Tamminga and the people now working in the same unit that you started?

AK: They're using the facilities, but they've kept me hands off, never invited me to anything, and never acknowledged anything that we've done to bring this facility into existence. Sometimes I wonder about it, but then I figure, well maybe that's part of the cultural system.

LH: That's what the Eskimos do; when you get old, they put you on an ice floe and let you go to sea.

AK: Right. At one time, I would go down to the university because they gave me the title, Research Professor of Psychiatry, never Professor of Psychiatry, but Research Professor of Psychiatry. I didn't check it. I don't care what they call me, as long as I could get in there and do something I felt was useful. What they asked me to do was to supervise the residents in terms of the psychopharmacology they were employing, and my feeling was, okay, I'll do it. I did that for a number of years, but then they started getting more and more administrative – you've got to sign off on all the charts and you've got to do this, and I don't even know when they follow through what they're doing – and I thought, I can't do that, because I can't assume responsibility that I really can't follow through on. They said we have to do this. Well, I said, "I can't do it. Goodbye." So I quietly departed, and I tried to get a number of drugs at Taylor Manor and I worked on a number of things with different drug companies. Then, finally, my last hurrah was trying to get established a specific research facility devoted to the exploration of the hallucinogenic drugs. I think there are phenomena going on in some individuals what I call a psychic healing influence. You have that in religious activities; and I've seen it enough times to realize that it reaches into an area which we know very little about. I think is going to be very important in the future as we move into the twenty first century and we start learning more about how we really develop maturity

within ourselves so we can deal with equanimity with a lot of the things we have to deal with. One of the elements in the psychedelic peak experience is this transcendental experience. It's something that's way out of the ordinary and has to be explored.

LH: The work with hallucinogens sort fell apart after about 1957.

AK: It fell apart.

LH: And, then, it's only been in the last four or five years that a chap named Rick Strassman, whom I don't know, but he's in Arizona, has been getting some grants and doing some publications on it.

AK: Rick Strassman, I'm familiar with his work. I'm familiar with what's going on in the past several years, because this institute that I'm talking about is called the Orenda Institute. They just got their foundation. They're tax-free. It was set up by a chap by the name of Rich Yensen and his wife Donna Dryer. She's a psychiatrist and he is a psychologist. He was involved years ago with us in our work with LSD, and they decided to pick it up and work with it, so they've gone through this laborious process. They've been to a lot of meetings on the West Coast and in Europe. Some of the Europeans are still interested in it. It has to be pursued because you know and I know that when we take a schizophrenic who has gotten better up to a certain point, there's a certain residue of symptomatology. Many times we find individuals who get to a certain point and then somehow there remains something that's unresolved. The only powerful element that I feel that might have some impact on it, at least from our observation, is in some way to create what we call a peak or transcendental experience. Now, the question is how to differentiate it from that which happens in a religious revival? What's the difference? Are the same things occurring? Many of these people have been through religious revivals or thereabouts, but that doesn't work. But, with this "transcendental experience," it seems to work. And then, in the cancer patient studies, there was no uncertainty that we were doing something that was important, because where we got these experiences, the amount of narcotics these patients were using decreased. The patients began to have a more wholesome relationship to the people around them. The conspiracy of silence seemed to be ameliorated, and in whatever time was left, there was a much better relationship between the individual and the family, because the individual seemed to have a better way of communicating and was more philosophical about things. There's much to be done, but I think it will be done in the future, because we know the limitations of the drugs we're using today. We treat a panic

disorder, we treat alcoholism, we treat depression, and we ameliorate the symptoms, but what are we doing so far in adding to the individual's capacity for development?

LH: Each person has a somewhat different experience with hallucinogens. I remember Jack Shelton, who used to be one of my collaborators, had extensive experience with LSD, and he always likened it to a near-death experience, where he felt that he had been close to the edge, and then came back. My own experience was a feeling like I'd been terribly ill, and now I'd recovered, and felt so vibrant to be back with the living. So, you know, it's a different kind of reaction, I guess depending on our own personality, to so much of an extent that it's hard to quantitate it.

AK: It's hard. I went through a couple of years of analysis and I sometimes say to myself, well, what did it accomplish for me? I'm not so sure, maybe better insights, maybe a more humble attitude towards myself, my fellow man, maybe a capacity for tolerating the shortcomings of others.

The other thing that's very important, that nobody realizes, is that the organization of the ACNP, with the structure and the role it has played in getting drugs, getting people interested, and making it available for the younger generation, the people that are about to carry on the organization was a tremendously important development. Carpenter presents his papers, Tamminga presents her papers at the ACNP, and we need that. We need those kinds of activities.

LH: Well, the remarkable thing about the ACNP is the ability to bring together so many different disciplines, so we can talk to one another. For instance, when I go to the ACNP meetings, I don't go for the things that I know about. I always go for the things that I don't know about; but, of course, every year there's more and more to learn, so I have trouble making my selection. And, of course, some people like Don Klein overreacted to it by saying, we're no longer interested in clinical psychopharmacology, and therefore he started a separate organization. Do you remember that?

AK: No.

LH: The American College of Clinical Psychopharmacology?

AK: I'm not a member of it, but I follow their proceedings, because I like to keep abreast, because I need it every day in terms of the work that I do. I see a lot of patients and I use a lot of drugs. I don't just use drugs, because I have the advantage of having had a background and training in psychotherapy and analysis, so I can integrate these things, sometimes, much more meaningfully with a patient.

LH: Have you retired from the state hospital system?

AK: I retired about fifteen years ago.

LH: And now you're doing private practice?

AK: I'm working for the Taylor Manor Hospital organization.

LH: Which?

AK: Taylor Manor.

LH: Oh, Taylor Manor, which is essentially a private hospital.

AK: A private hospital.

LH: Does Joe Taylor still live out in California now, PalmSprings?

AK: Yes, the old man and his wife live out in California. They moved out to some other place on the West Coast.

LH: The son has taken over?

AK: Bruce is very bright, very knowledgeable and he handles a very, very difficult situation with all this managed care and all the issues and things that are going today, which would drive me up the wall. They're providing a service. They're trying to deal with the demands. I'm studying and trying to constantly think of ways of dealing with new things, For example, at my age, would you think that I would be involved in the study of Attention Deficit Hyperactive Disorder? The stimulants are the only things that seem to do a pretty good job there, and the question is, why? So I get involved with comparisons, and then I get involved with bupropion, and I get mad at myself, because, "Geez, I say, you're getting grandiose; you're getting caught up in all these things and nothing is going to be accomplished."

LH: You had too much analysis.

AK: I think I'll stop with one.

LH: Well, from your vantage point, what do you see in the future?

AK: The way I see the future is that this is just the beginning. It's like Churchill said a long time ago, "This is not the beginning of the end, but it may be the end of the beginning" – because we're just getting oriented. We're getting some awareness of the techniques and the sciences and everything else. In neuroscience alone, we've got thousands of people working on different aspects of these problems, and if you're trying to keep abreast of all this, it's very difficult, but we need to have people in there who are knowledgeable and can tell us what is going on, and they need support. For example, somebody starts talking about dopamine receptors to me, and when he starts

getting into the pharmacology, it's like Greek. They can say what they want. I can't criticize it one way or another, because I don't know when they're right, but I know that they're doing something that may ultimately be meaningful and it's important that they have an audience, that there's interaction. I think the needs are going to become even greater. They'll become greater because there are a lot of things in our society that we don't even have a handle on yet; for example, in learning difficulties, kids that develop all kinds of problems, and then they're mistreated and become psychopathic, because the parents and the people working with them don't understand. We've got to deal with the parents, because otherwise they become sociopathic in one way or another. And how do we affect our learning capabilities? How do we go about making what we're doing more effective? We've had neuroleptics for fifty years, and you know what, we still don't know how to regulate a dose in a really precise way. The other day I got a letter, written by a man by the name of Haase, saying "Get people just to write a simple verse and repeat it a number of times, and then look at the handwriting and the way it changes in structure and space, and you can tell very quickly whether your drugs are too much, too little or whatever." There are all kinds of crazy things we measured: prolactin, dopamine receptor assays, and neuroleptic plasma levels and try to correlate them. Nothing works – but the point is, one thing does work. We look at the patient. We make a judgment as to whether he is getting better or not, and we go along from that.

LH: All right. What you touched upon is a major point in all of medicine. The technology has become so powerful that people tend to rely on that rather than looking at the patient and deciding. I remember about three or four years ago, I came in to my urologist and said, "I have an atonic bladder." So what does he do? He does an urodynamic test to prove that I have an atonic bladder. It doesn't make sense to use some of this technology when you can make the diagnosis, clinically, but that's the story. You mentioned Frank Ayd, who of course has been a neighbor of yours, although he worked out of a different hospital. Do you ever have much interaction with him?

AK: Yes, I see him occasionally. Frank is very busy. He's put out this encyclopedia now with the different terms.

LH: Didn't Frank have some contact or consult with Taylor Manor, too?

AK: He's emeritus. He was the first Director of Research and Education. Incidentally, I have a title there, but I always keep forgetting about it. I'm supposed to be the Director of Research, but for me, it's just like being back in the state hospital. If you want to do something, you figure out

how to do it, and if I get outside funds, I can go ahead and do it. But most of the times, I get shot down, because it's hard to do things without the proper logistical background.

LH: Do you know Fritz Freyhan very well?

AK: I met Fritz Freyhan when he was up at Delaware. Then, he came down and took over, I think from Elkes, when Elkes left the directorship of the research unit over at the St. Elizabeth's.

LH: I'd forgotten that.

AK: He took over, and then he got divorced and subsequently remarried, and then he dropped dead.

LH: He died young, but he did a fairly large study of drugs over in the Delaware system.

AK: Yes, he was one of the first people that got involved on a large scale; he did careful work. He started that *Comprehensive Psychiatry*.

LH: He was an old fashioned clinician like you are.

AK: But, let me tell you something, clinicians, good clinicians never go out of style. They may get old, but if they know what they're doing, they don't go out of style.

LH: Well, whether you like it or not, you fade away. I was recently in the Far East, sponsored by Pfizer and all these young employees, most of whom could have been my grandchildren, would come up to me and say, "What's your name?" And, I'd say, "Dr. Hollister." And, "What do you do?" Oh, god, fame is so fleeting, you know. My name meant nothing to them.

AK: Yeah, but you know what you did. Nobody can take that away from you.

LH: No. Maybe that's the consolation of old age.

AK: We're leaving things a lot better than we found them. Do you agree with that?

LH: Yes.

AK: Okay.

LH: Well, that's the only thing. Everyone I've talked to in these series has been so happy with their career and wouldn't have changed it a bit. Is that true with you?

AK: I'm not sure, and I'll tell you why. I've always had a passion for Space.

LH: You mean you would have liked to become an astronaut?

AK: Yes, I wanted to go out there and explore those planets, and one of my secret fantasies was that if I had unlimited wealth, what I would do is, I would make a deal with the world organizations, and I'd say, "Look, if you'll let me have a couple of hundred thousand square miles of land on the moon, I will go ahead and develop a transportation system that will get man from the earth to the

moon, so he can communicate in a regular fashion.” Now, is there a precedent for what I’m doing? Yes. In the nineteenth century, after the Civil War, when they were discussing whether they should build a railroad from the East Coast to the West Coast, there was a lot of commotion in Congress, because they said, “Well, why do you need the railroad out there? The only thing out there is Indians and buffalos. Why do you need it for them?” And the companies that were interested in promoting this said, “We’ll make you a deal. You give us land grants and we’ll build that railroad.” And, so, they said, all right. The land didn’t cost us anything, so take what you want. So, they did and they’re still profiting and so is the rest of the country.

LH: You need another life. I tell you, if you’d invested in that SK&F stock, you probably would have had enough money to do that.

AK: All right. It wasn’t my fate or my karma, whatever you want to call it.

LH: Well, we all missed opportunities in life but it’s a lot of fun.

AK: It’s a lot of fun, and that’s the important thing. We can make it a lot of fun for a lot of people if we get to know more about what we’re trying to do.

LH: Very nice talking to you, Al. Good to see you after all these years.

AK: All right. I’m glad to be here.

## 22. ROGER P. MAICKEL

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, 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 and 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 every day. 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; that's when you had to take an exam for fellowships, graduate 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, absolutely nothing! He said we've got some positions open and we're looking for young baccalaureates who

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\*Roger P. Maickel was born in Long Island, New York in 1933. Dr. Maickel worked at the National Institute of Health as a research scientist from 1956 to 1965 while he received his PhD, was professor of pharmacology in the medical sciences program at Indiana University from 1965 to 1977 and was department head of pharmacology and toxicology at Purdue University from 1977 to 1983, and then returned as professor to Purdue to continue his research. Maickel died December 28, 2006. He was interviewed in Waikoloa, Hawaii on December 11, 1997.

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 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. And Hence was working on the metabolism of reserpine and trying to isolate the metabolites from dog urine, 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, neuropharmacologist; 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, stay over tonight, and visit with him at 10 o'clock tomorrow morning." 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 that 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: That was the way he worked. 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; did work on the drug metabolism enzymes, liver enzymes, in everything.

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, of which I never heard. 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. Oh, 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: Yes, in days, literally. 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 the, 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 the telescope 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 spectrophotofluorimeter was a revolutionary tool.

RM: I stayed on 5 years after I finished my PhD, as a post-doc. Another story that tells how Brodie was, beautifully: 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. He came in one day and dragged Mike and me 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 norepinephrine tritiated. And, he said "I can't, I don't want to spend that much money."

LH: Make it.

RM: No, no, he didn't say that would have been easy. He said, "There has got to be a way to find out when you give DL norepinephrine 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 knew where he'd been. 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 17-½ 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 my laboratory, and if you want to collaborate on a problem with

someone 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, you get up for that type of exam, and breakfast doesn't exist. It's a cup of coffee and 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. And, 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 I, 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." He said, "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. "Don't do anything until Monday." 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. Okay 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 ask you, 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 she 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." 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 he 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 pathologist in the country, "Ben Hyman 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, or just shortly after that, Parkhurst Shore--who had been Brodie's specialist, if you will, in radioisotopes, because C-14 and Tritium 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 6 weeks' vacation in Oak Ridge, Tennessee." I said, "Vacation?" "Yes, I'm sending you down to Oak Ridge Institute for Nuclear Studies for a 6 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 and 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. I had written my thesis. "What are you doing?" I said, "I'm studying my thesis." "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; you can go." Okay, I figured it's my work. Hey, 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 D.C. 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. "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 mid-west 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 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 1960's, and he was going to take four of us with him. And he came back from Wisconsin with their whole departmental lists of people, equipment, rooms. Now, you're talking about Wisconsin Medical 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 Elizabeth's 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 master's 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, and it looked very good. 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, my office and my labs were in the psych building, I was supposed to have a joint appointment with the pharmacology department at the IU Medical 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; 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 I made 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 lifelong 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 medicine 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 things, because this is another little Brodie antidote 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 1/3rd 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 in the unit, one of whom was an ASPET member; the other three were not. We had 12 graduate students, a 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 ACP Fellows: Ron Kuntzman and Lew Lemburger. I think I've even 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.

### 23. ALEKSANDER A. MATHÉ

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 videotaped 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.

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\* Aleksander A. Mathé was born in Zagreb, Yugoslavia (Croatia) in 1934. After graduating from medical school in Yugoslavia, he completed a psychiatry residency at Bellevue Hospital, NYU in New York City, New York. After research at the Massachusetts General Hospital, he left the the United States and went to Sweden for a residency in Internal Medicine at the Karolinska Institute. He has worked for periods of time at Boston University School of Medicine, Mt. Sinai School of Medicine in New York City and now is at the Department of Psychiatry at the Karolinska Institute in Stockholm, Sweden. He was interviewed in Waikoloa, Hawaii on December 12, 1997.

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 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. So I really took a two-year fellowship in Psychosomatic Medicine. 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 there 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  $\beta$ -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  $\beta$ -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 '69 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. Lenfant, who was 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 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 '74 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's, 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 the 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 enkephalin, 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.

## 24. DOUGLAS M. MCNAIR

LH: We're in Hawaii at the 36th Annual Meeting of the American College of Neuropsychopharmacology. These are history task force recordings of people who have had an impact in the field and who have many connections with it. Today we're starting off with Doug McNair\* who's been in the field as long as I can remember and probably longer, actually, and who's had a very illustrious career in it. Doug, you're a psychologist by training, aren't you?

DM: Yes, that's right.

LH: What impelled you to become a psychologist?

DM: Well, when I was a teenager I guess I started reading Freud and Karl Menninger, and things like that, and I decided I was going to be a psychiatrist, probably from going to popular movies. At any rate, I got interested in becoming a psychiatrist by what I would now call the lay literature. And I went to the University of North Carolina intending to go to medical school until I was about a junior in college. I had two years of college and then I went away a year for the Army, because I was at the age where I was drafted right after World War II. I went in for my physical exam on VJ Day, or the day after VJ Day. Then I got back to Chapel Hill, probably at the end of my junior year, and the VA training program came along.

LH: When the VA was trying to increase the number of psychologists?

DM: Yes. It was the clinical psychology training program. At that time it was a four year program. I was majoring in psychology and liked it a lot, although my minor was chemistry, so I was still building up a lot of pre-med courses. Then I decided to switch and go into psychology instead. I applied for and was accepted into the University of North Carolina, Chapel Hill program. Stayed there from 1948 until I got my PhD in 1954. The first job I had after that was at Woman's College of the University of North Carolina, what is now called University of North Carolina, Greensboro. I was working in the Greensboro Mental Health Clinic and teaching part-time at the University and then I switched over.

LH: This was after you had gotten your PhD?

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\* Douglas M. McNair was born in Rockingham, North Carolina, 1927. He received his PhD in 1954 from the University of North Carolina at Chapel Hill. He was widely recognized for his psychometric research, especially development of the Psychiatric Out-Patient Mood Scales or POMS during his time at Boston University starting in 1964. McNair died on June 4, 2008. He was interviewed in Waikoloa, Hawaii on December 11, 1997.

DM: Yes.

LH: Were you under any obligation to stay with the VA at that time?

DM: Not post-PhD. We did two years of work in the VA hospital while we were in the training program.

LH: Oh, I see. But, you had no obligation to do work at the VA after you got your PhD?

DM: No, not at all. I worked a couple of years in the Psychology Department at UNC-Greensboro. It was during those years that I decided that I really wanted to do research. We had to teach four courses a semester and three of those were in educational psychology, which I did not like at all. I started looking around for a job and the job that appealed to me most was with Maury Lorr in Washington, when he was running the Outpatient Psychiatric Research Laboratory, OPRL. When I went there we were doing mostly psychotherapy type research. We did a great big collaborative study in which we wanted to find out whether twice weekly psychotherapy offers any advantage to once a week, and once a week over every other week. Then drugs came along and the collaborative studies in chemotherapy started going and our group at the VA in Washington started meeting with you all and going to some of the meetings. We finally did a study which included meprobamate and chlorpromazine as adjuncts to psychotherapy with outpatients. I think that was the first drug study I was involved in.

LH: By that time the In-patient Multi-dimensional Psychiatric Scale, the IMPS, had been developed, hadn't it?

DM: The IMPS had not, but the MSRPP, the Multi-dimensional Scale for Rating Psychiatric Patients, developed by Maury Lorr and Eli Rubinstein was. The IMPS was a successor of it. I think in everybody's opinion the IMPS was a big improvement over the MSRPP. The MSRPP pre-dated the IMPS, maybe by about 5 or 6 years.

LH: I see. But, you were instrumental in development of the IMPS?

DM: Yes. I think most of that work was done in the very late 1950s, in '57, '58, and '59.

LH: I think it was the only really multi-dimensional scale for psychiatric inpatients, wasn't it?

DM: I think you are right. It wasn't long after we had the IMPS that John Overall and you developed the BPRS.

LH: Yes, Overall and Gorham took the IMPS and streamlined it covering the same domains.

DM: Yes, I think the BPRS has the same 10 factors of psychosis as the IMPS. Lorr, Klett, Jack Lasky and I were the authors of the first version of the IMPS. I believe it was in that order. It

was widely used in research that was going on at that time. Then we sort of moved out of research in the psychotherapy area and exclusively into out-patient psychopharmacology. We did research mainly with drugs and without psychotherapy. I think the first study we did was with meprobamate and the drug did not have any particular benefit, but then we had some evidence that combining chlorpromazine with psychotherapy offers advantages. As we got into that research we started to see more and more the need for measuring instruments. There had been the IMPS for the inpatients, but we needed psychometrics for the out-patients, too. So, we started developing "feeling and attitude" scales, as well as symptom rating scales that were very much like, what's now called the SCL-90 or the Hopkins Symptom Checklist. The origin of the SCL-90 was in scales that could be traced back, I guess, to Adolph Meyer at Hopkins. The aim of these scales has been in getting systematic ratings on how people felt. We were involved in some of the shaping of these scales and as part of that we got started on what I think was one of my main projects, the development of the Psychiatric Out-Patient Mood Scales or POMS. And we kept the same acronym for the plainer version once we realized it was much more broadly useful and utilized than just in psychiatric patients. In fact, I'm involved right now in trying to update the manual and the bibliography and so on. After I retired from BU, Boston University, in 1991, I did the first survey of the literature of articles in which reference was made to the POMS, and at that time there were more than 2,000 articles. In the last five years, there have been another 500 or so. It's used in almost every branch of medicine you can imagine, except, I don't think it has been used in radiology.

LH: Well, those were the first series of psychiatric rating scales, weren't they?

DM: Yes, right, they were.

LH: I don't remember any before the war.

DM: There was a predecessor or an ancestor to the MSRPP, done by a Catholic Priest at a Catholic University. I think his name was Father Brown, but I'm not really sure; he developed a rating scale that I know that Maury Lorr used to have a lot of respect for. I also think that he borrowed from it in developing these other scales. But you're right, there was very, very little.

LH: Of course, now it seems as though there's a scale for every ailment. The scale business is thriving. I haven't seen Maury Lorr in years. What's happened to him?

DM: Well, I talked to him some this summer. I think right about now he may be back from a trip over to Vietnam. He's in his 80's and is still moving around pretty well. He's Emeritus at Catholic University in Washington and still maintains an office there. He's pretty active.

LH: Well, that's great. So, I remember when we started off the VA Cooperative Studies Program that you were part of the group that we got together. And as I recall, we used the IMPS for the first two or three studies.

DM: Yes it was very sensitive in picking up drug effects.

LH: Oh boy, those were the old days.

DM: It picked up not only the difference between drugs and placebo, but also between drug comparisons.

LH: Oh yes, that was amazing that it could not only tell the drug placebo differences, but also the differences between drugs like chlorpromazine and mepazine, which at that time was thought to be a useful antipsychotic. It had some effect but not nearly as much as chlorpromazine. So, that was quite an achievement.

DM: Around the late 1950s, every year we had a VA Collaborative Studies meeting we would go from Cincinnati to Kansas City or from Kansas to Cincinnati, and I remember those meetings very fondly. You had a big part in those studies and I always looked forward to your stellar presentations at those meetings.

LH: Who was Chief of Psychology at the VA during that period of time?

DM: Max Houchins for most of the time and he was assisted by Cecil Peck.

LH: Cecil Peck was the one I remember.

DM: We used to have poker games after the meetings in the evenings.

LH: Could you say something about the research discussed in those meetings?

DM: The research we discussed was more and more in the outpatient area, and we got involved in more and more drug studies. I think every study in psychopharmacology I was ever involved in, involved psychotherapy as a component. In the early days, we were involved with all kinds of drugs, but later on, we moved more to studies with antidepressants in outpatients. While I was in Washington, Maury and I did some of the early work with Librium (chlordiazepoxide), a tranquilizer.

LH: That would have been around 1959-60?

DM: Yes. Librium was succeeded by Valium (diazepam), and I think we did one of the early outpatient studies of Valium. That class, benzodiazepines, appeared to be considerably more effective than meprobamate, which was what we started out looking at, and produced less side effects and complications in outpatients than chlorpromazine.

LH: In those days, most psychotherapy was still more or less analytically based, wasn't it?

DM: Yes, very much so.

LH: As compared to today's more tailored psychotherapies, which go after specific areas in schizophrenia, for example, largely what I would call rehabilitative psychotherapy.

DM: Yes, you are quite right, psychotherapy is more focused now. They are highlighted for specific disorders. Of course back then, DSM-II was in use for diagnosing and that was not a rigorous way of classifying patients.

LH: In DSM-II, there was no entry called schizophrenia; there was schizophrenic reaction, as though schizophrenia was still a reaction to interpersonal problems or problems of the environment, rather than an intrinsic illness.

DM: That's correct, not exactly the medical model.

LH: Well, when did you move to Boston University?

DM: I worked with Lorr in Washington from late 1956 to mid 1964, and then I moved to Boston University School of Medicine. In 1970 I became a full Professor there in Psychiatry, with a joint appointment in the Psychology Department; I worked with both departments. In 1980, I became Director of Training in Clinical Psychology. They asked me to consider taking it; I certainly would have never considered applying for the job because I thought I was much too research orientated for the group. But it did work out and I think I became sort of a token researcher. I moved my lab over to what we called the main campus of Boston University, which was on the other side of town from the medical campus.

LH: The medical campus I think is down near the old City Hospital; whereas, the main campus is over across the Charles River from Harvard.

DM: Yes. Then, I stayed there another ten to twelve years until I retired in 1991. By that time, we were studying tricyclic antidepressants and focused on their possible effects on cognitive functions. We were working on the assumption that the cholinergic system was related to memory and we found that the anticholinergic properties of tricyclics varied a lot.

LH: Oh, yes.

DM: Amitriptyline was strongly anticholinergic, imipramine was in the middle, and desipramine was fairly low in anticholinergic effects. We were looking at using measures of short and long-term memory, semantic memory, psychomotor function, and attention.

LH: Were you using the drugs, more or less, as tools for exploring hypotheses about memory, learning, and things of that sort.

DM: Yes. We began to look at the effects of these agents on elderly people. The focus was on cognitive effects, but we were also looking at dose-effect relationships. We were trying them in normal elderly subjects and we had them come in once a week for a few weeks while they were taking very, very low doses of tricyclics.

LH: Was this done in collaboration with the VA Unit studying aging, in Boston?

DM: No, it was something we were doing on our own. We were using doses of 5 or 10 milligrams of amitriptyline and of the other two agents and found that even such low doses had quite strong cognitive effects in people over 65.

LH: Well, one of the paradoxes that have been true of these drugs is that most of the time in normal people they're noxious. Most of the antipsychotics, at least the older kind, and most of the tricyclics, were very obnoxious to normal people. And yet, the crazier you were, or the more depressed you were, the better you tolerated them.

DM: I've known you for about forty years; time goes by very, very fast.

LH: I've always been a little bit discouraged by the fact that the VA collaborative studies with psychotropic drugs have never gotten the amount of credit that they should have gotten; they pioneered the whole field of using a very advanced technique, for the time, to study drugs. Later on, several states emulated those studies and of course, the Psychopharmacology Service Center at NIMH did it as well, but the VA studies were really the first.

DM: They were the original studies and I have been concerned about that, too. The Collaborative V.A. studies were clearly first. Nothing like that had been done before, and the collaborative studies that followed were very much "me too" studies.

LH: Well in retrospect I'd call all those studies a massive scientific overkill because, by that time, people who had any eyes and ears or powers of observation at all could tell that these drugs were doing something vastly different from any of the drugs we had before. But in those days, people in psychiatry were still very much against the notion that drugs would really have an effect and we had to do that massive scientific overkill.

DM: I suppose so. I think a lot of those studies had to be done. When I came into this field most people in medicine sort of looked at psychiatry as almost anti-science and as know-nothing about scientific stuff, and I think that by doing those studies psychiatry pioneered in the development of

clinical trial methodology and was far ahead of the rest of medicine. Some of the stuff today that you read in other fields is amazingly naïve about the standards of clinical trials in psychiatry.

LH: Well, I think, of course, the concept of the controlled clinical trials didn't start with us, because I think they were first used to test anti-tuberculosis drugs in 1945-46. Harry Gold at Cornell was talking about controlled blind studies way back in the 1940's. But I think our groups advanced the cause more than any of the other groups.

DM: I agree.

LH: Earlier in this meeting, for instance, there was a big session on how to study drugs in multi-clinic trials. It could have been the same damned thing we were talking about 40 years ago.

DM: I had told my wife that I had seen that title over and over.

LH: Well, it was sort of exciting times then because nobody knew for sure what the answers were and what the proper procedures were.

DM: I know and I think one great thing that ACNP did was to provide the mechanism for all these people to come together and meet.

LH: Oh, yes. The ACNP has been a wonderful organization for cross fertilization between disciplines. I'm a little fearful personally, that we are going too much toward the neuroscience side and concerned for example what can a psychologist get out of this year's meeting?

DM: That concerns me, too. There are many papers here that I can't even get through the title. But, I've never spent much time trying to predict the future, so I don't know where it's all going.

LH: Well, I suppose you've never had any regrets about the course you took?

DM: No, I think I'm lucky. I've certainly had regrets on doing things I don't like, but they have been minor, compared to the fact that I was able to do something I really like to do and making a fairly decent living doing it. I suppose if I had known how to make a living from statistics and quantification mathematics I might have considered doing that. Once I got into the field, one of the people who influenced me most was Ben Wiener, who wrote that famous book on experimental design. He was a professor at Chapel Hill when I was there. I got very interested in the whole business of analysis of variance because he showed us what we could do with it. When I came to this group the first time, it seemed to me that clinical psychology was closer to being a good hard science than at the present time. There were a lot of people like Jim Klett, me, and John Overall with psychology training, who were into quantification.

LH: People, I would call, psychometricians, biostatisticians.

DM: Yes, I think we contributed something to the development of study designs.

LH: Oh, yes, from the statistical point of view.

DM: But I don't think this is the place any longer for psychology. It bothers me, in a way, that there are not more people with the kind of orientation and background we have coming into this organization. I think they are not coming into this organization because they don't see their place in it any longer. .

LH: Well, that's been one of the great concerns I think among some of us, that we're getting a little imbalanced. I wonder who is going to replace the people you mentioned, like Klett, Overall, you, and several others. Well, you retired in 1991?

DM: Yes, I became emeritus then.

LH: Lots of difference, isn't it?

DM: Oh, I get along because I have my computer at home and I can get into the big computers at BU for data analysis. I find things like Medline on the internet just wonderful. In the year I retired, I got a contract with the Defense Department to evaluate its' training program, a demonstration project in training psychologists to prescribe psychotropic drugs, and that's been going on for almost seven years now. An ACNP committee of four psychiatrists and four psychologists, we constitute what we call the evaluation panel. We have visited this training project several times a year.

LH: Is the program still on?

DM: They have stopped admitting any new people, and there's no one in the formal training program right now. The formal training program included one year didactic medical school courses and one year intensive clinical work on the psychiatric ward at Walter Reed. Everybody has finished those stages and there are no new people admitted. I think there may be another contract to follow, but I'm not sure of that. The probability is that there will be something.

LH: There's always been a turf battle between psychologists and psychiatrists about psychotherapy; now, here it is about drugs, and of course, a lot of other people getting into the psychotherapy business.

DM: I don't know what's going to happen. Our job is to evaluate what's going on. There is no consensus among members of the panel whether these people will ever reach the point of independent practice of prescribing medications. I think it's fair to say that some of us think that some of them will, but we may have doubts about the medical safety of prescribing by them. If

you think these people have had two years of very intensive training after their post graduate training and they are still not ready to be turned loose as independent practitioners, I would say that if you are a psychologist, and want to prescribe drugs, you would be better off going to medical school.

LH: It almost becomes the equivalent in time, anyway. What surprises me is that psychologists want to go into that field rather than pharmacists, because pharmacists are trying to get a hand in drug substitution or actually making suggestions about the proper drug. I suppose in some state hospitals most of the drug prescribing is actually done by pharmacists and signed off by psychiatrists.

DM: Probably so.

LH: Where do you envision the place of psychologists in the ACNP, say in the next ten years? I think we're both worried about the fact that the role of psychologists has diminished in the last ten years. Is it going to improve in the future?

DM: I honestly don't know. If the job needs to be done and the psychologists aren't there to do it, somebody else is going to pick it up and do it, I think. In the last 30 years or so, there has been a decline in the number of psychologists working with the field. I think some of the psychiatrists have become extremely good at data analysis, so that they may pick it up. Or they will go and hire people who are more sort of real statisticians than psychologists ever were. I personally think it helps to know something about the field where the data come from, what you're dealing with.

LH: Well, it seems to me, and you know this better than I do, that the trend in psychology is toward the experimental or physiological approach, rather than the purely clinical, as it used to be. For instance, the other night I met a young woman, who's a psychologist and very much into brain imaging techniques. That's something that, well of course, 15 or 20 years ago, none of us could have foreseen.

DM: It's very true that psychologists do everything under the sun. They practice in clinics, also they are Deans in a lot of schools, and they're into MRI and PET scans. Neuropsychologists, I admire for the testing and measurement procedures, especially in the area of memory and so on, but I think their statistical sophistication has been rather lacking. There is no reason that this couldn't improve. I don't think we will ever reach the time when we don't need to measure.

LH: A few years ago, I did a little pilot study with a neuropsychologist in our hospital and he would compare findings with brain scan and neuropsychological testing, and the agreement wasn't very good.

DM: That's a real validity check.

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

DM: The two things I hope may happen in the future, and these may be clichés: I would like to see something developed to control anger and violence. Maybe psychopharmacology will develop something that can contribute to reducing violence.

LH: That would be quite an achievement, wouldn't it?

DM: That would be a great achievement. I think there are people working on it and maybe it will happen.

LH: Every time you turn on the television set, there's a guy standing there with a gun or knife in the movies. You know, violence is so pervasive. Doesn't it make sense to feel that that must have some influence on the viewer?

DM: It certainly makes sense. I think there is some fairly solid evidence that if children are exposed to it, their play is more violent.

LH: Well, I remember when I was a kid, we used to play games of cowboys versus Indians.

DM: Right. I did the same.

LH: And, you know, if your cap pistol went off, your "enemy" would drop like they were killed. But of course, we didn't connect to the fact that somebody who fell to the ground was never going to get up. They were going to get up in the next two or three minutes and the game resumed.

DM: Play dead.

LH: It's almost as if people now are taking that juvenile approach and extending it to their thinking into their adult life.

DM: Yes. There's a violence in the ages from fifteen to twenty-five, and then in Alzheimer's at the other end. It looks like there's some hope for drug research for Alzheimer's. A lot of the studies look very promising.

LH: Well the most encouraging part about Alzheimer's is the fact that if you keep using your brain, you're likely to keep it, and I think you are a good example of how to avoid Alzheimer's.

DM: I don't know about that. Sometimes my memory for names is not what it used to be.

LH: This business of remembering names is tough. Well, it's been nice talking to you, Doug.

DM: I appreciate being asked. You were a role model for me in the early days, and I appreciate you asking me.

LH: The biggest thing that I had sense enough to do was to know what I didn't know and get people who could teach me, like John Overall, of course, who has been my main mentor.

DM: You were one of those who really understood all this stuff.

LH: OK, Doug. Thanks for coming by and having this interview with us, and I hope you have many more years and we can interview you again.

DM: Twenty more years and I have something to say. That would be great. Thanks a lot, Leo.

## 25. CHARLES P. O'BRIEN

LH: We are at Las Croabas, Puerto Rico for the Annual Meeting of the American College of Neuropsychopharmacology and for the interviews of historical interest, we are going to be interviewing, today, Charles O'Brien,\* and the two interviewers will be Tom Ban and myself, Leo Hollister. Thank you for coming to the interview, Chuck. We're always curious as to how people got started and what influences made them choose, first, the career in medicine, second, the career in psychiatry, and then third, the career in whatever the specialty of psychiatry they're in.

CO: Well, I got interested in medicine while I was in high school, because the only other professional in my family was my uncle, who's a dentist, and so, my mother said, well, you should be a dentist. And so, I said, OK, fine, I'll be a dentist. At that point, I was about in the 10th grade. People were talking about what they were going to be, and I said, dentist, and one of my friends said, well, you're really smart you could be a doctor. Yeah, maybe you're right. I've never really thought of it before. So, I went to medical school. I grew up in New Orleans, so I went to Tulane.

LH: You were born in New Orleans, right?

CO: Born in New Orleans.

LH: And, you've got an Irish name, are you part Irish? You don't talk like one.

CO: Well, this is pretty much the way New Orleanians talk. The accent is more of a Brooklyn accent. It's not a southern accent, at all.

LH: That's right. It's long gone.

CO: That's right, but I've lived away from New Orleans for a long time. At one time I lived in England, for example, and I speak French, fluently, and I just sort of lost all that.

LH: Tempered your accent.

CO: Yes, I think so. So, I went through pre-med really fast and went to medical school at Tulane. I was really trying to get through, because it seemed like such a long time. I was

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\*Charles P. O'Brien was born in New Orleans, Louisiana in 1939. Dr. O'Brien received his MD (1964) and PhD (1966) from Tulane University. His residency training in psychiatry, neurology, and medicine were completed at Harvard, the University of London, Tulane, and the University of Pennsylvania. He founded the Penn/VA Addiction Treatment Program in 1971 and was Chief of Psychiatry at the Philadelphia Veterans Medical Center from 1980. He was also the Vice-Chair of Psychiatry at Penn and the Director of the Center for Studies in Addiction. He was interviewed by Leo E. Hollister and Thomas A. Ban in Las Croabas on December 12, 1998.

in a big rush to do things. I got interested in neurophysiology while I was a first year medical student. Actually, I did some research in high school and got started in research early, which I think was really important. I was in the Westinghouse Science talent search and I did research as an undergraduate at Tulane in genetics, actually. Genetics was my big interest, as an undergraduate, and then, in medical school I got interested in physiology and my PhD, actually, is in physiology, but with an emphasis in neurophysiology. And, the brain just really fascinated me.

LH: Did you get your PhD before your MD or after?

CO: After, but I really did my work simultaneously. I actually was the first wave of the MD PhD Fellows of the Life Insurance Medical Research Fund. This was in 1963. They had a national competition for medical students who wanted to get a PhD and they gave out a few MD PhD Fellowships. I got one of the first ones in 1963.

LH: So, you did Neurophysiology?

CO: And Medicine, at the same time. I was interested in all the different areas of medicine, cardiology, pulmonary, endocrine and all that. I went to Harvard for my internship at MGH, after medical school, which was straight internal medicine. I knew that I wanted to go back and finish my PhD at Tulane and decided I would also do what was a combined neurology/psychiatry residency. I was just too embarrassed to be a straight psychiatrist, because in those days, psychiatry was really a joke, in the sense that on the boards they asked mostly questions about the history of psychiatry. So you had to know what was the oldest mental hospital in the country, about Freud's patient, the Wolf Man, and what was Wolf Man's real name. Did you ever get asked that kind of question?

LH: No kidding.

CO: I mean it's really stupid stuff.

LH: Dismal science.

CO There was no information base. And incidentally, in the 1960s, when I was a medical student and a resident, I'm sure you all remember this, psychoanalytic professors were saying that all these antidepressants are just a phony kind of treatment. Their idea was that one has to work through one's depression. It's really good for people to be psychotic for a while, so you should not put them on neuroleptics quickly. Nowadays, we see the same replayed in alcoholism. We discovered that naltrexone works in alcoholism, but all the alcohol specialists are saying, I don't believe in

giving drugs to alcoholics and it's the same kind of thing that I heard in the 1960's related to other psychiatric illnesses. There was a big resistance against treatment with drugs. So, I thought that I would try to learn as much as I could about the brain and so, I did a Neurology residency, as well, as a Psychiatry residency.

LH: I imagine you're the only member of this society that ever did a rotation at Queen Square.

CO: I'm not sure about that, but I did. I was Chief Resident in Neurology at Charity Hospital in New Orleans. Then, I went to Queen Square as an Academic Registrar in London for a year, and I finished up my psychiatry training at the University of Pennsylvania in Philadelphia. After that, I went in the Navy, and that's where I got interested in drug abuse, because during the Vietnam War, the major psychiatric casualties were all related to drugs. I mean it was just amazing how many people were coming back, taking drugs. Since I had so much training they didn't send me to Vietnam. They put me on the faculty at the Philadelphia Naval Hospital where we trained residents in Neurology and Psychiatry. People from Vietnam arrived in 24 hours to Philadelphia and they got them medicated to prevent drug withdrawal effects. It was in Philadelphia where I first saw people going into opiate withdrawal from smoking opiates. They were smoking very potent opiates in Vietnam and they would be in opiate withdrawal by the time they got to Philadelphia.

LH: What year was that?

CO: 1969 to '71.

LH: That was about the time when we were having the big problem with it.

CO: That's right. So, you know, I got interested in treating all the drug problems and, of course, alcohol was a big problem, as well. So we treated a lot of alcoholism and got used to dual diagnoses there, because we saw a lot of that.

LH: So, you weren't put off by the fact that most psychiatrists, even in those days, didn't actively treat drug dependent people?

CO: Well, these were nice young men that I was taking care of and when I got them off of drugs, they were OK, not that they didn't relapse later on. But that's how I got interested and Mickey Stunkard recruited me to Penn. And, while I was still in the Navy, I went around to all the various substance abuse programs in the country — on my own ticket, actually, so I flew with my Navy uniform on, so as to get a 50 percent reduction — and I visited Vince Dole in New York and Jerry Jaffe in Chicago, as well as various other places to see what was being done. So, in 1971, I set up a substance abuse program at the Philadelphia Veterans Hospital.

LH: And, you've been there ever since.

CO: That's right.

LH: So, I know one of your great interests has been the translating of Abe Wikler's Conditioned Avoidance Hypothesis into clinical practice, but, am I correct—you never knew Wikler, did you?

CO: I did know him. As a matter of fact, there were three people who had a big influence on me as I was training. The first one was Matt Boch, who was a neurophysiologist. He worked with Horace Magoun. Boch did a lot of research on the reticular formation. My dissertation was on hypothalamic function. I was putting in electrodes and recorded changes after stimulating them and all that kind of stuff. Boch was really a good mentor for me. Another mentor was Bob Heath, one of the founding members of this society. At the anniversary celebration last year, or the year before, here in Puerto Rico, when I looked at a list of deceased members and saw Bob Heath on that list, I said, my God, I didn't think Bob had died. And I called him up, and, in fact, he didn't die. He's still alive, so we got that fixed. So, as a matter of fact, Bob Heath is an ACNP member, who probably hasn't been to a meeting in many years. He was a prominent psychiatrist, who was ahead of his time.

LH: That's exactly what I was going to say. His biggest fault was, he was too far ahead.

CO: As a matter of fact, we talk about the nucleus accumbens now; what he was studying was the septal region which really included the nucleus accumbens. Neuroanatomically, he was working in reward systems really long before Olds did. Actually, he was doing it in human beings who could tell you that they were stimulated, that they were euphoric and all that. And people raised all sorts of questions about doing the kind of research he did.

LH: I would like to have the needle he put in that make them sexually stimulated.

CO: Oh, yeah. All he had to do was to stimulate the reward systems; I saw some of those patients. As a matter of fact, to earn extra money when I was a medical student, I worked as a nurse taking care of those patients, staying up with them at night and helping them when they first got their neurosurgery. And, the third person that had a great influence on me was Abe Wikler. Since I have started to read about addiction, relapse and conditioning have always been an important focus to me. So I wrote to Wikler and I said, you know, I've been reading your work with rats and your theories, and I'd like to do some studies on the same line you are doing with human beings. He immediately wrote back to me and said he'd help me; he was in the latter part of his career at the time. This was 1971, and he came to Philadelphia and he helped me on several occasions. We

had a lot of correspondence. My early experiments with naltrexone were based on Wikler's theories. And, also, all "cue screening" were based on his theories. We were doing the "cue screening" back when we were the only ones doing it. Nobody else was showing drug-cues to drug addicts and nobody else was having drug addicts self-inject heroin like drugs while they were on naltrexone to see if we could extinguish it with the drug. We did many studies of conditioning. Wikler was assisting me the whole time, giving me ideas, and helping me as much as he could. I think he died around 1980 or '81, something like that.

LH: I should know, because I did a review of his classic book some time ago for Tom, but I can't recall.

TB: It was around '56, when he wrote the book. I don't know when he died.

CO: His last book came out around 1980, just before he died. It was called *Opioid Dependence* or something like that.

LH: It looks like you spent some time in Lexington.

CO: I did, right. I was on the Board of Psychoanalytic Counselors at Lexington for a while. And I, also, went to Lexington when Wikler retired, and I gave a lecture there, in his honor. But, then, he still continued to write for several years after that.

LH: So, you really got interested in substance abuse while you were doing your term in the Navy?

CO: That's right.

LH: And, then, you went to the Philadelphia VA and continued, which you do till this day?

CO: That's correct.

LH: Now, one of your longest associates has been George Woody. It goes back almost 30 years.

CO: Well yes, 28 anyway, 27 or 28. What happened was, there was nothing at the Philadelphia VA, at the time, for any kind of substance abuse, and so, I started the program there and in 1971, the first person I hired was George Woody as a part time psychiatrist. And then, my whole group has stayed with me the whole time. We've had a very stable group, which I think has really helped our productivity. We haven't had a lot of fighting and disputes and people leaving and all that, so, I've had a very long-term association with George Woody, Tom McLellan, Anna Rose Childress, Arthur Alterman, and then, more recently, with Joe Volpicelli and Jim McKay. There's been a whole group of people that have really stayed for a long time in Philadelphia. Everybody gets along pretty well and we share work and authorship and things like that and, you know, it's been a very happy group.

LH: You, very quickly, established a multi-disciplinary group.

CO: Yes, we did. It was hard getting started. One of the biggest difficulties was the 1972 presidential election, because Richard Nixon was concerned that the heroin addicts coming home from Vietnam would hurt his chances of being reelected, so he declared that every — you probably remember it, because you were in the VA at this time, too — drug problem was considered a medical emergency, equivalent to a myocardial infarction or a stroke, or whatever. If a person came to the hospital with a drug problem, you had to put them in a bed immediately, and we were just overflowing with drug addicts, but we didn't even have a ward for them. They were just all over surgery and medicine and everywhere. It was really difficult to cope with all that. It took me a couple of years to get the clinical problems in hand, so that I could really start building a research center. I got my first NIH grant in 1973. Then, I got a VA grant and we've got continuous funding ever since, we've just gradually grown in building centers throughout the VA ever since. It's always been built on a very good treatment program, where then, you can superimpose research on the basis of good treatment. And then, we do basic research, as well, pre-clinical research, but the bulk of it is clinical research.

TB: What is your research focused on at the Philadelphia VA?

CO: It's behavioral pharmacology, screening drugs. We do things that complement the clinical research; we do conditioning studies, drug discrimination, and the effects of drugs on self-administration, whether it's cocaine or opiates or alcohol.

TB: Is your research based on the conditioning paradigm?

CO: We've been studying the conditioning paradigm, and now, of course, there are really exciting developments in molecular biology, and addiction is becoming a very important model for memory. I think in some of the work that's coming out of the molecular biology labs, now, relates to what we've been seeing, and I think that we're going to understand addiction much better in the future.

LH: Whatever led you to use naltrexone in alcoholics? There's no pharmacology of this stuff that would lead you in that way?

CO: Well, that's an interesting story; we were really already doing animal studies and human studies and I was impressed with findings in the animal studies. The first one was showing that certain monkeys just love alcohol and if you give them an opiate antagonist, such as naloxone or naltrexone, it cuts out their drinking alcohol. That was impressive to me and there were a few

other animal studies. A young MD PhD student at Penn, whose name was Joe Volpicelli, who did a post stress-drinking test in rats, did one of them. He showed that if you give the rat foot shock and you stop the foot shock, then, they drink more alcohol in comparison to water, but then, if you put them on naltrexone, you block the post stress drinking of alcohol. So, it seemed to me that based on these studies that came out in the 1970's and early '80's, we had some presumptive evidence that alcohol liberated endogenous opioids, and therefore, we should try naltrexone, a substance that worked for some heroin addicts very well by reliably blocking endogenous opiate receptors, in alcoholics. So, I went to DuPont trying to get some funds, but they said this was a crazy idea, basically, and they wouldn't give me any funding. So we put in a NIAAA grant and they didn't fund us either. So, I had a post-doc, a psychiatric resident, at the time that was doing an elective year with me, and after we got a protocol through the Human Studies Committee, we started a double blind, placebo controlled study with him, in our alcohol program in about '83, maybe. The resident was a good guy, but he was not all that energetic and in a whole year he got 2 or 3 subjects. The clinicians resisted the idea of giving naltrexone to alcoholics. They just wanted this straight abstinence, based on AA. It didn't matter that most of the subjects relapsed pretty soon after they left our program. This was an abstinence AA program and they didn't want any medications. So, this guy, then, left and went out on his own, to another city and finished his training. And then, Volpicelli came along, and I told him that he had shown the effectiveness of the substance on alcohol intake in animals, and now, he should find out whether it also works in human. He told me that he was going to make it work, and he became so enthusiastic that he was able to mobilize the clinicians. He got a full sample very quickly, and I couldn't believe it, but the people on naltrexone really weren't relapsing. It was just amazing. So, we did a preliminary report, in which we reviewed the literature. After Stephanie O'Malley read our paper, and heard our presentations, she tried and got very similar results to ours. And then, somebody asked whether we have a "use patent"? I didn't know what that was and asked, "What's a use patent?" And then, they told me what a use patent is. It was news to me; nobody ever taught me about patents in the medical school or residency.

LH: This is an artifact of the entrepreneurial society in which we live.

CO: I missed all that. So, it's actually an interesting story, because I guessed that the VA owned the "use patent" of naltrexone, because we did the study with VA funding. So, I called up the VA counsel in Washington and there was a lady there, who was in charge of patents, and she told me

that the VA has a very generous “use patent” policy and “You get the rights. You can make the money off it. All you have to do is agree that the VA will get a cut and won’t have to pay.” I said, that’s fine, and she was going to send me all the papers to sign, when I told her that we had already published our findings. And all she said was, “Oh, too bad.”

LH: You made it public domain.

CO: That’s it. It’s gone. And so, you know, by publishing it too quickly, we completely lost the opportunity to get a patent.

LH: That’s sad when you have to do that.

TB: When, did this actually happen?

CO: Well, the first publication was about in 1989. And then, with the major publication, they made us wait a little bit. As a matter of fact, the first time we submitted it to the Archives, the referees just couldn’t believe it. Then, Stephanie O’Malley submitted her paper and they said, well, she got exactly the same results, and we’ll publish them together as back-to-back papers. And this is what they did in 1992.

TB: It has been followed up, so?

CO: Yes, it has been.

LH: It seems to me there was a woman, from Texas, who had the idea that alcohol caused dopamine to condense into  $\beta$ -carbolines.

CO:  $\beta$  carbolines, yes, it’s a condensation hypothesis. Actually, Ken Blume was another person associated with that, and George Siggins and Floyd Bloom also investigated that. What they essentially said was that products that were morphine-like were theoretical condensation products of alcohol in the brain. But since there was hardly any of it, actually, ever produced under normal conditions, the theory fell by the wayside. That’s not what we think is happening, and there are some people who feel that the condensation hypothesis was the forerunner of the endogenous opioid hypothesis. I consider it something very different, because what happens is that alcohol acts as a stimulus to release endogenous opioids, in the same way as giving the rat a tail shock or a foot shock causes endogenous opioids to be released. Some people get a big release, and if you measure plasma  $\beta$ -endorphin, which of course, is not the same thing as brain  $\beta$ -endorphin, there’s evidence that people with a strong family history of alcoholism get a large increase in  $\beta$ -endorphin, whereas, people without a family history do not get this big increase. So, what we think is

happening is that there is a euphoria that occurs in some alcoholics when they drink alcohol and blocking this euphoria by naltrexone improves the results of treatment.

TB: Prior to naltrexone, some people used naloxone, right?

CO: Naloxone, of course, has such a short action that it's not effective orally. But, naltrexone is. We're about to do some PET studies on the duration of the action of naltrexone at the  $\mu$ -receptor. There's a study that came up several years ago using an older PET process, the findings of which suggests that a 50 milligram dose of naltrexone blocks in the neighborhood of 80 to 85 percent of  $\mu$ -receptors, for 72-hours. So, even though the half-life in the blood is maybe 8 hours, or so, naltrexone seems to be held in the brain. It must have a very strong affinity for the receptor. This is a speculation at this point, but it appears on the PET that it holds in the brain much longer than one would predict on the basis of its plasma pharmacokinetics.

LH: I was skeptical, because when we did the naltrexone study that was sponsored by the NAS, we had to sweat like hell to show any good effect in opiate users, and of course, one of the big problems was, you could never keep anybody on the damn stuff. Well, I took some people who had never had any opiates in their life and gave them the same regimen that we put the opiate dependents on, and they felt lousy, which you might expect if the endogenous opiates have a physiological importance. And, I always wondered if there could have been some action like that, that really accounts for its effect. That is an aversive action, rather than a block of euphoria. What do you think of that?

CO: I think that's true for some people. Alcoholics are much more compliant with naltrexone than opiate addicts; however, in the neighborhood of 8 to 10 percent, can't take it, because they get a lot of nausea and dysphoria. Actually, we've done 2 studies with normal, and we found some people who just get very dysphoric on it. They just sort of lose their initiative and their ability to get anything done, so that they just don't want to be on it. On the other hand, most of our alcoholics and most of the physicians that I treat with naltrexone are able to take it. I've had anesthesiologists on naltrexone for 10 or 12 years, and they do very well on it. It enables them to go back to work and handle opiates and not have any temptation to get re-addicted.

LH: This is only a temporary phenomenon that people get tolerant to.

CO: It could well be; although, some people just never can go back on it. I have an alcoholic, right now, that I'm trying to get to stay on naltrexone, but when he takes even a small dose, he gets nauseated, and he just can't take it. It's as many as 10 percent that get this side effect, but for

the rest, it seems to be agreeable, and the effects size for alcoholics is pretty good. It seems to double the non-relapse rate. But it really should be given along with some kind of rehabilitation psychotherapy, rather than just as a prescription given it to the subjects. It doesn't work very well that way.

LH: Another thing that came from your laboratory that I think is very useful is the Addiction Severity Inventory. Now, that must have been done in collaboration with George Woody and Tom McLellan?

CO: With Tom McLellan, actually. There was a meeting in about 1974 that NIDA convened in Reston, Virginia on stimulating clinical research in addiction, and I was on a panel on measurements. I gave a talk saying, what we needed was an index of severity of addiction, something like a depression inventory or a brief psychiatric rating scale. We didn't have that, and what people were using at the time was, number of bags of heroin per day, or number of ounces of absolute alcohol. They were just focusing on the drug, but as a clinician, I could see that addiction was not just drug taking behavior, it involved also all other areas of people's lives.

LH: Work, family and social relationships.

CO: Also legal problems and medical problems. So, when I went back to Philadelphia, I started a series of seminars on measurement and addiction. Jim Mintz was working with us at the time, and I thought he might be the one to develop it. But then, he decided to move out to California. He's now at UCLA. But Tom McLellan came to work for us. He was already interested in this sort of thing, so I gave him the task of developing it. We had already come up with seven domains so, what Tom did was he made a structured interview for each of these areas, and the clinician would make an assessment of the need for treatment in each of them. One of the areas was drugs, another alcohol. Social, occupational, legal, and psychiatric problems turned out to be major areas. I guess we first published our structured interview, ASI, in about 1979 after a lot of reliability testing and so forth. It's gone through a number of reiterations; it's computerized now. It's translated into 14 different languages, and it's used all over the world. It's the official measurement used in the European Union. There's a Quebec French version and a European French version. The Russians use it; it turned out to be pretty useful. We also have something called a treatment services review, TSR, that we use in conjunction with the ASI; and what this does is, it measures what treatment occurs, because, indeed, every treatment program says that they tailor the treatment to the patient's needs, but, in fact, almost none of them do that. So, we

go to the patient once a week when we're doing a treatment study, and we ask the patient what services they receive in each of these areas and record it on the TSR. It is really fascinating. Some of the outpatient programs give more treatment than expensive inpatient programs, and the amount of treatment you get, it's not correlated very well with the cost of the program. But the amount of treatment you get is correlated very well with the results. So, if somebody has, say, alcoholism with a lot of marital problems and they don't get treatment for the marital problems, the marital problems don't get better and they relapse very quickly. But, if you give them treatment, it works. We have some findings in a project in which we used match vs. un- match. It is very different from the match that NIAAA did, where they matched very similar kinds of therapy to see if there was one that worked better than the other. We're matching on the basis of patient needs. We match the patient to the treatment, based on what areas are severely affected in the addiction.

LH: As in the old saying, drug abuse treatment is different strokes for different folks.

CO: Right. It's not as complex as it sounds, but it's amazing how rarely it is done. There is a tendency to give everyone the same thing.

TB: It's interesting and very important. It seems that by now it has been in use for over 20 years.

CO: Yes, it's been approved, and I think, it's a pretty practical tool. The VA requires its use with substance abuse and many treatment programs all over the country. We have always tried to do research, based on clinicians needs. In other words, we're looking for what improves the delivery of patient care, and I think, that helped us in the VA. We were always focused on improving the care of the veterans. A lot of administrators came through the VA over the years and said, oh, those guys in psychiatry are doing too much research; they must be not caring about the veterans, but, in fact, when they looked into it, they saw that the veterans loved the program and they were getting good care while we kept on developing new treatments, based on the needs of the patients.

LH: Well, we've covered the topics of conditioned avoidance, naltrexone, and addiction- severity inventory. What else?

CO: We've done a lot of psychotherapy studies, actually. In the first psychotherapy studies in methadone patients, we used random assignment to different kinds of psychotherapy, and no psychotherapy, and we demonstrated the effectiveness of psychotherapy in heroin addicts on methadone. We actually measure the dose of psychotherapy, just as you measure the dose of medication. We found that there's a dose- related phenomenon. For example, if you randomly assign patients on methadone, to minimal psychotherapy, medium psychotherapy, or high

psychotherapy, the results follow the dose relationship. If they were all on the same dose of methadone and you varied the dose of psychotherapy, you can produce better results with more psychotherapy. I think that was interesting. Now, everybody uses treatment manuals to measure the doses of psychotherapy when they do studies. We were the first to use treatment manuals back in the 1970's.

TB: Again, something you introduced, and it survived like the treatment with naltrexone and the Addiction Severity Inventory.

CO: We keep improving our treatment manuals but everybody is doing treatment manuals now. We, also, did a lot of medication control studies. Our first study with antidepressants in heroin addicts was done in 1974. We were studying the treatment of depression, in people on methadone maintenance. It was a study of doxepin vs. placebo.

TB: Why did you choose doxepin?

CO: Well, because, clinically, it seemed more helpful than the other antidepressants for the heroin addicts. A lot of heroin addicts are depressed. Then, subsequently, we studied desipramine and imipramine. Now, of course, we have some studies with sertraline in alcoholics. But in those days, early on, there were no randomized clinical trials with heroin addicts. Most people in those days thought that they were not suitable for that kind of clinical research. But it turns out that they're somewhat difficult to study, but you could do clinical trials about as effectively with them as you can with other patients.

TB: Did you find desipramine better than other antidepressants?

CO: What we found was that any of the depressants relieve depression in heroin addicts but antidepressants don't work particularly well for the heroin taking. You have to deal with that differently. But, on the other hand, we have evidence that if there is a psychiatric disorder, and especially, if it's depression or anxiety, you have to treat that in order to deal with the addiction. So the treating of the psychiatric disorder doesn't necessarily make the addiction go away, but you have to treat that first in order to be able to have any success with the addiction.

TB: Well, you seem to have started this program a long, long time ago. What is your research focused on now?

CO: At the present time, we're focusing on cocaine. We don't have anything, as yet, that is reliably effective, but we have learned that all cocaine addicts are not alike, and we have evidence that some have a good prognosis, whereas others have a poor prognosis, and you can separate

them based on their cocaine withdrawal symptoms. Now, of course, many years ago people claimed that there were no withdrawal symptoms with cocaine, but that's not true, and we have evidence that there is. We can measure its severity, and the group with high withdrawal symptoms is really tough to treat. The low withdrawal symptoms group tends to do much better. But if you mix them all up, your results are obscured. So we're trying to improve clinical trials by selecting patients, based on their characteristics.

LH: But, how do these characteristics correlate with the dose they are taking? Is there a correlation between more severe withdrawal reaction and heavier usage?

CO: You know, cocaine is not one of those drugs that you use every day, like alcohol or heroin that are used in a fairly regular amount. It is used in spurts, and the average cocaine use is about 12 or 13 times a month, but some of the heavy users are using it, maybe on 18 or 20 days a month. Nobody can use it 30 days a month. That's why I have a lot of debates with my colleagues about animal models, because the most common animal model is one where you have limited access to cocaine for 2 hours a day, so that the animal bar presses avidly during that 2 hour period for the cocaine, and you give them drugs to see if it suppresses the bar pressing. But this doesn't predict very well what happens in the clinic, because the patients just don't use cocaine in that manner. A drug that may suppress cocaine use in this model doesn't seem to predict very well what happens in the clinic.

TB: Is most of the animal work done with that model?

CO: Yes.

LH: Well, I'm sure you've got many awards, but didn't I read of something recently that you just received?

CO: Well, I did get a Founder's Award from the American Academy of Addiction Psychiatry, AAAP Award, which I just received last week.

LH: And, nothing from the VA?

CO: No. For some of these awards, you have to sort of nominate yourself. I've never nominated myself.

LH: Too modest.

CO: I don't think I've gotten anything from the VA; although, I brought the President to the VA. I suppose that was historic. Shortly after the Gulf War, I got a call from the White House. Bush had about an 80 percent popularity. Everybody thought he was a great guy at the time. And the

White House said, "We'd like to have the President come and visit your program to publicize the War on Drugs." So, I said, gee, that's great. We'd love to have him. And they said, "We will come to the University of Pennsylvania." And I said, "No, if the President is going to come, he has to come to the VA." And so, they said, "OK," and started making arrangements by sending the Secret Service and all that. They had to build a big wall to make sure that somebody wouldn't shoot him, and find a place for his helicopter to land, and all this kind of stuff. So, I called the director of the hospital and said, "You know, the President is coming." And he said, "Yeah, yeah." I said, "No, seriously, no joke we're going to have a visit from the President of the United States." He really thought I was crazy. I told him to call the guys in Washington and tell them. He called the guys in Washington and they said, "Yeah, yeah." They didn't believe him. It was really amazing with bureaucracy; it was a grass roots thing. Normally the White House would call the VA and would go down to Philadelphia. But in this case, it came to me, and then, I went up to tell them. Then, they said, "Well, I guess you'd better have the Secretary come too." So Derwinski and the drug czar all came to the VA. I had them come to this old laundry building where we had our methadone program, and we have a picture of the President there meeting with us. He spent the whole afternoon there, and George Woody and I got a ride in his limousine. It was nice. He was a very nice guy. We talked to him about our research and explained the naltrexone, the conditioning, and the HIV studies. I have not told you yet about some of those studies we're doing on AIDS. But, anyway, we had the data, and we had a patient or two from each study, so the President could talk to the patient, as well as see the data. It was pretty neat. And, of course, we have literally dozens of TV cameras and huge Press Corps there. Plus, we had the guy, who was carrying the football. You know, the football is the nuclear trigger. It was a Marine Colonel who carried, and you can't get between this Marine Colonel and the President. He always has to have direct access to this guy. So, anyway, that was kind of an interesting thing for the VA.

TB: Did he understand?

CO: The President asked a lot of good questions. He seemed like a very smart guy who got a lot out of it. And, indeed, he seemed to be generally interested. He invited us to the White House a number of times. It seemed that he had a lot of interest in the Drug War. I think that was the time when they were starting to shift a little bit from supply reduction to demand reduction.

LH: At least, encouraging.

CO: Yes, yes.

TB: You mentioned that you have you a program in AIDS?

CO: Yes, we realized, early on, that HIV was a major problem for the IV drug abusers, and so we started studying it in Philadelphia, early in the epidemic, when the HIV positives had soared in the neighborhood about 10 or 11 percent. It was later on, in New York, where it was up to 60 percent. Philadelphia was a little bit off the beaten track, at least, at the time. So, we studied a group of IV drug abusers in methadone treatment and another group out of treatment, and we found that people in treatment had a stable level of HIV positivity, because they weren't using opiates and they weren't sharing needles and all that. The number of HIV positives in the group that was out of treatment just went up and in about 18 months, they were up to about 39 percent or so. So, we've been following that up, and we published lots of papers comparing the two groups. As a matter of fact, psychiatric disorders were a major problem. Those people, who were sharing needles and engaging in high-risk behavior, were mostly depressed. So we devised another tool called the RAB, the Risk Assessment Behaviors. What this instrument does is it measures risky behaviors. We put this instrument on a computer. We found that people are very honest with a computer, more so than in a one to one interview. We could predict who was going to convert from negative to positive, based on their responses on this behavioral questionnaire. And then, this led us to the vaccine trials. So, we are now participating in the vaccine trials. We have also produced some videos to help people get volunteers for the vaccine trials, because, it turns out, that a lot of people in this population are minorities and they don't trust the government. They, actually, believe that the government has a cure for AIDS, but they won't give it, and they've actually put AIDS in the community so as to reduce the number of...

LH: Genocide hypotheses.

CO: Yes, and so, we have a couple of videos that have won awards and have been presented all over the country, in which some NIH neurologists and researchers are talking with a group of people, are interacting with them, answering their questions, and trying to reassure them. This helps to diffuse the situation and we're very successful. As a result of this program, the trust of people increased and we have plenty of volunteers for our vaccine trials.

TB: So you have developed a new methodology for educating people. Aren't you having an office at the university, as well as at the VA?

CO: Penn is very lucky, because the VA is right across the street from the university. So we, initially, were fully at the VA, but then, in about '87 or '88, we started getting space at the

university, and now, we have a pretty nice center at the university. So I park my car between two places and I walk back and forth.

TB: And, I assume, you are involved in teaching students at the university.

CO: As a matter of fact, that's another thing that I think is very interesting, because we have possibly the only required course on addiction, in any medical school. We had electives in the '70's and '80's, but in the late '80's, while we had a curriculum revision, I got on the committee and managed to get addiction as part of the regular curriculum. So we have now, like 25 or 28 hours of courses, that includes lectures, seminars, and interviewing of patients, as well as a very practical course about the pharmacology, psychology, and diagnosis of addictive disorders. To avoid some of the problems that the average physician has, where they confuse physical dependence and addiction, we teach them how to treat chronic pain, for example. And then, we have a pretty tough final exam. And if they want to get honors in the course, they can do a research project or a paper. The last year, we had about 25 or 30 students, who got honors by doing a paper, and this year, I'm not sure how many we'll have, but we teach 150 students at a time. We just finished a course and they're working on their honors papers now. I don't know how many will get honors. I think that all medical schools should teach about this subject, but, indeed, very few do. Those that do are giving 2 or 3 hours, maybe, you know.

LH: There's so much competition for teaching time. Well, you said that a lot of people get awards by self-nominating. I recently had the occasion to write the CPDD and suggest that, perhaps, they were overlooking some people, and I have you and two others in mind. I hope you get the Eddy award, because you sure as hell deserve it.

CO: Thank you, Leo. I appreciate that, coming from you.

TB: And you have also trained many people.

CO: Yes, we have a pretty big post-doc program. We have a training program, and we also teach a lot of medical students. We have MD's and PhD's in our post-doc program. One of my best trainees received the Elkes Award, the Joel Elkes Award, this year.

LH: The amphetamine drug abuse scene that you have covered is amazing. Now, it's certainly been educational to listen to you. One of the big, big benefits of doing these interviews is learning so much about what people are doing, because their CVs or even bibliographies don't tell you a whole lot.

CO: I agree. Anyway, thank you very much.

TB: Thank you.

LH: Thank you for your time. This was very interesting.

## 26. CANDICE B. PERT<sup>7</sup>

LH: Candace, can you tell us how you got started in the field?

CP: Well, in the beginning I wanted a Ph.D. and I wasn't really sure what it should be in. At Bryn Mawr, Agu and I had studied psychopharmacology with Larry Stein. I wanted to be in some biological science in order to understand the "black box" of the brain underlying behavior — and through a series of interesting quirks, I wound up in Sol Snyder's lab.

LH: What were the quirks that got you there?

CP: Oh, things like, I only had Delaware and Hopkins to choose from, because my husband, Agu, would be stationed at Edgewood Arsenal, where they were doing some psychopharmacology of their own.

LH: Oh, that's right, he was in the military.

CP: He was in the military, yeah, the chief of the psychology branch and actually I had applied to Johns Hopkins, the Homewood Campus, and at the last minute I heard about Sol Snyder, who was doing the brain and behavior. I actually sent my graduate application to Joe Brady, whom I had met at a seminar at Bryn Mawr. He said, "Send it on to Sol," and Sol called me up and he said, "You're accepted; now apply." I was the first Ph.D student at Johns Hopkins' pharmacology program; the program was brand new.

LH: So, you wanted to be a pharmacologist, but not a Behavioral Pharmacologist.

CP: Not really. I was married to a Behavioral Pharmacologist, and I was extremely interested in, you know, for years, Agu, and I had been interested in how the brain and behavior go together.

LH: Agu's degree is in what?

CP: His degree is in psychology, physiological and behavioral psychology from Bryn Mawr with M.E. Bitterman, Earl Thomas and Dick Gonzales. He is a classical behaviorist, so I had his part, but what we really wanted to do together, was to map the brain. So Sol's lab sounded pretty

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<sup>7</sup> Candice Pert was born in New York, New York in 1946. She received her Ph.D. in pharmacology from Johns Hopkins University School of Medicine, where she worked in the laboratory of Solomon Snyder and discovered the brain's opiate receptor. She conducted research at the National Institute of Mental Health from 1975 to 1987. She left to found and direct a private biotech laboratory in 1987. Pert was a Research Professor in the Department of Physiology and Biophysics at Georgetown University School of Medicine in Washington, DC. She died in Potomac, Maryland on September 12, 2013. She was interviewed in Waikoloa, Hawaii on December 1997.

exciting, and I thought, "Ooh, a Ph.D. in pharmacology, I don't really know what that means, but I'll take it." I didn't realize at the time how incredibly wonderful it would turn out to be.

LH: You got into a wonderful laboratory and very creative place and you did get your degree there?

CP: In 1974, I got my PhD with distinction from Johns Hopkins School of Medicine.

LH: And, I read the title of your PhD thesis. It reminded me of the fact that I guess there were a couple of physicists who won Nobel prizes on the basis of their PhD thesis. I never heard of anybody in biology doing that, but yours was certainly an important PhD thesis.

CP: It was amazing—the title was "The Opiate Receptor, its Demonstration, Distribution and Properties" and, of course, it was a very long shot project. Now, Sol, he didn't want me to spend time after it didn't work the first couple of months.

LH: Sol likes to jump around, doesn't he?

CP: It was one of these things where I fell in love with the project. I had a bread and butter, meat and potatoes project going, that was going to get me a PhD. And, Sol, he was really only thinking of me. He said, man you've been on this thing for two months now, three months. Forget it; you're never going to crack it; you haven't found it and there are papers in the literature that say it doesn't exist, and I just, I kept plugging away. I wrote a book about exactly how it went down, called *Molecules of Emotion: the Science Behind Mind-Body Medicine* (Simon and Schuster, 1998).

LH: And, by a strange coincidence, there were two other laboratories, Eric Simon's and Lars Terenius', who were working on the same problem.

CP: Well, we didn't know a thing about Lars, of course. He published around the same time as us, but he was much more understated and jargon, and he didn't really come out and call it the "opiate receptor." Now, Eric, I had helped Eric. Eric came by. Sol sent him into the lab and Eric said, "My gosh, you have all these techniques. You have Sol's knowledge; you have Pedro Cuatrecasa's knowledge." You know, Pedro was a famous NIH scientist, endocrinologist, who had just found the insulin receptor. So, Sol said, "Learn everything from Pedro." I'd actually been five months in Pedro's lab, so I was putting Pedro's receptor techniques together with Sol's knowledge of the brain.

LH: I remember that in 1971, I think it was the INRC meeting in San Francisco, Avram Goldstein gave a paper called "The Search for the Opiate Receptor," and he recommended the stereospecificity approach he had come up with and told of the preliminary data with binding sites. He

couldn't distinguish specific from non-specific binding at that time. And many people thought it was due to the fact that he didn't have high enough specific activity; do you think that was the problem?

CP: I think that was one of the problems, but Avram is kind of like the unsung hero, in many ways. In the classic Pert and Synder Science (1973) paper, I wish that I had insisted that his work be cited right in the introduction, not the discussion only. In the discussion, there was a lot of stuff about, you know, where he fell short, which he did. He basically had the idea. He was searching for years but, sure, his specific activity was a technical problem, but there were a lot of other things. He didn't have the rapid filtration technology that I had learned from Pedro and several other things. I mean, it's hard to understand why an experiment doesn't work. There may be a hundred important variables—every one of them has to be perfectly chosen.

LH: But, you had the insight to think of using the antagonist, rather than the agonist.

CP: That was indeed a key and that was a really amazing story. And here, the ACNP, which has been interweaving in my life for so many years, comes into play. And, what happened was, I was chosen as one of the fifty or sixty graduate students from across the country to come to the ACNP summer camp in 1972, at Vanderbilt in Nashville, where all the big famous pharmacologists flew in, and it was all very exciting. But, for me, I had been plugging away for months in the lab and it gave me the chance I needed to think. I came down there with a huge stack of papers I had gathered that I hadn't really had time to read. I'd been so busy doing one failed experiment after the other. And, the one that really helped me crack it was Patton's paper.

LH: Who's Patton?

CP: Patton, the famous Chairman of Oxford University's pharmacology department.

LH: There's another one in Australia with a similar name, and I got them confused.

CP: He had written about a "ping pong" theory. He thought the antagonist must just stick on the receptor. He thought the agonist action is due to the number of repeated pings as it binds while the antagonist competes with the same receptor, but stays stuck there, never pinging on or off. I said, "Aha, I need an antagonist, because I want something to stay stuck on the tissue as long as possible, while I was washing away the non-specific binding."

LH: So, you didn't think that it was more tightly bound or...

CP: Well, yes, higher affinity, and the affinity is the ratio of the off rate to the on rate—the idea that antagonists could stay on much longer seemed perfect. So, luckily, Agu had some naloxone

because he was using it as a reversal control in his experiments with Tony Yatsch at Edgewood, resulting in the classic "Yatsh and Pert" (1972) paper highlighting the PAG. He was mapping the brain sites of opiate analgesia.

LH: Was it labeled naloxone?

CP: No, just cold naloxone; I had to get it labeled. When I came back from Nashville, I was all set to get the naloxone, but Sol said, "Drop the project; you've spent enough time; you'll never get a Ph.D." He was really only thinking of me, I think, but I kind of like, I persevere; I'm funny; I was just in love with this project and wouldn't give it up. I had read the literature and knew it was there. I didn't care if I hadn't found it yet. I knew if you can just find the right combination of conditions you would get it right. So, I sent Agu's naloxone off, kind of secretly, to be custom labeled by New England Nuclear. They made it hot, got it back; to me, those were the old days, when you got tons of millicuries and purified yourself. I don't think they let that happen anymore, at least not at Georgetown, where I am now. And, once I got the new radioactive opiate, the very first experiment, it was unbelievable! You know, then, I got to be a famous graduate student.

LH: Well, that's quite an achievement for a graduate student. My goodness!

CP: It's being in love with an idea, what you are trying to do, believing in it, and not giving up.

LH: That's the beauty about the field we're in. You know, you can do it. I always feel so sorry for people who think of work as drudgery, when we think of it as fun.

CP: Yeah, we get paid for having fun. We do, we do. It's a great field.

LH: Don't you feel ashamed for being paid for what you enjoy doing so much?

CP: [Laughing] Of course. Once the opiate receptor assay worked, the next person in Sol's lab to crack a receptor was Anne Young who is now the Chairman of Neurology at Harvard. She worked on the bench next to mine.

LH: Who was that?

CP: Anne Buckingham Young, she's now Chairman of Neurology at Harvard; she's not in our field so much, but she went for the glycine receptor and succeeded with the antagonist, strychnine. And, what happened was, the same technology that launched the opiate receptor was able to be applied to any neurotransmitter. So, Sol's lab, over the next few months, with me and my technician, were helping to teach the others how to go about it.

LH: Was the dopamine receptor studied in that laboratory?

CP: Ian Creese really ran with it and tweaked it to screen for antipsychotics. Because Ian had done a lot of the dopamine behavioral work with Susan Iversen, he was able to really nail conditions that were "pharmacologically relevant" to screen for anti-psychotic drugs. You see, once you have the technology and you knew how to do the filtration, every receptor had its special little requirements. Whereas before, receptors had eluded capture for decades, now, within a few months, every student in Sol's lab was working up a different receptor.

LH: Now, you're a peptide expert, but in those days you weren't much involved in the endorphin story, were you?

CP: Well, there were no endorphins.

LH: Well, that came in 1973, wasn't it?

CP: No, 1976. The opiate receptor, our paper in Science, Pert and Snyder, was published in 1973, and that kind of touched off the effort to find the brain's own morphine. And then, when it turned out to be a peptide, everybody went bonkers over it. Peptides are easy; they're wonderful; they're easily synthesized; they're easily worked with, and so, there was a big peptide explosion.

LH: Today, you can make any kind of peptide you want.

CP: Absolutely, well, you could, even back then, but it took a few days to make a peptide. Now, you can order a peptide, and it takes longer to ship it to you than it does to make it.

LH: You went to the NIMH right after you finished your Ph.D at Hopkins?

CP: Actually, not quite. I did a one year mini post-doc, with Mike Kuhar, who was a professor in Sol's department, and there, Mike and I developed *in vivo* receptor autoradiography, the first autoradiography for the opiate receptor. We were injecting the drug into the tail of the animal, the hot labeled drug, and then, sectioning the brain. It was very tedious, but we got the first real pictures of the opiate receptor distribution. And then, when I went on to the NIMH, I, well, refined autoradiography with receptors with my colleague, Miles Herkenham. We developed *in vitro* methodology, which is what's really used today. At the NIH, you know, everybody wanted to work with me, because I was Ms. Receptor.

LH: That was the hot ticket then.

CP: That was a hot deal—and frankly still is—the key to drug design. I had many job offers. Sol was always very generous and smart about placing his students with superb recommendations. Actually, I had twelve job offers. This was 1975 when I took the NIMH offer, because it was pure research. There were no teaching responsibilities, nothing but focused research. When I was hired

by [William] Biff Bunney, there were lots of peptides that NIH scientists had biological activity for, and they knew there had to be a receptor for it, but before the opiate receptor, they didn't have the technology to go after them. So I was soon collaborating with many labs and over the years identified many new peptide receptors.

LH: Of course, not all receptor agonists are necessarily peptides, are they?

CP: No, absolutely not. You mean, drug receptors. But, I think at this point every exogenous drug binds to a receptor meant for an internally produced juice.

LH: That's always puzzled me when, how the hell does nature know to make all these receptors for drugs that we haven't synthesized? You got any idea? I always felt we needed somebody to come up with a theory sort of like, I can never remember his name, the Japanese fellow did for antibodies, the way he could explain how you could get the diversity of antibodies.

CP: I've given a lot of thought to that and I actually have a theory. I'm actually publishing my theory in, what I hope will be, a popular book.

LH: Well, that will be a major contribution. Are you going to publish it as a book, rather than a scientific work?

CP: Correct, but it will be scientifically accurate as well as personal, historical, and hopefully entertaining. It's being published by Scribner in September. It's called *Molecules of Emotion*. (Note added in proof: now in its 15th printing and still in the top 10 of the Neuroscience list). I believe that these internal juices, of which there's now over a hundred with their receptors, are the internal homeostatic molecules that give you mood states and run every physiological system in your body. I think that our natural chemicals should keep us pretty on keel and when things go out of whack, then, you need to come in with drugs.

LH: Well, I remember thinking naltrexone was, of course, the perfect drug. It does everything you want it to do, but nobody will take it. It's been disappointing as far as having much impact on opiate dependence, and one of the studies we did, a number of years back, was to give it in the same way, give it not only to opiate dependent people, but give it to normal people. And, most of them found it unpleasant to take. I did a similar study with naloxone and it makes sense, you know, if the endorphins have any function, you can't block their receptor without having an effect. Maybe they're there to make us all happy.

CP: Absolutely.

LH: Instead of the happiness gene, we also rely on endorphins.

CP: Absolutely, I think we rely on them a lot and the other peptide ligands, too (you know, endorphins get a lot of the spotlight because they're so sexy) but the other ninety eight, many of them are just as interesting. We just don't have as much good science on them, as on the endorphins. Actually, substance P was the first peptide isolated from the brain. An axiom of pharmacology is now not only, "No drug acts unless it's fixed to a receptor," but also, those receptors were made for other things and pharmacologists accidentally discover ways to get in there.

LH: You were involved when Sol founded that company based on searching for drugs by receptor binding techniques.

CP: Nova.

LH: Nova, yeah.

CP: No, I wasn't involved. My techniques were involved, but I wasn't involved. By that time, I had gone on to NIMH and I had been there a couple of years.

LH: But, it proved to be very successful, wasn't it?

CP: I don't know much about it, frankly. Sol and I were once very close, you know, doing some cool science together. But after I started my lab at the NIH, and after the Lasker Award controversy, we were not so friendly.

LH: I didn't want to bring it up.

CP: Well, it's okay. I wrote about it in my book and its pretty much ancient history at this point.

LH: But, what led you to follow a career in your professional work, as well as now in your present work, to go looking for peptides as possible therapeutic agents?

CP: I think it was just a natural progression from being completely immersed in peptide neuropsychopharmacology from 1976 until about 1980—when the endorphins and enkephalins were in their heyday—all the big pharma were looking for a non-addictive opiate, and I was going to like 4 or 5 meetings a year, getting to study enormous amounts of data, and learn the principles of peptide modification to make drugs. Knowing that natural ligands are usually peptides was important. Then there was a key paper that I published in 1976 in Science, where Agu and I developed an analog of enkephalin that was very stable. Before that, we found that if you drop enkephalin directly into the brain, all analgesia went away in twenty seconds.

LH: Doesn't last very long.

CP: Doesn't last very long. And we figured out that it was a rapid enzymatic degradation of enkephalin, and I managed to make a lucky substitution of the critical amino acid which preserved the receptor activity, and we really lucked out. We got a peptide that was as potent, as long lasting as morphine. And, so, that told me that, although even today, people say, oh, peptides can't be drugs, because they get chewed up too quickly, that's not true. We can use many clever strategies to chemically modify a peptide to achieve stability to degradation, or enhanced delivery, or even alter the agonist/antagonist properties.

LH: It would be pretty hard to get them down the mouth since all peptides are pretty susceptible to stomach enzymes.

CP: Oh, I agree with that, but it is possible to make peptides delivered by mouth with the proper "pill."

LH: You can give them by inhalation.

CP: Intranasal is very big.

LH: Will they go through the skin?

CP: Yeah, sure, nowadays, people have all these special creams and transdermal patches.

LH: I would think they'd be too big a molecule to go through the skin.

CP: No, they can. You can get things to go through the skin. One of the peptides we are working with now is actually being tested for psoriasis.

LH: You apply to the psoriatic patch, and then it works locally?

CP: It works locally. Yeah, it's kind of an inflamed skin and it just may not be....

LH: Hyperplasia of the skin, really.

CP: Exactly.

LH: Well, of course, that kind of skin might be more permeable than, say, regular skin, but I've given TRH, which apparently can have some activity, but it's only a tripeptide that's not long enough to make entry difficult.

CP: Right, right.

LH: But, I guess when you get up in the higher numbers they tend to get chewed up.

CP: Well, this is an octapeptide. Yeah, the chewing up, the point is, there's no problem about a peptide that you can't solve. I mean, there's too much emphasis to switch to non-peptide—"peptidomimetics" which have a tendency toward toxicities. I mean, you can solve the pharmacokinetics. There are ways to do it, you can solve the enzyme resistance, and the key is

always to have that receptor assay to make sure it still works on the receptor while you're trying all these modifications.

LH: What's "Neuroprotectin"?

CP: Oh, how'd you hear that? What, are you searching the obscure scientific literature?

LH: Well you know, that's a big deal these days to try to find ways to protect the nervous system, both after injury and after stroke.

CP: We were maybe a little ahead of our time. That was a project in my biotech company, my short-lived first biotech company, which I founded in 1988 to advance a peptide discovery for HIV/AIDS. The neuroprotectin papers we published in the late 1980's were a minor part of that enterprise.

LH: It blocks the cascade of injury?

CP: Exactly, this peptide blocks the excitotoxic effects of glutamate receptor activation. Quite well actually. We were interested in this as an approach to stroke and head trauma where the later actions of excitotoxicity are responsible for the bulk of neuronal loss. The idea was there was a window of opportunity of an hour or so where such a drug could be highly useful, as protective to glutamate toxicities. Hence, the name, "neuroprotectin."

LH: Interesting, maybe in the brain with its own protection.

CP: Yes, it's very interesting. The brain has its own potential protection, for times of stress or whatever, but, of course, we had the head trauma and stroke as the main commercial interests. You could give this drug, during that critical period after the initial injury, and it's still a good idea. It's still a good drug, waiting for the kiss of pecunia. At the moment, there are just too many other things to do, mostly focused on the main project, a receptor-blocking peptide for HIV/AIDS. And, yet, what I've learned, it's not enough to do a great experiment, or publish a great paper. Then, the fun begins, but not really fun; then, if you have the courage of your convictions you need to follow up your discoveries to practical application. You have to find the people who are going to advance the millions of dollars to take the drug from the preclinical stage to the testing in human beings, which as you know as a pioneer in this endeavor, it is not so easy to do those human experiments.

LH: Well, the enthusiasm these days is vastly different from just a few years ago, and the idea that a stroke trauma is a treatable disorder. Ever since I was an intern, you came in with a stroke, you kept your fingers crossed, and that was it. You couldn't do anything specifically. But, now, with

the idea of clot busters, at least in highly selected strokes, it looks like they are pretty good. So the idea of an intervention to treat after the stroke is fully validated. Now, getting back to Sol, you were not very happy with his 1977 Lasker award?

CP: No, I wasn't. No, I was not happy with his Lasker award at all and I'm not coy. He called me up and invited me to come to the Lasker luncheon. And, I said, who else is getting the award? And what's the award for? If it had been an award for Sol, only, I would have been in the front row cheering, cause I really think he had had great accomplishments over the years, but when I heard it was Sol and two other men, Hughes and Kosterlitz, in my mind, Hughes had the same relationship to Kosterlitz as I did to Sol. Hughes was the younger guy that actually did the work with his hands. Kosterlitz was head of the lab, who raised the money and recruited him for the project, and I felt that it was very unfair, and the rash gal that I was, even though everyone in the world advised me to just shut up, I publicly complained. The award was for the opiate receptor and endorphins and I couldn't sit quietly for an award being given for my thesis work!

LH: I remember I was talking to Avram (Goldstein) about that time, too, and he wasn't very happy with that award, too. You know, Avram, in addition to paving the way for the opiate receptor, I remember he came up with something he called a pituitary derived opiate peptide...which ultimately turned out to be dynorphin so he was a pioneer both in the peptide side and the receptor side.

CP: Absolutely. There's no doubt about it. But, the prize, you know, has these rules—so the Lasker award—which is the forerunner for the Nobel Prize, can be shared by no more than three people. I turned down Sol's invitation to the Lasker luncheon. Since I declined to show up, and my candid letter stating why ("I initiated the research and followed it up."), appeared in an editorial in Science which created quite a brouhaha discussions of me as the first author, the whole feminist issue, and who from Johns Hopkins had actually submitted the prize nomination. It's not entirely a feminist issue. Women are usually the ones that suffer in these situations, but a lot of men do also. It has to do with the scientific hierarchy and who has the skills and stomach and influence for prize seeking, I mean, I don't think Avram suffered so much. He has tremendous recognition; he's highly respected; he's had his own institutes over the years, but, for me, it was professionally a disaster to think that the work that I had been so closely identified with was being given a prize excluding me. It's not like I had done five percent of it, or even fifty percent of it. I mean, I was

really running that whole project in Sol's lab, had first authored many key papers, including the first one, and had continued productive work in my lab at the NIH.

LH: Actually, Julie Axelrod was telling me that the reason he parted from Brodie was he did an experiment all by himself and Brodie said, well, we ought to put the names of everybody in the lab on it and do them alphabetically. So, that B would come first.

CP: (Laughter)

LH: That's when he decided it was time to part company.

CP: Well, there have always been these little scientific brouhahas. I mean, for me, it was particularly sad, because I really adored Sol. I mean, I had learned so much from this man about how to do science—hot science, great science! I mean, I really wanted to do for him in a very nurturing kind of a female way, and he had always been extremely kind to me—that was what was so ironic. I mean, I was the first author on all the key papers. He sent me out to all the meetings. I mean, he wasn't hiding me under a barrel or anything, so when it came to this moment of truth, when only three people could win the Nobel, I was soft, and my theory is that Sol, since I was always so femininely nice about everything, figured that I wouldn't complain, it was easier to cut me out, than to cut out Hughes or Kosterlitz.

LH: When you're tempted by the great prize, I guess it's difficult to sit back and say, look, I've got to share the credit. The only one I can think of, at least that's common knowledge, is the 1954 Nobel Prize for culturing the poliovirus. Enders, the biologist at Harvard who was selected by the committee, heard about it and said, nope, you've got to take Weller and Robbins who were graduate students, but they'd done a lot of the work on the growth of the polio virus in monkey kidneys.

CP: Right...very interesting.

LH: And, he insisted that they would share the prize, which was the only time I can think of such generosity in face of temptation, you know. Like the Devil offering you the world....

CP: Well for me it was a mad and sad feeling and for years afterwards I was always like hoping Sol and I would make up, and, finally, I realized there was a hopeless chasm there. I did a lot of personal transformative forgiveness work around this that helped me in my life.

LH: I remember once I had occasion to talk to the guy who was the senior author on the paper on essentially, sex and bacteria, Joshua Lederberg won the prize. And, I said, how does it feel to be

the senior author on a paper that wins the Nobel Prize for somebody else? But he wasn't unhappy. He said it helped his career immensely.

CP: Right. Well, this wasn't the Nobel — it was the Lasker, and I just had to express what was in my heart. That December 1978, it is common knowledge that the Nobel committee was at a stalemate for the Nobel Prize for Opiate Receptors and Endorphins, with several combinations of three scientists, some of which included me. After an unusual pause of many hours, the prize was awarded, unexpectedly, for a medical scanning device.

LH: Now let's talk about peptide T, which I want to understand and its therapeutic possibilities.

CP: Right. The initial discovery was made at the time I was still Section Chief at the NIMH, with help from many NIH collaborators. It was an example of a style of work that is harder to do now, to bring diverse scientists, in this case neuroscientists, neuropharmacologists, virologists and immunologists into a team to crack a completely new problem. There was no prior research on the topic, which as we defined it was to identify which part of the virus bound to its receptor, and to then design a peptide inhibitor that blocked virus binding and infection. This work marked a real milestone in my career. For one it was just the most amazing discovery. I feel I can't take credit for it. It had so many seemingly miraculous aspects. Firstly, that we derived the structure from one computer-assisted database search, and secondly, had enough faith, or in this case NIH funding, to roll the dice and have it made, and thirdly, the collaborators to study HIV infection at a time when this work was not routine and few labs could do it. But, to put this work in a context, at the time, there was a lot of politics, including international competition between governments around HIV/AIDS virology, AIDS testing, and creation of AIDS drugs. This was an expanding global pandemic with no treatments, a lot of public fear, and nobody wanted to believe that an AIDS drug could come out of the NIMH. At that time, it was all NIAID and the NCI that were controlling that turf. So, we got just about zero support. In fact, we got active hostility and resistance to even testing our ideas, including editorials in *Science* and *Nature*, as well as many major newspapers. It got so intense that even my bosses at NIMH were taking a lot of heat. So, something I never thought I would do, I left the NIH when I got an offer that would permit me to bring peptide T into clinical trials and bypass internecine battles for fame, glory, and ego. By this time Lennart Wetterberg and colleagues at Karolinska had put peptide T into four near terminal men with advanced HIV and reported significant brain and clinical benefits in a 1987 paper in the *Lancet*.

The calls for cessation of further clinical testing from NIH and Harvard virologists were revealed, at least to me, as being politically motivated. I got a strong whiff of this truth at the International AIDS Conference, held in Washington DC in 1987. There were five thousand scientists and ten thousand reporters. It was a feeding frenzy and sharp elbowed affair of jostling for position and pre-eminence, that the opiate receptor discovery, as big as that was, never came close to approaching.

LH: So, when you founded your own company, did you get public support?

CP: No, no, no. It was a small start-up with limited seed funding. No one got big offices and fat paychecks. It was lean.

LH: It wasn't a real IPQ, then?

CP: It didn't get to that stage. You know, the idea was to just start with the little thing and then, when you've got something attractive, then you launch the IPQ or hook up with a Pharma. This venture lasted until 1991 at which point the NIMH had begun to organize a major trial of peptide T for Neuro-AIDS. Ruff and I took faculty positions at Georgetown University Medical School and were eventually able to organize the next business venture which launched out of that university affiliation. (The NIH-funded investigators published a report of clinical benefits in a multi-site placebo-controlled study with peptide T for neuro-AIDS in Heseltine et al., Arch. Neurol. 1998, and reduction of viral levels in Goodkin, 2006. Note added in proof).

LH: Besides the politics, was there any scientific gap that slowed your progress? I mean sometimes discoveries seem "too good to be true."

CP: Exactly! Unbeknownst to us, by the time my team published the first peptide T paper (Pert et al 1986) in PNAS, a huge business/NIH/university consortium had spent 3 years and many millions of dollars making 30 twenty amino acid peptides to span the entire envelop protein called gp120. When none of these peptides tested positive in blocking HIV infectivity, the wrong conclusion was there was no simple short continuous peptide sequence! Instead a complicated bending and folding of "discontinuous epitopes" was invoked as the binding "site" that persists even today. There were no peptide neuropsychopharmacologists in the consortium and virologists couldn't imagine that peptides can have secondary structure or that they could be chewed up in the assays or that the assays could be pharmacologically irrelevant. We pharmacologists never assume that an in vitro assay is relevant—as you very well know—until we have carefully compared it to

excellent parallel in vivo data. But AIDS got a lot of funding really fast, and this created a "might makes right" situation; cool science did not prevail.

LH: Well tell me a bit more about peptide T and the therapeutic possibilities. What receptors does that bind to?

CP: Well, that's a very important question. We had identified, in 1986, this short peptide derived from the envelope of HIV that blocked infection, and protected, even reversed some Neuro-AIDS pathologies in people, but the relevant virus receptors would not be identified for another 10 years, an eternity, really. Usually, I get my scientific information from meetings or papers or colleagues. This time, I got faxes of New York Times and Wall Street Journal articles and what happened was, unexpectedly, the AIDS researchers deduced that two chemokine receptors were the receptors for the AIDS virus. And, this, of course, was a really big deal. Up until then, they were saying CD4 was the HIV receptor; it was a bit of a dogma even, although there were clear early signs that some other receptor(s) must be involved. But in 1986, in our PNAS first report, we had said peptide T was binding to CD4 based on the prevailing thinking. But with the new reports, we instantly began to examine the interactions of peptide T with chemokine receptors. We had heard of them because Michael Ruff, my very close colleague, had been a chemokineologist. He had been studying peptides that controlled the chemotaxis of monocytes. So, in fact, we had done a lot of work together since we started hanging out in 1983, showing that these same receptors in brain are also in the immune cells, and vice versa. We had a lot of papers on this topic, which evolved into "psychoneuroimmunology", so we were able to get into this work pretty quickly and set up that technology in our lab at Georgetown. Ruff had just come back from the Keystone Symposia Chemokine Meeting in Colorado, where, unexpectedly, his poster was promoted to be a plenary address. In that talk, we showed that peptide T is an extremely potent antagonist at the chemokine CCR5 receptor, the more important of the two, as it is the receptor used to infect the body.

LH: So, it blocks it.

CP: Blocks chemokine RS ligands and HIV entry that occurs at that receptor. We came up with this octapeptide that works at picomolar, and lower doses. It seems there are major neuro-inflammatory complications of AIDS, and some neuropathies that peptide T has shown some remarkable efficacy on. The effect of peptide T to block neuro-AIDS likely results from both its ability to block the actions of gp120, but perhaps even more, to suppress microglial activation that

leads to neuronal loss. As such, I think it is obvious that peptide T would have benefits in many other inflammatory diseases, including Alzheimers or arthritis, to cite some significant illnesses with few treatments.

LH: Now, is it possible that with a human growth hormone you could produce a bacterial factory to make these peptides?

CP: Interesting. But the technology for manufacturing peptides is so advanced that Merrifield Solid Phase Synthesis technology seems very good. The drug is potent and so low doses are needed, and easily administered as a nasal spray, so we hope it can be cost effectively made available in the developing world.

LH: Did you think you were ever going to be a scientist business person?

CP: The business part? I don't have any company now. I'm on the faculty of Georgetown and I'm a scientific advisor to the company that's developing peptide T, but as much as I've had to get involved in business, that's the biggest surprise, never, in my wildest dreams, science, yes. I was really interested in science and going for a PhD, interested in basic research, then slowly starting to see that this work can have treatment benefits; it's not just publishing papers; you can maybe cure or treat a disease; you can help people; that's very addictive, you know, when you can actually do something like that. But, the business angle, I never thought that I would have to learn some of those ropes to survive.

## 27. ROY W. PICKENS

LH: I am Leo Hollister and this is for the History Archives. We are at the meeting of the American College of Neuropsychopharmacology and this interview is being taped in Washington, DC, largely, because there are so many people in this area, who are very important in the history of neuropsychopharmacology. Today, we have one of our own, Dr. Roy Pickens,\* who has a very long history in this field and he'll tell us about it. Roy, how did you get interested in, first of all, Psychology, in which you have your PhD, and later on, into what we all know as Behavioral Pharmacology?

RP: Well, I got interested in Psychology early on in my career, and I'm not exactly sure how I got interested in it, other than reading some class work or something like that. But, I went to the University of Mississippi for my graduate training, which was between 1962 and 1965, and while I was there, a guy named James Weeks from Upjohn, published an article in Science on Self Administration of Morphine by Rats, and I thought that was the greatest thing that I had ever read.

LH: That was the first one, wasn't it?

RP: Well, Jim Nichols down in Louisiana, had published some intraperitoneal self-administration of opiates at about the same time, and I'm not sure exactly when, but I remember reading the Jim Weeks article, because it appeared in Science. Then, I got very interested in that, and I read the Nichols work, and, I went back and read a lot of the old history where they had experimental addiction in chimpanzees, and things like that, and became fascinated with that. I do remember that while I was a graduate student at Mississippi, I actually took off one night, left Oxford, MS about 5:00 o'clock in the afternoon on a train, and took the train overnight to Kalamazoo, Michigan.

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\*Roy W. Pickens was born in Greenville, Alabama in 1939. He received a Ph.D. degree in experimental psychology from the University of Mississippi in 1965. After a year of postdoctoral training in psychopharmacology at the University of Minnesota with Travis Thompson, he served on the faculty in the Departments of Psychiatry and Psychology, where he conducted research on drug self-administration, drug dependence, and genetic influences in alcoholism and drug abuse. In 1985, he became the Director of the Division of Clinical Research at the National Institute on Drug Abuse (NIDA) in Rockville, Maryland. In 1989 he was appointed Scientific Director of the NIDA intramural research program (Addiction Research Center) in Baltimore. In 1994 he returned to the laboratory, where he currently serves as Chief, Clinical Neurogenetics Section and Associate Director for Training and Education. He was interviewed in Washington, D.C. on April 14, 1997.

LH: To visit Weeks?

RP: To visit Weeks, that's right. I spent one day in his laboratory. He was very nice. He showed me how to cannulate rats. He gave me some of the cannulae that was being used, and I thought I had died and gone to heaven. And, I remember getting back to the train station that night in Kalamazoo and catching a train out to get back to Oxford. It was an overnight train.

LH: And, that was a long trip in those days.

RP: It was a very long trip, but I was so euphoric. I mean, this was the most exciting thing that had happened to me, and so, from that moment on, I've been interested in addiction and experimental addiction and the factors that control addiction.

LH: I'm glad you brought up Weeks, because most people have forgotten him.

RP: He played a very important role.

LH: And, hasn't been given enough credit, I think.

RP: Weeks and Collins that was the publication in Science in 1962.

LH: Sometimes, there's a phenomena, I guess, that people come around to prematurely, I guess in Science, but sometimes you're too far ahead of the field, and you get lost in the shuffle.

RP: You know, it was after that, that I read some of the work by Travis Thompson and Bob Schuster. Bob Schuster was an assistant professor at the University of Maryland at the time, and Travis was a postdoctoral student at the University of Maryland, and they published an article on Experimental Morphine Self-Administration in rhesus monkeys. And a few months after that, I saw that Travis had gone back to the University of Minnesota, where he had received his graduate training and he was on the faculty there. They had a training program, postdoctoral training program, and there was a call for people that might be interested, and I sent my application forms in, and I got accepted there. And I was at Minnesota and doing intravenous drug self-administration work for the early part of my career.

LH: So, you were one of the first postgraduate students that Travis had?

RP: Yes, I like to think that I was in the second generation. The first generation was Weeks and Collins and people like Schuster and Thompson, and then, I was a student of Travis Thompson. This is sort of as I view myself. So, I did that for a number of years, and we got away from the opiates, which had been the focus up to that time. My first grant from NIMH was on Behavioral Dependence of Non-narcotic Drugs, and it was to study self-administration of drugs that were not

opiates. And we looked at a drug at the time called cocaine, and didn't think anything about it, because it wasn't a very big problem.

LH: People are now putting it up their noses to do operations with.

RP: And, amphetamine. But, I think it was very interesting, because it started to focus attention on the behavioral factors in addiction. Up to that time, the focus was on the physiological dependence on drugs and tolerance, and then, the amphetamines came along and were producing major problems. And, there was quite a controversy. I'm sure you remember this, Leo, when some people were saying that amphetamine dependence wasn't really dependence, because you didn't see the classical opiate or barbiturate type of withdrawal symptoms.

LH: None of those actions are comparable to the actions of opiates or barbiturates.

RP: Well, the only one that is comparable is the fact that they can control behavior and lead to self-administration. And, of course, I think, historically, that was a very important discovery, because it changed our conceptualization.

LH: It generalized the possibility of using the technique of self-administration.

RP: Right, and now, if you look at the latest diagnostic criteria that are used for substance use disorders by the American Psychiatric Association, it's mainly based on behavioral criteria, loss of control and ability to control use of the drug, and things like this. And so, the behavioral part, along with the physiological part and tolerance, have become a very important hallmarks of drug dependence.

LH: Well, at that time, what was going on in Michigan? Weren't Yanagita and Seevers doing similar work? In fact, didn't Yanagita devise the free ranging cannula where the animals could move about without being restrained?

RP: Yes, they had a very impressive setup there. There was Deneau and Yanagita, then, Schuster, and eventually, Jim Woods came in. They were studying dependence liability of various drugs, and these sort of studies gave way to the self-administration paradigm. And they, then, had two entirely separate, but interrelated, facilities there to look at the physiological dependence producing capabilities of drugs, as well as the reinforcing properties of drugs. And so, that was a very big operation.

LH: When was that going on?

RP: From the 1960's until the 1970's.

LH: That's right.

RP: It was quite impressive. They used the substitution technique. You may have seen that with rhesus monkeys, where they would have, actually, three cages that were attached. They'd have the monkeys that were in one of the cages, passing through a middle cage to get to the third cage. And, when they passed through the middle cage, they were given a subcutaneous injection of morphine typically, but at known times, they would substitute other drugs to see if it would block the withdrawal symptoms. I don't know if you ever saw that or not, but it was quite an impressive setup. When the person would go in the middle cage with a syringe, it was a very large syringe with 20 to 40 cc solution, the monkeys would get very excited in the first cage and start to just move around the walls like this, and then, they would peel off. It was the alpha animal, first, which would come in and grab onto the cage wall like this, receive the injection, and just almost instantaneously fly off into the next cage. And then, the moment that this animal left, the next animal would be right in its place, and so, it was very noisy.

LH: Now, these were not naïve animals?

RP: No, these animals that were involved in the substitution in trials; they were physiologically dependent.

LH: They were essentially in withdrawal.

RP: Every six hours, I guess, they would be in withdrawal.

LH: And then, they were going to get their fix.

RP: They would get their fix, and then, they'd move off into the next cage. But then, they would substitute a test compound, and they would study the withdrawal symptoms that possibly ensued to see whether the test compound blocked the withdrawal or did not block the withdrawal. Now, that was quite an impressive operation at the time. After Deneau died, Schuster took over, and stayed there for a number of years; he eventually left and went to the University of Chicago.

LH: Let's go back to Minnesota, now. You claim to be the second generation of Travis' students. When did he start his work there?

RP: Travis did his undergraduate and his graduate work there, and I'm not exactly sure when. He must have returned there right around 1965, I guess, from doing a postdoctoral stint at the University of Maryland. And Travis stayed there until around 1980, 1981, 1982, somewhere around that time, and then, left and went to Vanderbilt. Dick Meisch was there as a graduate student and a medical student when I was there as an assistant professor. I think, so I guess, Dick would be sort of in the third generation.

LH: Now, even before Travis, according to Dick, Minnesota had some history in Behavioral Pharmacology. B. F. Skinner, the father of it all was there.

RP: He was at Minnesota for a while. And the pharmacology department at Minnesota was very strong, too. Fred Silliman was the Chair of it and Gil Mannerling, Takimori, Jack Miller and a number of other people were there.

LH: Oh, I knew Silliman very well. I was shocked to hear of his death. I think we were both on USP board of directors and Fred was president. He died suddenly, I guess.

RP: I think so.

LH: And Gil, I guess, is still on the PMF, or Foundation of Clinical Pharmacology group. He's always got a few jokes up his sleeve.

RP: So anyway, at Minnesota, I started off doing the intravenous drug self-administration work in rats and monkeys.

LH: But, you were still under the Department of Psychology rather than Psychiatry?

RP: No, Psychiatry, we were in the Psychiatry Research Unit. We were labeled a semi-autonomous branch of the Psychiatry Department, and that was because we were located across the street from the main Psychiatry Department.

LH: Now, who was in charge of Psychiatry, then?

RP: There were several people over the years; Don Hastings, early on, and after he left, a guy from Hopkins came in, Dale Hoffman, I think was his name, and then, he left and Paula Clayton came in. And she's been there for a number of years. She's the current Chair.

LH: She's been there a long time. Now, I also understand Peter Dews had a connection with Minnesota.

RP: In some way, I'm not sure exactly if he was there on the faculty or what. I'm not exactly clear about that. But, Minnesota was a great environment from the point of view that we had a psychiatry research unit and had Paul Neal, a past president of the American Psychological Association, in it. David Lichen, who was doing human genetic research, myself, and Travis Thompson were there, and Gordon Histed was the director of it at the time.

LH: Now, did the MMPI originate in that division, or under the Department of Psychology?

RP: Under the Department of Psychiatry.

LH: Psychiatry?

RP: Psychiatry, right. It came out of there.

LH: So, Hathaway and Neal and that group were in that division of the Department of Psychiatry?

RP: Well, Neal was in the Psychiatry Research Unit, but the work on that really didn't come out of the research unit. It came out of the main department, earlier, several years earlier. But my office was right next to Paul Neal's, and we were in the same suite of offices, and he is, by far, the smartest man I have ever met. He was just phenomenal, and I felt like I learned a lot just by being next to him, just the conversations we had in the hall and things like that.

LH: That's what I used to say about living in Palo Alto, that every day I'd meet a half dozen people, who would make me feel like an idiot. But that was just an average, some days I met a lot more. You know, it is kind of fun to be in a place like that where you've got a lot of stimulation.

RP: Oh, that's right. I think that's very important, right. Paul Neal was a psychoanalyst and I was more of a behaviorist, and so, we were just in two different plains, almost, but I found out that he was a guy I could talk to, and he could talk to me, and we'd sit there and talk about many things.

LH: That's the interesting thing, talk to people who are not in the field, and get their point of view.

RP: One thing that captures the mood of that psychiatry research unit, is the fact that we would have one faculty meeting every year, and that's because we thought we ought to have at least one staff meeting every year, and invariably, when we had that meeting, everyone would complain about the fact that we were having too many damn many staff meetings. So, a lot of time wasn't tied up, you know, in the bureaucracy of academia. Mostly, you did your research, talked to people, published, and got grants, and you did things like that. It was a good atmosphere.

LH: Yes. So, after you started off in self-administration studies and went over to drugs, other than the opiates, where did you go, then?

RP: Well, then, the next thing was that I looked to see if cocaine would be self-administered, if amphetamine would be self-administered, if barbiturates would be self-administered. I think we looked at methohexitol, and the answer was, yes, they would be, and, essentially, we were finding that the same drugs that humans abused were the drugs that animals would self-administer. And, again, that shows the biological basis of addiction. We studied those, under some schedules of reinforcement, and looked to see how dose affected self-administration and rate of responding, that kind of things. And then, the natural place to go was to extend the studies into humans, and so, we had a ward in the hospital. I switched at that point over to human research. We had a ward called Station 61 at the University of Minnesota Hospitals. It was an experimental psychiatry ward, and on that ward, we were allowed to do experimental addiction research. So, we studied

barbiturate self-administration in women, some alcohol self-administration in humans, and so forth. I got very interested in that. About that time we got a new director of the research unit, his name was Leonard Heston. And Heston and I turned out to be good friends. We played racquetball together for years and years and years, and just had a good time together.

LH: But, his field was genetics.

RP: His field was genetics, and I can remember in some of my studies, I was looking at what affected the rate of self-administration of barbiturates in humans, and there was a large segment of the variance that I just could not account for, and Heston was just pestering me by saying, it's genetics; it's genetics. So, we would play racquetball and drink beer and talk science, and he would always point out that genetics influenced some things, and I would always pointed out the environment influenced some things. So, I think he got more interested in the environment as a result of that, and I got more interested in genetics. At the time, I also had a research consultantship with Hazelden Foundation, a large alcohol/drug treatment program, located just north of Minneapolis, and I would spend one day a week there. LH: They're still very much in operation.

RP: Oh, they are. I think they serve as model of the drug treatment programs like the Betty Ford type and are being duplicated around the country. And, we would look at various things, like the patients that came in that eventually had seizures, and then, we'd go back and find that in a high percentage of the cases, they didn't report barbiturate use when they came in, and that was likely the cause of the seizures, that type of things. But, they were seeing 1600 patients there every year. So, I said, "Why don't you ask if there are any twins in this group", and if you figure that twins occur at a rate of about one out of every eighty or so births, out of 1600 you'd have quite a few twins that come through there.

LH: You could have twenty pairs.

RP: Well, you should have plenty. So, I started collecting information. Then, we would give questionnaires to these people, and eventually, this got to yield some very interesting data. So, we went to the National Institute on Alcohol Abuse and Alcoholism and got a grant and did a Twin Study. I was getting funded from NIDA at the time, and also, from NIAAA. Then, in about 1985, I took a job with the National Institute on Drug Abuse and put all my research on hold. I went down to Washington, to Rockville, as the Director of the Division of Clinical Research. And, about a year later, Bob Schuster came in as the Director of NIDA. Then, I was also asked to be in charge of our institute's AIDS program, because AIDS was growing rapidly, and one of the

vectors for the spread of HIV was intravenous drug use. At the time, NIDA had a very small budget devoted to the study of AIDS and IV drug abusers, and they felt like we should expand. I sort of came in on top of this, during a period of expansion, so I was there as the Associate Director for AIDS until 1989, when I went to the Addiction Research Center. But, over the course of like three years, our budget in the AIDS area went from three million up to one hundred and forty two million dollars. The question was how to spend the money the best way.

LH: Now, when you were at NIDA and working on AIDS transmission, were you involved in any of the Needle Exchange programs?

RP: At that time, there were no Needle Exchange programs.

LH: That came later, then?

RP: That came later and there was a prohibition against Needle Exchange.

LH: And, to this day, I guess there's no funding for it.

RP: There is now funding so people can evaluate the effectiveness of those programs. But I know that, in 1986, we were really faced with a problem that most of the intravenous drug abusers had no information about HIV infection and how it is spread. So, we were given our first sizable budget increase to get the message out. Now, we were a research institute, yet we were being asked to, in effect, to get a message out, and so, we immediately started to issue contracts to major cities around the country, and also, down at Puerto Rico, where outreach workers would go out on the street, contact intravenous drug abusers, tell them about the risk factors for AIDS, tell them what they can do to prevent the spread of HIV, and then, ask them if they knew of other intravenous drug abusers. So, it's called the snowballing technique, where you go out and ask one person; and they tell you the name of another person.

LH: Pyramid scheme.

RP: So, the first year was spent largely getting the message out, and then, the second year, we said, "Well, you've got to put an evaluation component into your contracts to show that you, in effect, accomplish some change." By the third year, we were asking them to also evaluate the effectiveness of different approaches, the high intensity vs. low intensity programs, and so forth. So, that was a really interesting time.

LH: But, this was truly educational. It had nothing to do with, say, giving them bleach or any kind of solutions to self-sterilize the needle.

RP: It initially, started off as educational, but very quickly it got into bleach. And some of the outreach programs were actually giving out little bottles of bleach like that; it was amazing. It was just household bleach.

LH: Clorox, wasn't it?

RP: Yes, but there was a sort of allure that developed around bleach, and people thought, well, certain types of bleach were better than other types of bleach and things like that. It was real hectic chaotic time, because we had our own clinical research program to manage, but at the same time, we had this tiger by the tail, which was AIDS. It was rapidly increasing. The CDC was projecting that by 1991 or 1993, so many thousands of people would die because of AIDS. We were seeing the spread of HIV by needle sharing, and by sexual contact, and also by intrauterine contact with infected mothers. And so, I think we did a good job in terms of doing what was expected of us at the time, and eventually, actually gaining some knowledge in the process. One of the things that came out of this program was a comprehensive look at intravenous drug abusers on the street. Before that time, all we knew about intravenous drug abusers was based on those who showed up for treatment and that was not a representative sample of all intravenous drug abusers. But, by going out on the street and contacting and giving them the information, and at the same time, collecting some data, we got our first good look at people. And I know that a surprisingly large number of intravenous drug abusers have never really been in contact with the treatment system before, so, we would have never found these individuals otherwise. So, we accomplished both purposes. I think it was a public health mission, but also, a knowledge advancement mission.

LH: I think IV drug use contributes more new infections of AIDS now than it did then.

RP: That's right.

LH: And, proportionately, the number of new cases in homosexuals has declined appreciably.

RP: Yes, dramatically, right.

LH: And, the message seems to have gotten across there. But it looks as though they need more effort on the message for IV drug users.

RP: Oh, absolutely, because the message has not reached them while the condition they have is affecting their sexual partners and their children, as well. So, it's still a sizable problem out there, and particularly, among the substance using community. Then, in 1989, Bob Schuster asked me to go up to the Addiction Research Center, which is NIDA's intramural program, and I was the

director up there from 1989 until 1994, when I stepped down and went back into the lab. But, I still run a section up there on Clinical Neurogenetics at the present time.

LH: So, you started off with lab research, and then, got into the administrative side, and then, returned back to the laboratory.

RP: Yes, I guess I'm a researcher at heart. I never have really enjoyed the administrative aspects of it too much, but the research is something that I've always found interesting. And it's been all around drug abuse, drug addiction, and right now, for example, we're very much interested in identifying subtypes of addiction that have a strong genetic influence. We don't think that all addiction has a genetic basis, by any means, but we think that some addiction does have a strong genetic basis.

LH: There's a guy in Oregon that does these genetic studies with inbred rats.

RP: John Crabbe, and there are a number of people out there that do that. Genetics is a good example where the animal research and the human research complement each other. They use entirely different methods, but they come out with the same results. And there are things that you can do with the animal method that you can't do with the human method, and there are things you can do with the human method that you can't do with the animal method that makes these very complimentary approaches.

LH: Well, of course, what Crabbe is really dealing with, of course, is an artifact, because that's not the way the humans are.

RP: You can identify in the QTL studies, hot spots that are associated with tolerance and things like that. I think, what's happening in addition, though it's not genes and it's not environment, but it's a combination of the two. It's an interaction between the two. So, there are gene environment interactions, and then, you have to take into account, not only the genetics that are involved, but also, the environmental factors that are involved and how they might interact. And, they are also gene-gene interaction, so it's a very complicated system. But, again, I think the main thing is that both are involved in some way and we shouldn't get too attached either to the genetics or to the environment, because they really go together.

LH: Now, the argument no longer is nature vs. nurture, but nature and nurture.

RP: That's right, both together, absolutely.

LH: And, it's not just a question what system you're looking at, but also, which system might be more important than the other.

RP: Right, but the time, since 1989, since I've been at the Addiction Research Center, has been a very interesting time. This organization has a very long history, going way back to 1935, and it has contributed an enormous amount to our knowledge about drug abuse. So, there's a history about the place. If you walk into the front lobby of the building, there are some glass display cases of research apparatus that show ways in which people have taken drugs. It also shows old manuscripts that existed. And we've got a very good library there, with quite a bit of material that's archived from way back.

LH: So, was that was brought to Baltimore when they closed down Lexington?

RP: Yes. Do you want me to trace the history of the Addiction Research Center for you?

LH: Sure.

RP: It actually started informally, in 1935.

LH: Narcotics farm, wasn't it?

RP: That's right. Congress created two hospitals, one in Lexington, Kentucky, and the other in Ft. Worth, Texas, and they were narcotic farms, or "Narcos", as they were referred to. And the Lexington facility was there for the treatment of criminal addicts, east of the Mississippi, and the Ft. Worth one was for west of the Mississippi. And, as part of the Lexington facility, there was a small research unit there that was headed by Dr. Himmelsbach.

LH: Himmelsbach was a very young man at that time, wasn't he?

RP: Very young, that's right, but he had been around for quite a few years. He had done research that went back to 1931, I think. They were charged with understanding the opiate dependence syndrome, but they also wanted to understand what caused addiction, how do you treat addiction and how do you prevent addiction, so it was quite a challenge for this group. And so, the group continued and, initially, it was focused on opiate drugs. Then, eventually, this gave way to also studying barbiturate withdrawal and alcohol withdrawal. In 1948, the administrative responsibility for the unit was shifted from the public health service hospital bureau of prisons to the National Institute of Mental Health. So, in 1948, it became part of the National Institute of Mental Health. And, at that time, it officially acquired the name, Addiction Research Center. Before that, it was just known as a research center.

LH: During the 1940's, the nature of, say alcohol withdrawal, was settled definitively. I remember when I went to medical school, we still believed that some toxin is involved from drinking that

would cause the withdrawal symptoms. But in the 1940s, we learned that it's simply the fact that you had changed yourselves, and as a result, you were going to suffer with alcohol withdrawal.

RP: That's right. And actually, it was in some of the early animal research studies, going on back to 1931, to Lawrence Kolb's work, in which it was demonstrated that monkeys could develop physiological dependence. I think it was a very important discovery, because it showed that physiological dependence wasn't just in your mind. It showed that you could by treating monkeys with opiate drugs produce physiological dependence and withdrawal, if the drug that produced the dependence is taken away. So, all of this was very important. And eventually, like I said, the Addiction Research Center was part of NIMH, and then, when NIDA was created in 1973-1974, the Addiction Research Center was shifted over to become a part of NIDA. It became NIDA's intramural research partner.

LH: Now, besides Himmelsbach, who were some of the early pioneers? When did Harris Isbell join?

RP: Clifton Himmelsbach was there from 1935 until 1944 as the director. Edwin G. Williams was the director from '44 to '45, and then, Harris Isbell came in, in 1945, and was the director until 1963. During that time, Frank Frazier was the associate director, and a guy named Abraham Wikler was also the associate director. And Wikler was the associate director from about 1942 until 1963. And, of course, Wikler's section there on Experimental Neuropharmacology was an area that was very important.

LH: The relationship between psychiatry and pharmacology.

RP: That's right. It was a very important lab.

LH: Like the monograph. I recently had occasion to re-review it.

RP: We, at the Addiction Research Center, have, up until the last few years, given an award each year to the individual we think had made significant lifetime contributions to the drug abuse field, and it's the Abraham Wikler Award. I took a lot of pleasure in this ceremony each year, because it gave me chance to go back and review Abraham Wikler's accomplishments. And it was just quite impressive what the guy did.

LH: And, his theory of Conditioned Abstinence is still quite germane.

RP: Very much so.

LH: I think Chuck O'Brien has done more with it than anybody. It still sounds pretty reasonable.

RP: It's still a factor out there in why people relapse to drugs and something that has to be dealt with as part of treatment. People are coming to increasingly recognize that. Then, after Isbell, Bill Martin came on as the director, from 1963 until around 1978 or so. Around 1976, it was decided that prisoners could no longer give informed consent. And prisoners were the main source of the subject population at the Addiction Research Center. So that left the Addiction Research Center without any human subjects for their studies. And, at that time, the Addiction Research Center was moved to Baltimore. It was moved to Baltimore in two separate moves. The first move was the clinical program that came there in around 1979, 1980, somewhere around then. And then, a few years later, the animal part of the program came to Baltimore, and they were officially reunited in 1985, in the building that the Addiction Research Center is currently located in.

LH: I remember when that move was contemplated. The chairman of the Committee on Problems of Drug Dependence, of which I was on, was very concerned that moving from Lexington would impair the program. So, I was in Lexington one day and I got an appointment with the guy, who was the director of the federal prison system, a Scandinavian name that I forget. He was a very nice chap, and after I was ushered into his office, I told him my story about how concerned we were that by closing Lexington, the valuable program they had there might be jeopardized. So, he pulls out the Washington Post, which was on his desk, and says, look at that. It was an article by the Supreme Court that they'd already decided that prisoners could no longer be used. So I was shot down about as fast as anybody has been. The move turned out to be far more successful than any of us thought it would be.

RP: It also brought the Addiction Research Center into contact with some educational institutions, such as Johns Hopkins and the University of Maryland. And now, the Addiction Research Center is located on one of the campuses of Johns Hopkins.

LH: Now, didn't Lexington, eventually, get sort of tied into the University of Kentucky, too?

RP: Tied into Kentucky, right, and Colorado. As a matter of fact, some of the early graduate training was done in association with the University of Colorado, which is surprising to a lot of people. But, in 1984, Jerry Jaffe came in as the director; and he was there from '84 to '89. And, while Bill Martin was the director, Don Jasinski was in charge of the Clinical Program, and Chuck Gordetsky was in charge of the Animal Program. And John Skanum was also there as the overall director of the program. Well, Jerry Jaffe was director from 1984 to '89. I was there from 1989

to '94. And, now, since last fall, we have a new permanent director, who is Barry Hoffer, from the University of Colorado.

LH: Barry Hoffer?

RP: Yes.

LH: Wasn't he involved in brain transplants?

RP: Yes, plasticity function, correct.

LH: Doing injections of brain cells in Parkinson's patients?

RP: I think so.

LH: How did he get involved in substance abuse?

RP: Well, I think he's involved in it at a very basic level. I think, at some point in science, as you know, you start off with the clinical work, which is very specific, but then, as you go back to more and more basic work that has application in a whole number of areas. I think that's where Barry makes contact with addiction. He is very much interested in addiction though. But, one of the things that I want to say, for the record, is that the ARC has a magnificent library, and we have all kinds of documents archived there. We have old movies of the experimental addictions program, and if professional audiences are interested in some of these movies, they can write or contact our librarian there and these films can be loaned to them. We loaned these to a number of educational institutions to show the experimental addiction, the effects of barbiturates, what barbiturate withdrawal looks like, what opiate withdrawal looks like, and so forth. So, all that material is there and just loads of other material. Historical information is there, too. They have really never been, unfortunately, properly archived. It's classified and it's mostly there in stacks.

LH: I think you'd be the perfect man for the job. When you think of it, tell me this: when you start off with Lexington on one side and Ft. Worth on the other, Lexington has always seemed to be a major scientific enterprise that's internationally known, and Ft. Worth, you never heard of it. What happened?

RP: I don't know what happened. I know that there are some very good researchers out there. Fred Maddox, for example, is still out in San Antonio, and still doing good work. There were people out there doing good work. But it was, somehow the Lexington facility that has become internationally known. It's hard to point to any one person, but again, I think Abraham Wikler played a major role in drawing attention to that program, because of the quality of his research and

his vision, in terms of the importance of certain things. And also, Bill Martin played a tremendous role.

LH: They were all giants and it was just an amazingly talented group. And, of course, there was nothing like it anywhere else in the world. So they had a worldwide influence. It was truly a remarkable institution, and I think it deserves a good history, which we're trying to do right now.

RP: It would be nice for somebody to sit down and write the history. There's a lot of archive material there at the ARC, at the present time. It just needs to be pulled together by somebody and a coherent story written about it.

LH: Now, Nathan Eddy did a similar job with the Committee on Problems of Drug Dependence before he died. And, of course, that stopped the history of the Committee around 1970. So I guess it needs to be updated, but it seems to me you are in a perfect position to be the official historian.

RP: If I had time, it would be something I would do. Another thing that has come out of the Addiction Research Center that people don't often recognize and should be recognized, is the fact that it has been a training site for many students and a number of these individuals have gone on to very influential positions, Jerry Jaffe, Herb Kleber, Everett Ellingwood. I won't even start to name them, because I'm afraid I would skip over someone, but quite a few people have been through there, and received some training there. And, of course, training has always been a very important function of the Addiction Research Center, which, now, incidentally, is known officially as the NIDA Intramural Program at the Addiction Research Center. At the present time, we have, I think, approximately 60 postdoctoral Fellows there receiving training in a wide variety of areas, and a number of pre-doctoral Fellows, as well.

LH: I remember a chap who was hoping to make a name for himself in the field and wanted to escape military service. So he went and applied to the Public Health Service and when they suggested that he should go to Lexington, he said, well, I don't want to go to Lexington. And when I heard that, I said, he's an idiot. Nobody in his right mind with aspiration in the substance abuse field should refuse that opportunity.

RP: That's right. It was a great facility. And what happened was that World War II led to the development of a number of synthetic compounds that had to be tested. And there was animal testing and there was human testing that was going on there.

LH: And, methadone came from Germany, from Schering.

RP: That's right, and a lot of the fundamental work on methadone, naloxone, and drugs like them came right out of the Addiction Research Center. I don't want to have the Addiction Research Center take credit for everything. I just want it to be recognized as it was.

LH: I think the first time I ran into methadone was at an exhibit of Lilly. It came from a German company that was seized after World War II. It was called Dolophine, the phine from morphine and dolo from pain, and it was a very effective oral analgesic. I've always been surprised that it never caught on more for clinical use.

RP: Yes, and there were other things, too, not just methadone that came out of there. Chuck Hartzen, for example, who retired not too many years back, developed the ARCI, the Addiction Research Center Inventory, which is based on the MMPI, and it is still widely used in research.

LH: Oh, yes. I have a copy of it in my files. Of course, I haven't done any studies for some years now, but I used it before, and it was extremely useful in screening. Well, I must confess that over the years, I've been a little bit less enthusiastic about the behavioral pharmacology approach than, perhaps, I should be. It always seemed to me that things happen in the clinic, where people start abusing a drug, and then, behavioral pharmacologists come afterwards and say, yes, that's correct, that is a drug with abuse potential. Can you think of any new drug that came along and there was no clinical experience with it in addiction, and yet, behavioral pharmacology predicted its abuse potential?

RP: Well, you know, the drug abuse screening effort in this country goes way back. We're screening drugs for physiological dependence capability, and also, for the reinforcing properties, and I don't know how many of the new drugs that are being developed get screened at a number of sites at any given time.

LH: That was the main thrust of the CPDD. Was it successful?

RP: Well, yes, they have picked out a number of drugs with very potent reinforcing properties that would predict abuse potential.

LH: But, these were drugs destined for clinical use, and the amount of, say, opiate dependence that occurs as a consequence of clinical use, is minuscule as compared to the total amount of opiate dependence.

RP: Well, that gets to the issue of abuse liability, and whether everyone has the same abuse potential, or do some people have a greater potential for abuse than others? And, that's a very interesting question, because a person like myself would say that the individual contributes a lot

to that, that some individuals have a greater propensity to abuse drugs than other individuals do. So it's not all in the drug and if you're screening the drug, you're only screening one side of the addiction equation. The other side is the individual, and I think that if you look in medical practice, you'll see that drugs with substantial abuse liability are given to people in medical practice every day without resulting in dependence.

LH: Most people would like to get off them. I was in the hospital not too long ago, after a prostate surgery, and they gave me one of these little gadgets to take opiates. I said I don't take opiates. It would paralyze my gut and give me more trouble than they are worth. Just give me Aspirin. But, on the other hand, a friend of mine got one of those things when he had a very severe sciatic pain, and he went through withdrawal. He didn't want it, and he has no inclination to ever take it again.

RP: Right. I guess, what we do, in this country, is that we screen drugs, but we don't screen individuals, and again, it gets back to this gene environment interaction.

LH: Now, pentazocine was a drug, I think, that looked pretty clean in animal self-administration, yet turned out, clinically, to be of abuse potential.

RP: That's kind of like a banana peel. Remember that?

LH: Oh, banana-peel. I tried that myself.

RP: But again, there are a lot of factors in addiction other than the drug, itself. That's part of the interest that we have in this area.

LH: Well, I'm sure there's a great future for it, and of course, one of the beauties of behavioral pharmacology is that it's now also so neat. You've got these nice protocols and everything computerized these days.

RP: But, that area has changed a lot. If you go back and look at what behavioral pharmacology was like in the 1970's, when most of the research was focused on schedules or reinforcement, we just don't see that anymore. You know, a lot of that is now involved in drug screening, and people had gone off into neurochemistry that affects drug taking behavior, rather than just studying the drugs themselves. I think they've gotten away from a lot of the focus on the drugs and they have a greater focus now on factors that contribute to drug action.

LH: Different strokes for different folks.

RP: I guess so.

LH: Roy, it's been wonderful talking to you.

RP: I enjoyed it.

LH: And, I think you've had quite a career, but I strongly urge you to go ahead with that history of the Addiction Research Center.

RP: I wish we could.

LH: If you don't do it, it probably won't be done.

RP: Well, I think it needs to be done, because we have so much material up there and somebody, at least, ought to bring this out and make sure people know what is there.

LH: Well, your memory is still fresh enough, and you've been in contact with people, that it would be awesome for you to do it, but if you were not to do it and had to wait another generation, it might be too late to really capture the past.

RP: That's true. I think, right now, a few years back, I tried to reconstruct who the directors of the ARC had been over the years and found out that it was not clear who was there at one time or another. So just documenting that, and getting that down is an important first step. But, there's a lot more material there.

LH: See, you and I recognize these names of the giants, but I don't know how many people just entering the field have any idea that they existed.

RP: Right.

LH: Anyway, thank you very much for coming and sharing your view of the history with us.

RP: Enjoyed it.

## 28. ALLEN RASKIN

LH: We are in Washington, DC, recording another videotape of an interview with someone concerned with the early history of psychopharmacology. This is the series that is sponsored by the American College of Neuropsychopharmacology. I am Leo Hollister and I have as my guest today, Allen Raskin,\* who has been around psychopharmacology for a long time. Welcome aboard!

AR: Thank you, Leo.

LH: It is always interesting to know how people got started in their field and what impelled you to become a psychologist and how you got involved with psychotherapeutic drugs.

AR: Well, I am not sure what impelled me to become a psychologist except that I got good grades in psychology when I was in college. So, I decided I would continue.

LH: Really!

AR: I got my degree in clinical psychology at the University of Illinois. And Illinois was characterized at that time for being a haven for dust bowl empiricism and really had a strong emphasis on research and statistics. And some of that took. When I left Illinois I went into the VA for a few years as a staff psychologist. And then, I was fortunate I got a job with Maury Lorr doing psychotherapy research and that was in Washington, DC.

LH: Was that when you were still with the VA, then?

AR: This was still the VA, right, because Maury was with the VA. So, we were doing collaborative outpatient studies and looking at things associated with psychotherapy. We looked at frequency of occurrence, whether twice a week was better than once a week or better than once a month. It turned out that the frequency was not the critical variable; just staying in treatment was the critical variable.

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\* Allen Raskin was born in Brooklyn, New York in 1926. He obtained his Ph.D. from the University of Illinois in 1954. After three years as a staff psychologist at a Veterans Administration general hospital, he joined the VA hospital at Perry Point as one of a group of psychometrists who participated in the development of research designs and rating scales for the pioneer multi-center studies at the V.A. Outpatient Research Laboratory. In 1964, he moved to NIMH to join what became the Psychopharmacology Research Branch, where he remained until 1986, becoming Chief of the Anxiety Disorders Section and developed the Raskin Rating Scale, designed to measure the severity of depression. In 1986, Dr. Raskin retired from NIMH and moved to Detroit where he became Professor of Psychiatry and Psychology at Wayne State University at the Lafayette Clinic. He closed his career at University of Maryland where he once again worked at Perry Point VA. He was interviewed in Washington DC on April 17, 1997.

LH: You mean the total duration?

AR: Yes, the total duration you remained in treatment. You know, now, just to mention some names, there was a comparable group that, I think, you were involved with. It included Jack Lasky and the group, out at the Perry Point VA Hospital that was doing collaborative drug trials with schizophrenic patients. Others in that group included Jim Klett, John Overall, and Gill Honigfeld.

LH: Well, yes.

AR: So, we would all meet annually in Cincinnati, sort of the middle of the country. Maury started getting involved in some drug trials while I was there. He looked at chlordiazepoxide (Librium) at one point. Mostly, the interest of our group was in reducing the anxiety in psychotherapy patients, the notion being, that if you could get anxiety down to a reasonable level, it would facilitate the psychotherapy.

LH: Psychotherapy.

AR: Yes, right, that's sort of ironic. My memory may not be quite accurate, but my recollection is the last project I was involved with him was something called, Chlordiazepoxide as an Adjunct to Psychotherapy. But, that was a very good experience for me. You said you didn't know Maury, then, or were you not sure?

LH: Well, I first ran into Maury when the VA Cooperative Studies were being done in the late 1950's.

AR: Right, right.

LH: I think 1958 or '59.

AR: Well he was a great mentor; I mean he was a very capable statistician and a lot of my interest in instrument development began with him. He did the IMPS (Inpatient Multidimensional Scales). The BPRS (Brief Psychiatric Rating Scales) evolved from the IMPS.

LH: Oh yes, yes.

AR: OK.

LH: Well, I remember when the IMPS was all we had.

AR: Right, and then John Overall created the BPRS. When I left Maury, I went to DC General Hospital and I was working on a project that Sol Goldberg was coordinating. That was one of the first multi-site trials that the Psychopharmacology Service Center (PSC) got involved with. This was a drug trial with schizophrenic patients. The drugs were chlorpromazine and placebo. And I

was a Co-Principal Investigator. That was sort of an eye opener because DC General, at that time, had very acute psychotic patients who were climbing the walls and doing that kind of things. And they were giving them 25 and 50 mg of chlorpromazine a day. So, when we came on, we were giving 600 mg a day and we were getting some effects and this was very interesting. I mean, it was just a whole different thing. At the end of my stay, I was invited to.....

LH: Now what year are we talking about?

AR: 1960 or something like that. At the end of my stay, I was invited to the PSC that was to become later the Psychopharmacology Research Branch (PRB). Jon Cole, of course was the director. I was hired by Sol Goldberg who knew my work over at DC General, and Jon. They were looking for someone to do a collaborative depression project. That was a ten-hospital study.

LH: In depression?

AR: Yes, it was with hospitalized patients with depression.

LH: Oh, that came after the ten-hospital schizophrenia study.

AR: Right, that came after the schizophrenia project. So, there is kind of an interesting aspect to that. The original intent was to compare chlorpromazine, which had been shown with imipramine and a placebo. Max Fink was on our review group at that time, and Max had done a trial with chlorpromazine in depression. I think it was done with Don Klein, as a matter of fact.

LH: Oh yes.

AR: Well, he was pushing the combination of chlorpromazine and procyclidine for us to use in the trial, rather than chlorpromazine, alone. So, we took a time out and for a year we looked at the combination versus chlorpromazine, alone, to see whether there was a difference. And, the results showed the combination was no more effective than chlorpromazine, alone, so we opted to go with chlorpromazine, alone.

LH: Didn't the procyclidine reduce the number of extrapyramidal signs?

AR: Yes, but it didn't really have a great impact on depression. So, then we started the ten hospital trial, a rather large trial that ended up with 500 patients.

LH: Will you review for me that trial?

AR: These were hospitalized depressed patients and they came from both rural and urban hospitals that were nationwide. We were out in Rochester, Minnesota, and we were at Sheppard Pratt, here in Baltimore. It was an interesting group, because we had one hospital, Hartford Hospital, where the average patient stayed, and this was years before managed care came about, about ten days.

And then, at Sheppard Pratt, where, when you admitted the patient, they asked the relatives if they had brought seasonal changes of clothing for the patient. So, we had this wide range of settings and, actually, setting was one of the variables we looked at, and it made some difference. But, the drugs were imipramine 300 milligrams a day, as I remember, chlorpromazine 600 mg a day, and a placebo. In the study we were focusing on drug effects on patient subtypes. You know the idea of the right drug for the right patient, that kind of thing. And John Overall was invested in that, as well, and I guess you were also.

LH: Yeah, everybody took a crack at that and nobody ever hit it.

AR: Right! One of the groups we looked at was John Overall's three types, the hostile, the anxious, and the withdrawn-retarded depressions.

LH: And, retarded?

AR: And, retarded, right. And, actually, the retarded did best on imipramine, so that fit in with expectations. The anxious, I think, did show some beneficial effects on the chlorpromazine, so there was some differential effect from it. And, we also looked at the endogenous/neurotic distinction and patients with psychotic and neurotic diagnoses. The psychotic patients did better on the imipramine. Now, other people have had other results, but the neurotic patients in our study did reasonably well on placebo. It was one of the findings. Then, I looked at age and gender and I don't remember if there was anything else we looked at, but it was the subtype issue that was of major interest in the study. Of course, the imipramine was an effective treatment. It was only a six-week trial.

LH: Yes, yes.

AR: One of the things, as I remember though, was the finding at the end of the six weeks. The seventh week the patients were off meds. Patients on chlorpromazine showed improvement in the withdrawn/retarded area, when taken off the drug. That was really my first major entry into psychopharmacology.

LH: When was that published?

AR: 1971. This study generated a lot of articles because I had so much data to deal with.

LH: Now later, I seem to have a memory that you were involved with a study of anxious patients?

AR: At or toward the end of my stay at the branch. My next incarnation was with elderly patients. I did a hyperbaric oxygen study with patients with dementia. I don't know if you remember that.

LH: Uh, hum.

AR: Actually, that's one that I feel good about, because, it was a replication study, basically, with controls. The original study was done by Eleanor Jacobs, who was a psychologist at the Buffalo VA Hospital, and she reported that the hyperbaric oxygen was tapping into brain cells that had been dying because of a lack of oxygen. I subsequently learned there's a "ceiling" phenomenon that prevents the oxygen from getting into the brain beyond a certain point, but, anyway, these patients were paying a fair amount of money, about \$7000, to get these treatments and the social security people were providing the money. This study also provided a boon to Bethlehem Steel, who manufactures the hyperbaric chambers.

LH: Oh, Lord.

AR: To some extent I was mandated to do this study because of its importance. It was done with Sam Gershon in New York City. We used the hyperbaric chamber at the Rusk Rehabilitation Medical Center. We had hyperbaric air, which was a nitrogen oxygen mixture, and, hyperbaric oxygen. We also had normobaric, ground level oxygen and normobaric air. And, the results were interesting, because we didn't show a benefit of the hyperbaric oxygen over the hyperbaric air, but we did show a Western Electric effect, where the people, who went into the chamber, whether they got air or oxygen, seemed to do a little better than the ones who didn't go into the chamber. We attributed this to the mystic of the chamber. You know, you go in and they lock the doors.

LH: That's pretty impressive. It would have made me more anxious.

AR: So, maybe, that's what we should do just put people in the chamber for an hour and then let them out. But, that was an interesting trial and something entirely different.

LH: Now, this was done under the auspices, still, of the PRB?

AR: Right. We had a grant application that came in from NYU, with Sam Gershon. Steve Ferris was hired to coordinate the study. Steve who has now made a name for himself working with the elderly, Barry Reisberg was also brought in to work on this trial. So, the study had to pass through the review panel.

LH: If I recall, you were also testing imipramine and benzodiazepine and placebo in anxious patients?

AR: Imipramine?

LH: Maybe, I'm wrong.

AR: Well, we did one study where we looked at phenelzine and diazepam and a placebo in depressed patients.

LH: Well, I am probably wrong here.

AR: And my recollection on that was that the effects were not nearly as striking as the effects of imipramine had been in the prior trial. This was the same group of 10 hospitals as in the original imipramine vs. chlorpromazine study. I did get involved in the anxiety area in a funny way. I don't know if you knew of the controversy Don Klein was having with Isaac Marks on the relative benefits of drugs and psychotherapy in anxious patients.

LH: It's still going on.

AR: Yes, right, it hasn't stopped. And, I had access to some data that Isaac had collected. The question was if I reanalyzed the data that Isaac had collected, would I get the same results that he got. And, Don was interested in that. And, so, I made the mistake of doing it, and I didn't get the same results.

LH: Well, there was no reason that they both couldn't be right, you know.

AR: You are right. But, Don still comes up to me every once in a while and wants me to publish those findings in a journal, though I have already referred to them in a chapter.

LH: Well, Don has been a very creative thinker, but I have doubts that he could identify a new class of anxiety by the response to drugs. Who could do anything with them in a logical fashion just based on the response to the drug, because these drugs are far less specific than their names imply? Well, anyway. So, that brings you up to the 1980's?

AR: Can I back track?

LH: Well, of course!

AR: I think if I have any sort of a reputation in the field, it's really in terms of instrument development, and, of course, the whole Raskin Scale thing, which was picked up by the drug companies.

LH: Did that scale stem from your work with Maury?

AR: No, but other rating scales I developed did. The Raskin Scale was developed for use in the ten-hospital collaborative depression study. Most investigators, up to that time, when they entered patients into a trial, it was in terms of diagnostic criteria. They were not tapping into the intensity of symptoms. So, this was a crude effort to provide a screen, an entry screen, where you had to have a score of at least nine on three, five point rating scales measuring severity of symptoms in verbal report, behavior, and secondary symptoms of depression. There were just three items.

LH: So, this is the scale.....

AR: The scale I developed for use in this ten hospital study of depression.

LH: What's the official name of it?

AR: Well, I call it the Three Areas Severity of Depression Scale. It became known as the Raskin Scale.

LH: So, this was one of the first studies to put a barrier up to where you had to have a certain level of psychopathology before you get into it?

AR: Right, right, it's like a HAM-D now. I never intended it as a change measure; it wasn't designed for that. But, the drug companies adopted it as a change measure. You know, Jon Cole used to talk about a rating scale being "quick and dirty," and this three items scale appealed to some investigators. So, it became very popular and was used in many drug company depression trials. We also had other rating scales in this study that measured a wide range of symptoms and some of these were outgrowths of the IMPS and other scales.

LH: Well, at that time, there was much research going on for various rating devices that would capture parts of psychopathology. I remember when we started to develop a depression scale and reviewed the whole literature. By that time, there were thirty-five different scales, so.

AR: Right, well, so I'll tell you a funny story. Max Hamilton was on a year sabbatical at Saint Elizabeth's Hospital. I don't know if you know this story or not?

LH: Oh yes.

AR: Do you know about that? And, that's when he was developing the Hamilton Depression Scale. And he used to come up and see Maury and our group and we used to have little chats about it.

LH: Max was an interesting person.

AR: Yes, he was.

LH: He was somewhat compulsive. But, I guess his scale was next in popularity to the BPRS and has retained its popularity longer than any other.

AR: That's right.

LH: So, we still got you back to about the eighty's now. What have you been doing for about the last fifteen years?

AR: Well, I left the PRB.

LH: When?

AR: In 1985. And, I sort of took a retirement at that point and went to Detroit and worked at the Lafayette Clinic with Sam Gershon for a few years. We were trying to evaluate adolescents with suicide attempts and what the reasons were behind these attempts. That study was subsequently published and showed that most of the adolescent suicide attempters were young girls and the attempts were related to problems with boyfriends. Unfortunately, many attempted suicide is by taking large doses of Tylenol which can destroy the liver. I am currently working at the University of Maryland. But, this is sort of funny because my research is going on at Perry Point.

LH: Back to home!

AR: Yes, right. It was sort of interesting that the people at Perry Point, the staff there, really had no awareness of all that went on when the BPRS was developed there, and the whole collaborative study group was up there. That memory has disappeared.

LH: That's one of the reasons we are doing these interviews; we try to make sure they don't disappear. Well, I am blaming the fact that all those studies were done thirty years ago, and no one has any memories of the past.

AR: Right.

LH: I think this is due to the fact that when you tap into a computer to look up references they don't go back very far.

AR: No, they only go back about ten years.

LH: Anything that happened before then is just like it didn't happen at all.

AR: Yes, right. Well, actually, I did some work on race differences in terms of drug response that is now coming back. This was using data from the collaborative depression study. We also looked at age and gender differences. Those things were done, but they are not referenced anymore because they go back beyond the ten-year period. I am now serving as a mentor, quote, for the Geropsychiatry Fellowship program at the Psychiatry Department at University of Maryland. That's my current thing.

LH: Now what's that about?

AR: Well, these fellows are required to have a research experience.

LH: Now are they part of psychology?

AR: No, this is for psychiatrists.

LH: Oh, in the residency.

AR: It's a fellowship that is beyond the residency. The American Psychiatric Association awards an Advance Degree in Geropsychiatry and one of the requirements to that is to get a research experience. That has given us a better opportunity to recruit psychiatry fellows. I first came out there about nine years ago, I was involved with Jerry Levine and a young psychiatrist named Larry Alphs. I don't know if you know Larry Alphs?

LH: Oh, yes.

AR: He was in the process of developing a negative symptoms assessment scale. So, we followed up on that and collected data on 100 schizophrenic patients at Perry Point. I factor analyzed that data and we wrote up and published the results. And, I am really not convinced that there are drugs that are really effective for negative symptoms in schizophrenia.

LH: You mean that there are no drugs that are specifically good for negative symptoms?

AR: I am not sure that there are. I know Herb Meltzer has been working along those lines.

LH: I used to tell a story about negative symptoms and traditional antipsychotic drugs when we first started using chlorpromazine in our hospital. I spread it around to a number of wards and I remember calling up one of my good friends and saying, "Wally, would you like to get some more patients on chlorpromazine?" And, he said, "Leo, I have got so many patients talking to me now who had never talked to me before and this is all I can handle." Now, if that is not reversing negative symptoms, then, I don't know what is.

AR: Well, well...

LH: I don't know where all this fuss came about?

AR: Well, I have a different experience, I'll tell you, these patients are all talking, but their initiative is gone. I have been working lately with chronic schizophrenics, who are in community residences. The VA, Perry Point has a fairly large community residence program with about 200 patients.

LH: So, what you are saying is that they are sort of burned out.

AR: Yes, they talk to you, but the level of their activity, and everything else, is gone.

LH: Well, the name burned out schizophrenic has been around for several years. But, I think that is different than the presence of positive and negative symptoms. Some years ago I looked over some of our rough data that John Overall and I collected over the years, and his scales can be factored into sort of positive and negative elements. So, I was looking that over, it looked as if the negative symptoms improved in parallel with the positives, only not as much. That is, they were

improving but they didn't quite make as big of a change as the positives did. But, I guess that's an issue that I am in a minority on.

AR: Well, the burned out patients may be a whole different thing. We have done a variety of other things out there. We have looked at Vitamin E for tardive dyskinesia.

LH: Vitamin E for tardive dyskinesia?

AR: Yes, for tardive dyskinesia. And, we didn't find any very important or significant effects for a period of just over a year. Lately, I have been working with a neurologist on a dementia unit at Perry Point, who has some ideas about screening tests to distinguish Alzheimer's from multi-infarct patients. I don't know, but I am not terribly impressed with our findings, but it's one of the other areas I have been working on.

LH: You know, way back in the old days, we thought that most things were vascular in the dementias of older people. And, then, in the last fifteen to twenty years it has all swung over to Alzheimer's. You hardly ever hear anything about vascular dementia anymore. And, now, it's beginning to come back and, not only that, they are realizing what neuropathologists realized a long time ago, that they could be mixed.

AR: Oh yes.

LH: You know, you get some people who have both! That's a sizable number!

AR: I worked with a psychiatrist, and I can't think of his name off hand, who was working in a nursing home in New York City. He was able to get permission to autopsy patients and we collected some data. And, these data confirm what you were saying, that when he looked at the brain specimens they were mostly mixed.

LH: Well I remember the pathologist, who used to be the neuropathologist at the Langley Porter Clinic, and probably saw more brains of mental patients than almost any neuropathologists around, because there weren't very many that were fully employed by a psychiatric facility. And, as I recall, he reported that perhaps 35 to 40 percent were mixed where he couldn't make the distinction. It's just funny how the fashion in diagnoses changes. I remember the first study we did with Hydergine in, what I then called senile psychosis associated with old age. Found no effect, whatever, except in patients who had, what was then called hypertensive brain disease, which was essentially vascular dementia. And, there seemed to be some effect, but, otherwise, there was nothing. Well, that's what you would have expected of Hydergine.

AR: I think it had a little effect on depression, that's what I have understood, but I don't know.

LH: Did it work in depression?

AR: Well, I mean, in depressed patients with Alzheimer's or something. It was Gerri Schwartz who conducted the drug trial with Hydergine for the drug company. Do you know her?

LH: Who?

AR: Gerri Schwartz?

LH: Oh yes.

AR: Yeah right.

LH: Yeah, I know Gerri, sure. She took me to a fine dinner over in .....

AR: Right. Well, Hydergine was her area. And, she is the one, who developed a scale that was used in geriatrics.

LH: Yes....

AR: The scale was rated by relatives. I am finishing up a drug trial with physostigmine for Alzheimer patients these days.

LH: Are you using the slow release form?

AR: Yes; it's the oral slow release form. I didn't break the blind, but the parent company, Forrest Laboratories, has hopes that it may have some beneficial effects.

LH: Well, it makes sense. Of course, you know, ever since physostigmine came out for use in dementia in the early 1970's, people had been looking at it. I remember when Ken Davis was with me, we did some studies with it, but it's tricky and you have to find the right dose; and if you overshoot, it goes another way around. And, of course, that skews your results a little bit.

AR: Exactly right. Well, you know, that's an area that cries out for an effective treatment.

LH: Hurry, hurry!

AR: Hurry, right, as we get older.

LH: Every time I can't remember a name, I begin to worry.

AR: Right. I am sort of running out of steam. Do you have any other thoughts?

LH: We may have covered all that we need to. So, your interest has been very varied over the years.

AR: I kid myself and say that I am a renaissance man, because I have been in every area of psychopathology. Something else I did that I think is interesting. I served as the editor of the Psychopharmacology Bulletin; I became editor after Alice Leeds. LH: She was a character wasn't she?

AR: Yes, she was. She really built up the international aspect of the Bulletin in a big way.

LH: Yes, well, and it is the fact that the Pharmacology Bulletin still goes.

AR: Yes, when I was still there we were really under the gun; it was one of those times when the federal budget was being heavily cut. I became a very adept memo writer and was writing memos to everybody trying to justify keeping the Bulletin in existence. But, that was a nice experience, once I got over the anxiety of keeping it going. One of the things about the Bulletin was the quick turnaround. If something was presented at a meeting, you would see it in print in a fairly short time.

LH: Yes and a lot of your material came from the NCDEU.

AR: Right, actually, the ACNP for a while, but now they have cut that out.

LH: And then there was the Schizophrenia Bulletin.

AR: And, the beautiful pictures on the cover, paintings by schizophrenics.

LH: Yes.

AR: In the *Psychopharmacology Bulletin* we did special editions, and this was fun. We would do a special edition on pediatric psychopharmacology. I think Judy Rappaport was the editor for that edition. I did one about rating scales for geriatric patients.

LH: Didn't Steve Ferris come up with a rating scale for geriatric disorders?

AR: Barry Reisberg is the one that has developed scales in this area.

LH: Who?

AR: Barry Reisberg, who works with Steve Ferris.

LH: Well, I must confess that one of the most impressive developments in neuroscience is the greater understanding of Alzheimer's that has just come about in the last ten years.

AR: Yes. My wife can always tell when I have been over working on the Alzheimer's project. I come back with this very depressed aura, having talked to the relatives.

LH: It's an awesome burden, and such a tragedy to see productive people reduced to infancy almost.

AR: Yes. Maybe I shouldn't say this, but, there was one man that we had in the project who had been the head of the geography department at a large university and his wife was saying that he gets lost just going out the door now. So it's...

LH: Well, even it's very sad to see someone like Ronald Reagan go through something like this. What a way to terminate a rather successful four years. Some of us think he was more successful than he should have been. But, nonetheless, you still can't help but to feel sympathetic to his fight.

AR: Sure.

LH: Well, I guess we will have to keep plugging away.

AR: Okay, well I have enjoyed this. Thank you.

LH: Well thank you for coming by and doing this interview with us.

## 29. GEORGE M. SIMPSON

LH: This will be an interview with George Simpson<sup>8</sup> for the archives of the American College of Neuropsychopharmacology. We are in San Juan, Puerto Rico. It is December 12, 1994. I am Leo Hollister. What impelled you to get into medicine and psychiatry, in particular?

GS: Well, I suppose I would have to say A. J. Cronin got me interested in medicine as a boy in Scotland, and as I finished high school, I felt I could not go to medical school. I was not a very good high school student. I think when I reached puberty I was a bit wilder than most people. I actually did biochemistry at Glasgow University and I got a letter on a Friday saying that I would not be called up into the Army for a year, so I went in to Glasgow on a Friday to the university and I started on Monday. It was a little bit easier in those days to get into the university. I studied biochemistry and, then, went to Liverpool to do "Work of national importance" at Distillers, who made thirty three Scotches and two antibiotics; I was assigned to work with antibiotics. And, then, I went to medical school in Liverpool after seeing the Dean who was Scottish and he said, come here and you'll be alright. I didn't apply anywhere else. So, that, too, was easy. When it was over, I was dithering between pediatrics and psychiatry, and finally I decided to go into psychiatry. I was reading an article in the Lancet one day, while I was having tea, and there was an ad about their residency program in psychiatry from McGill by Ewen Cameron, and I wrote them a letter. They wrote a letter back accepting me, so I only applied for one residency program. So, I came to McGill.

LH: You came to North America to do your residency.

GS: Yes, and McGill was just an incredible place at that time. It was very unique, because it was a department of psychiatry in 1956 that had an endocrinologist, Murray Saffrin and Ted Sourkes, who was a catecholamine person. It also had Bruce Sloan who became a Chair, and it had Kral, who was a neuropsychiatrist, Clifford Scott, who was president of the International Psychoanalytic Society. And I used to say that Kral felt that if you couldn't see it, it didn't exist, and Clifford

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<sup>8</sup> George M. Simpson was born in Pennsylvania in 1926 to Scottish parents. He returned to Glasgow, United Kingdom, as a young lad, following the death of his father. He graduated as a physician in 1955 from Glasgow University. He trained in psychiatry at McGill University and Rockland State Psychiatric Hospital. He transitioned to becoming one of the early ECDEU investigators in which capacity he was able to take a look in his patients at almost every antipsychotic drug before it came on the market. Additional academic positions have included stays at UCLA and Medical College of Pennsylvania. He was interviewed in San Juan, Puerto Rico on December 12, 1994.

Scott felt that if you could see it, it wasn't important. So, that was the huge range. And, of course, Malmo, Wittkower, Shagass, Tyhurst, Boag, Cleghorn all were there, as well as Lehmann. He gave us lectures, not very many, since Lehmann and Cameron, did not get on well. Thirteen people who were there became chairs of departments. And then I decided to come to the states. I was going to spend a year in Canada, up to a year in the states, and some time in Mexico, and then on to London, England. I wrote letters one weekend and applied to umpteen places in the states and posted them on a Monday. And, then Cleghorn came and spoke to me on a Friday that I was being naughty, because Nate Kline had called him. I had included Rockland State Hospital in my brief application and mentioned an interest in research. The Hospital Director had given Nate Kline the letter, and as he knew Cleghorn, he phoned him to ask about me two days later. Early on a Sunday morning, I remember being less than pleased, when this breezy guy from New York called and was chatting away when I was barely awake. This soon changed to pleasant thoughts when Nate told me how he had awakened a more senior Dr. Simpson, an obstetrician, and offered him a Fellowship in psychiatry. So I ended up coming to New York, because Nate inundated me with phone calls.

LH: Gave you the hard sell.

GS: And, he could do that, so that was how I came to Rockland.

LH: So, you went there on a Research Fellowship?

GS: Right. In my brief residency application letter, I mentioned that I was interested in research. This letter was sent to all approved programs who took foreign medical graduates and paid \$300/month.

LH: And, were there any other fellows at Rockland doing research beside you?

GS: Well, there was a nucleus of a research group. Given that there was very little research in psychiatry going on in the United States at that time, this was a somewhat eccentric group.

LH: And, what year would this have been?

GS: This would have been in 1957.

LH: So, that was after Nate had done his work with reserpine and he was going with Marsilid (iproniazid)?

GS: Right, so that was going on at that time. But, the group was interested in Gjessing's Syndrome, doing longitudinal research in that, and I always felt to an extent that one of the things about longitudinal research was that if you missed a sample it didn't matter too much because you could

get it later. So we had people who were doing endocrine studies looking at periodic catatonics who were very scarce. We had a research ward and I was the doctor for the research ward. I think I was chosen to do that for who I was, where I came from, and my personality rather than what I knew—a typically Rockland thing. We had an investigator who appeared to believe that if you only had enough urine you could solve all the problems. Every time he got money, he bought another freezer and filled it with urine samples so that one, two or five years later, when he knew more, he could go back and analyze that urine. And, then, of course, there was the famous brown out in New York, and the urine flooded the whole place.

LH: The urine bank went down the drain.

GS: That's right and that was quite funny.

LH: Well, was there anything published from that time with your name on it?

GS: Well, very little was published. Nothing was happening therapeutically; we merely followed a small group of patients, some of whom were diagnosed as suffering from periodic catatonia. These patients were on continuous urine collection, thyroid measurements, etc. I put in a grant at this time which hypothesized that your baseline hormonal status would predict the therapeutic outcome to a pharmaceutical intervention. This was influenced by the work of Max Reiss and Hemphill's work in Bristol, who had suggested that resting steroid levels predicted the therapeutic outcome in insulin treatment. The grant, "Research on Endocrinology and Drugs" (RED) involved continuous monitoring of thyroid, adrenal, and gonadal indices while patients were given a range of therapeutic agents for a three month period, alternating with a three-month placebo period. Jonathan Cole site visited us, liked the proposal, suggested we enlarge it, ask for more money, and change the PI, as I was a third year resident at the time. Nate became PI and ran it very loosely. The very independent investigators did their own thing which ultimately resulted in producing very little. I did not put my name on the final report. Retrospectively it was not a bad idea but it was the wrong patient population for drug studies. We did a lot of thyroid studies and as I became more interested in thyroid and psychopharmacology we eventually opened a new ward for clinical trials of new agents.

LH: Those thyroid studies, at that time, were mainly protein bound iodine (PBI), weren't they?

GS: Yes, and they included studies with perphenazine.

LH: I remember that. Didn't you find elevations of PBI with perphenazine?

GS: Yes. What we felt was that perhaps some of the iodine used in the synthesis of perphenazine might have remained. You could not prove it. The actual effects were real but small. Our other studies were a very expensive way of showing that the hospital administration changed their salt to an iodine supplement without telling us. We had previously checked the iodine intake and it was OK. At all events, all our patients had under-active thyroids, and when we went to a prison to get a control group, the prisoners all had very large thyroids. It was clear they had an iodine deficient diet which made us come back and revisit the hospital food which was now loaded with iodine. It was a very expensive lesson but taught me a lot. After that came another strange finding that monoamine oxidase inhibitors influenced spermatogenesis.

LH: How did you find that out?

GS: Well, one of the investigators was interested in the testes.

LH: Did he do biopsy?

GS: No, he looked at spermatogenesis and it just so happened, that one of the people who worked there, became depressed and I treated him with a monoamine oxidase inhibitor. Then, I found out that he had been a control in the study that dealt with the testes and donating samples once or twice a week for the past two years with low counts and motility and abnormal morphology. A few weeks after starting Nardil (phenelzine), all these indices improved dramatically. It sounds improbable, but I ended up with three depressed subjects, all with baseline sperm data who all showed improvement after being on Nardil for a few weeks. It was difficult to write it up and I decided a letter to the editor would be the best thing to do. So one weekend I wrote a letter which was published in JAMA. One of the authors approached me to say that Nate wanted to be an author on this letter. This, at the time, seemed strange to me. However, later this person and I found out that Nate had put a patent on the use of MAOI's to treat infertility, and we both concluded that this was the reason for him wanting to be on the letter. Shortly after that, Newsweek or Time had a paragraph about someone in New England, who had bought an expensive Argentinian bull that was performing well but producing little, and they had brought in a New York psychiatrist who was giving the animal huge amounts of phenelzine. Of course, it was Nate. To complete this story, when I had placed the subjects on Nardil I had stressed not to take alcohol. At that time, we knew of hypertensive crises produced by alcohol in patients, but not too much that dietary stuff could be responsible for such crises. At all events, I later found out that all three

of the subjects drank heavily before this time. So my guess is that it was the absence of alcohol during the treatment that produced this finding, rather than the Nardil.

LH: That was a Nate Story. Are there other Nate stories?

GS: Well, there is the story that I tend to believe but did not confirm that when they evaluated reserpine, they did not find anything; you have to remember that it was ward clinicians with huge patient populations who evaluated these medications. The hospital glazier said he did not know what was going on, but that there was a diminished window brakeage in that unit. In those days the windows were glass reinforced with metal and wire.

LH: Did they give it for hypertension?

GS: No, the hypertension studies had been done before. The original Indian paper published in 1934 was on "Rawolfia Serpentina, a native Indian herb for the treatment of high blood pressure and insanity." The Swiss probably thought that if it worked for hypertension, maybe it would work in psychosis and, of course, the Indians were correct about both. Jack Saunders, who later came to Rockland, had been at Ciba Geigy, and arranged for those reserpine studies to be done after he moved to Rockland. I remember when I got involved I looked at some of the Rockland data on reserpine which might be half a page in a doctor's handwriting from one patient and that was all there was for the whole study, including demographics, outcome, side effects, etc. They didn't use rating scales at that time at Rockland, at all. So, I introduced rating scales to Rockland, probably in 1960, or somewhere around there.

LH: From the way you describe your experiences at Rockland, it sounds you were not very close to Nate, in terms of your working relationship.

GS: Well, by the time I got there, Nate had become well known and was very busy with all sorts of things. I covered his practice when he went away in the summer and, eventually, I opened a practice in the same suite of offices.

LH: Yeah, a practice in New York City.

GS: Yes, in New York City, and we tried to do some research there as well, which was interesting, because one year we saw over four hundred new depressed patients who wanted antidepressants. The reason for that was that few psychiatrists were using antidepressants and referrals came from strange sources. There was a man in New York who did conditioning therapy who sent patients; Albert Ellis referred patients, so they were sort of fringe referrals. I knew Nate like that in work, but he was always very busy and did not socialize with any of the staff. He was a very good

director when the times were good, because he was never there, and never bothered with what we were doing.

LH: That's commendable, isn't it? Of course, he probably was away a good bit of time down in Haiti then, too, wasn't he?

GS: Right. I remember another interesting story. One of the people on our staff was an Australian who had been in New Guinea during the war. He was a very bright chap and when Nate showed him his film about Haiti—you may remember they had no psychiatric hospitals at all in Haiti at the time, and Nate opened a new hospital with donated antipsychotics and vitamins that caused dramatic changes, which were related to the antipsychotics that Nate had got companies to donate—pointed out that one of the patients appeared to have beriberi. I had never seen a case of beriberi but I suspect he was right, and probably all the patients were suffering from avitaminosis. Nate did a lot of traveling and took pictures. So he went to Africa to visit Albert Schweitzer. He also went to visit the Dalai Lama one time. He clearly liked to do unusual and colorful things.

LH: Yes, he was an unforgettable character. Now, you mentioned Jack Saunders had come there from Ciba Geigy, it was Ciba then I assume. Then, later on there got to be some ill feeling between him and Nate. What happened there?

GS: Well, that was related to the iproniazid study and somebody should be able tell that in a bit more detail than I could. Clearly George Crane had reported that the monoamine oxidase inhibitor, iproniazid, had stimulating effects. He reported this as a side effect of the drug in patients treated for tuberculosis in Long Island, but I do not think he made the jump that Saunders and Nate did, i.e., to suggest it for the treatment of depression. In effect, what happened, at that time, was that a drug company became interested to give some patients with depression, iproniazid, and contacted Rockland, initially Nate or Saunders, to get another doctor to give out the drug. So Saunders and this psychiatrist were involved with the study and they were the senior authors. Nate also gave iproniazid to some of his private patients, and so, he was co-author in this paper which was reported more in the press than in scientific journals. Saunders was not a psychiatrist, he was a Southern gentleman, I suppose. He was also touchy and he clearly made a statement at the Academy of Sciences in New York about the discovery of iproniazid. And when Nate got another Lasker Award, now for iproniazid, Saunders was incensed that he was ignored. So, he and his colleague sued, and eventually, it took ten years or something; the verdict was in his favor.

Saunders, of course, left Rockland but I don't know what he did after that. My own feeling is that it was a question of Nate's style and Saunders' style and that clearly there was a discovery at Rockland. It was a joint discovery.

LH: Well, now, when did you cut loose from Rockland?

GS: Well, I stayed there for twenty years, mainly with the ECDEU grant. That is when I first met you at Palo Alto. I applied for a grant while Jonathan Cole was still in Washington and I got a grant. So, I was now in another building, and not in Nate's, and did my own thing with regard to evaluating new drugs. Everybody sort of did their own thing in the ECDEU program. There was a good group of people that I met all around at ECDEU meetings.

LH: You were one of the first ECDEU units.

GS: Yes, I ran a unit and did some.....

LH: During that period, you were studying mostly antipsychotics, though?

GS: Right, it was a bit easier then, but we did studies with other drugs as well. For instance, the most unquoted paper I ever wrote was one that I presented in your presence in Birmingham in 1964, about carbamazepine before it had a name. We evaluated epileptics who were psychotic. It was not only the first study of carbamazepine in psychiatry, but it also showed that in all patients, we could use one anticonvulsant to treat epileptic patients. We also felt that it improved mood, but that might have been an attention effect.

LH: You, Art Sugerman, and Don Gallant were sort of in the front trenches, so to speak, in taking the first look at many of these drugs.

GS: Right, we often were the first to give new agents to patients, and this worked well because of the practice at the time of keeping patients in hospitals. In any event, for long periods of time, with a very small number of patients, we were able to show that it was, or it was not, an active antipsychotic agent. And probably, Sugerman, Gallant, and I looked at every antipsychotic that we have today before it came on the market. Given that, we knew our patients very well and since we saw them every day, it was not really very difficult to tell whether a drug was active or not. It clearly was economical. I saw my patients every day, and by rating them once a week, I could confidently state whether the drug was active and whether it produced EPS with a sample size of ten patients.

LH: You called the shot right in front of you.

GS: Yes, and most of what we know today of clozapine was reported in our first study. We reported seizures, no EPS, improvement of tardive dyskinesia and withdrawal symptoms. We also did some collaborative studies, but not as big as the VA studies. I remember one study where we reported seizure and abnormal liver function tests in a sample of 10 or 12 patients. There was then a double-blind study of some 36 active patients which confirmed both these findings, and the drug was dropped at that time. Studies in depression were difficult to do at Rockland, but we did one in Nate's office where we compared high 300 mg vs. low 150 mg doses of imipramine. It was planned as a blood level study, which did not work out too well, but still we showed that 300 mg was superior to 150.

LH: When you were studying carbamazepine, it was kind of unique, first of all, in using it as a sole anticonvulsant and, secondly, using it for a psychiatric purpose.

GS: Yes, and it was published in the proceedings of the CINP meeting in Birmingham. I submitted it to the British Journal of Psychiatry and they rejected it. They said this drug would never be used, and certainly not in Britain.

LH: In those days it had a reputation for producing aplastic anemia.

GS: Right, so I never submitted the paper anywhere else, so it's still buried in that volume.

LH: You mentioned that your intention was to do a blood level study comparing low and high doses of imipramine.

GS: Right. I brought Tom Cooper over for the laboratory. Tom did a lot of extra work, including work in lithium long before lithium was on the market. Of course with lithium, we got involved in the dose prediction from a single time point. Tom did the same for tricyclics.

LH: Tom Cooper has had quite a career in the laboratory measurement of drug level concentration. Where is he now?

GS: He's still at Rockland. He spends some time at the Psychiatric Institute in New York. He worked early on in the RED project and set up the PBI lab. He also did a lot of work with Ted Cranswick who was interested in thyroid. Vestergard was interested in adrenal and Tom later did a lot of work on cortisol levels for DST. It is interesting we did dexamethasone suppression tests in the late nineteen-sixty's.

LH: It couldn't be dexamethasone that early.

GS: Vestergard, who was an endocrinologist, was doing some tests that might interfere with the pituitary adrenal axis.

LH: What led you to leave Rockland?

GS: Well, I think two things were happening. The ECDEU program was folding, perhaps because there were no new drugs particularly for schizophrenia, and so, I felt maybe it was time for a change. I knew Bruce Sloan who was the Chair at USC. There had been a scandal at the local state hospital, one of these public relations things that come up which hit the press. As part of the repair of the damage, there was a proposal to set up a modern clinical research treatment center where we would have wards for evaluations as well as labs to do things in.

LH: Was that at Metropolitan?

GS: Right. And so it seemed a good bet to go to California, it was something I was interested in. And the set up there at that time looked very good. Unfortunately, I was not smart enough to know that the MD in charge of the state worked for Governor Jerry Brown. He was a very nice guy, but he had a falling out with Governor Brown and became a non-person. His successor was not interested in a university connection, which I think was a mistake on his part.

LH: I see.

GS: In any event, I think one of the reasons I left Rockland was this opportunity at USC. In effect, history was running down the State hospitals and it was a question of where to go to set up clinical studies. I had set up a unit at Yonkers, opened a day hospital and outpatient clinic, some scatter beds in a general hospital and an eighty bed inpatient unit at Rockland, with the notion that this would all become part of a research unit population that would have acute inpatients as well as outpatients. Larry Kolb was in Albany at this time, and in order to set up this clinical program, which he agreed to, we would have to affiliate with Valhalla, New York Medical College. Nate agreed to do this, and then, at the last minute, changed his mind. It seemed to me that I was running a research unit and a routine clinical inpatient and outpatient program, and now, none of this was going to be part of a research center, and so, that pushed me to leave. I don't think Nate wanted to be reporting to the Chair at Westchester Medical School.

LH: You know Nate never liked to be tied in with the academic people.

GS: No.

LH: In New York, of course at that time, Henry Brill was working out at Pilgrim and Hy Denber over at Ward Island. Did you have any interaction with them at all?

GS: Yes, but I had more with Bill Turner and Sid Merlis out at Central Islip; we did one or two collaborative studies. Henry Brill was always a most helpful person for research. ECDEU units

like at Central Islip and Rockland were very independent and nobody pushed to do group or collaborative activities. ECDEU meetings were a lot of fun.

LH: One of the best hangovers in my life occurred at an ECDEU meeting.

GS: Yeah, well that is true, and that is where I first heard you tell jokes with a Scottish accent.

LH: Well, you were a pretty good joke teller, yourself. So, you went from New York to California to head up the Research Center at Metropolitan, but you didn't do all of your California career at USC Metropolitan, did you?

GS: No, that unit folded when Farabee became the director of Mental Health for the State in place of Jerry Lackner and the priorities changed. Incidentally, Jerry Brown's reaction to the claims of poorly prescribed drugs was to add an additional 30 pharmacists. Anyway, I moved back to USC full time. We did publish a paper on Research as an Impetus to Improve Treatment, which was a data oriented paper. We kept people off drugs for a week except for some manics, and PCP users. We gave them diazepam at bedtime and, of course, patients with all the different diagnoses improved at one week and then resumed treatment with much lower dosages of antipsychotics than was customarily used at that hospital. We did some pharmacokinetic studies in the outpatient clinic in an Asian population, as well as MAO studies.

LH: This is at LA County?

GS: Yes. We did the combined monoamine oxidase inhibitor/tricyclic studies, which were more safety than efficacy studies, and a study of trimipramine versus placebo. We also looked at L-deprenyl as well.

LH: Which one?

GS: L-deprenyl. I think everybody welcomed that study, which included also the use of Parnate. I took Parnate myself, and that was one of the biggest things I did for science. I didn't drink any red wine for two weeks after taking 10 mg.

LH: The MAO inhibitor puts the fear of God in you, doesn't it?

GS: It also gave me eighty percent inhibition about three hours after I took it and I still had about sixty percent inhibition fifteen days later.

LH: You were quite sensitive.

GS: Yes. Then, after that, they were closing wards to save money, even though there were patients waiting to get beds. And it was hard to do anything when it was like that. At about this time, Wagner Bridger invited me to come to Philadelphia.

LH: Now, this was what date?

GS: This was in 1983, so I came back to the Medical College of Pennsylvania to set up clinical research. There were no lectures in psychopharmacology in that medical school in 1984. It's hard to believe that when I first got there, I did one lecture on schizophrenia where I had to introduce them to Kraepelin diagnoses, tell them a little bit about the history and how to treat schizophrenia, and a bit about genetics. And, there were three hours on the psychodynamics of schizophrenia. That was in 1984.

LH: It's hard to believe that it occurred so late.

GS: Then, I think two years later, there were forty odd lectures in psychopharmacology, a research program, and a research Fellowship program. We started to do comparisons of different doses of fluphenazine, with measuring blood levels as well. Despite the fact that there was nothing taught in psychopharmacology, many patients received thirty, forty, or fifty milligrams of Haldol (haloperidol); nobody got more than 900 mg of lithium and very few got it at all. We set up two studies immediately. In one, we compared the effect of different doses of haloperidol and found that ten milligrams was as effective as twenty or thirty mg. In the lithium study, we were trying to push up the upper end of the blood level. There was little data about levels of 1.5 and 1.7 mEq/l, and so I tried to do a study where patients were randomly assigned to stay at a lower level or increase to a higher lithium level. It soon became obvious that we had influenced people, because the attending staff started to increase the levels of lithium because they realized that if acute manics were treated at around 0.8 to 1.0 mEq/l, they will not do as well as if treated at 1.5. Also, if you cut down the amount of Haldol, patients will feel better. We started this already in California. I also went back to using Sodium Amytal (amobarbital) to treat acute mania.

LH: That was the old treatment, 500 milligrams.

GS: Yes, four times a day, and that was because we saw patients where I could not decide whether their illness was getting worse, or if the treatment was making them worse. So I stopped using neuroleptics to treat acute manic patients.

LH: Now, on a different topic, there's a Simpson-Angus scale for rating involuntary movements. How did you happen to get into rating scales?

GS: Well, I think part of that was that all antipsychotics that we had, produced parkinsonism, and in looking for newer and better drugs, I thought that it might be easier to quantify the side effects than the psychopathology. That was a correct assumption. In 1964, we published a scale used in

a study where we showed there was a correlation between EPS and negative symptoms. We also showed that too much EPS resulted in overall behavioral ratings going down. These were all very small sample size studies. We knew nothing about power analysis in those days. We went on and developed this scale. It had some flaws in it. I also tried to use gadgetry to circumvent that, but that did not help, and so we went for a clinical rating that we could do comparisons of treatments and identify new agents. We included items that we thought easy to measure, and we also included items like glabellar tap since on one occasion we saw a patient who developed this sign on antipsychotics but not on placebo. We did a study to look at individual differences in EPS. We took a group of patients and increased their trifluoperazine every week until they reached a quantified amount of EPS on the scale. A rather heavy patient got 20 mg and met this minimal criterion. Another patient got 500 mg and never met criteria. We took everyone off medication, and resuming medication, we showed that patients took the same doses to meet criteria as in the first trial. This was also true for weight gain. We looked at relative potency of drugs. Eventually when Scott Angus was there, we published it as a monograph. There were five papers in that monograph, all related to EPS including controlled studies of handwriting as a guide to dose and studies that showed that low dosages of drugs worked as well as higher dosages.

LH: Anybody with a name like Angus must be a Scotsman, huh?

GS: Yes. Scott Angus was from Edinburgh. He went to Canada and I've kept in touch with him, but he hasn't been involved in research later on. An anecdote I remember, I was having lunch with him and there was a group of New Jerseyites, who were having J & B Scotch before lunch. The barman lined up the glasses and poured. I said, "I can't understand why Americans drink J & B. He said, "Don't knock it. It's not bad at 9:00 o'clock in the morning." He was a good lad, a very good clinician and he wrote very well. So, I was very sorry when he left, but we had a few good years when he was there.

LH: Now, in recent years, I think you've been associated more with treatment and complications of treatment in schizophrenia than with any other single topic. Is that your perception?

GS: Right. It was always an interest of mine and as fewer new drugs came along, I think that both psychosocial treatments and side effects of antipsychotics received more attention in outpatient research. I had also an interest in lower dosages. We did studies in the 1960's, looking at sub-clinical Parkinsonism as a measure of dosing, and I think that was a valid concept. We had the era of very high dosing, but low doses of antipsychotics, e.g., Haldol, are efficacious; and PET studies

from the Karolinska suggest that five milligrams of Haldol gave you eighty percent occupancy, a dose that Haase had suggested many years before. Then, of course, we looked at clozapine in the 1970s, and immediately recognized that it was different from anything that we had studied previously. We also realized that the rate limiting step in dosing any drug was EPS, but the question arose how you find the dose, if the drug did not produce EPS. After that we looked at other atypical antipsychotics, and then I participated in the Treatment Strategies Study, which was essentially a dosing study compared to a psychosocial treatment. That was an interesting study, which took about eight years. Now, I have a clozapine dose response study going on. Already the doses of clozapine are creeping up, so we are comparing a hundred, three hundred, and six hundred milligrams of clozapine in treatment resistant patients.

LH: Now, if you want to draw some blood, I've got a lab where we can measure the levels for you.

GS: Well, we're looking at blood levels and someone else has a supplemental grant looking at muscarinic receptors and cognition in that group of patients, so I feel that I am happy still working in schizophrenia.

LH: Well, you've had quite a career and now you're about to resume it back on the West Coast, and no doubt, you have many productive years ahead of you. Do you think we're going to get another grand step forward in the treatment of schizophrenia?

GS: Yes, I do. I would like to think that it would come, as it were, prospectively and not serendipitously, but I think that some things will come from imaging and neuropsychiatry and genetics. But, there will need to be a big step forward in terms of understanding more about the illness. If prenatal factors are involved, then prophylactic action could be helpful, i.e., good obstetrics. In 1939, probably for the first time in history, the people in Scotland were fed properly because of the war and food rationing people got bigger and pelvises got bigger. So, good antenatal care and good obstetrics will help. I think that birth trauma is down and nutritional status has improved. Hopefully, virus infections will be reduced and genetic research growing. I suspect that we will reach a point soon, that a drug like clozapine could be used early in the treatment of schizophrenia. We need earlier intervention and perhaps more specific treatments for different kinds of schizophrenia. I think the antipsychotics have improved outcome at least preserving affect and permitting patients to live outside hospital.

LH: We've made a lot of people better, but not well. Well, George, I wish you a lot of luck in your venture back in California.

GS: Thank you very much.

LH: And, probably before this historical session is over, we'll be calling on you to follow up with another interview.

GS: Thank you.

### 30. FRIDOLIN SULSER

LH: It's Friday, May 9, 1997. I'm Leo Hollister. We're doing a series of interviews that have been done under the auspices of the American College of Neuropsychopharmacology with people who are instrumental in the field and have seen its' development and contributing to it. Today, we're in Nashville and we'll be interviewing Fridolin Sulser,\* who probably spent more of his life in Nashville than any other single place, so it's quite fitting to interview him here. Welcome aboard.

FS: Thank you, Leo.

LH: Well, Fridolin, it's always interesting to find out, first of all, how people made their career choice, because I think all bright people have probably a lot of different choices to make and, of course, there's several choices along the way, whether you go for, not only the profession you choose, but how far you want to go in each, and what choice to pick. How did you decide to go into medicine?

FS: Well, I think this had something to do with my wife's uncle, who was a physician in a little town close to Maienfeld in the state of Graubuenden, Switzerland. He was a general practitioner in that town and I thought it would be a wonderful thing to be a physician. I really thought this to be a profession that is beyond any other profession.

LH: Were you having visions of yourself being a general practitioner taking care of people?

FS: Yes, really, that's what I wanted to do, Leo. It turned out a little bit differently in the long run. I went to medical school at the University of Zurich and Basel after I finished the gymnasium and got my M.D. degree in 1955.

LH: Your MD?

FS: Yes, my MD degree. And during my medical studies in Basel, I met the most remarkable man

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\*Fridolin Sulser was born in Grabs, Switzerland in 1926. He received his MD degree in 1955 from the University of Basel, Switzerland. From 1956 to 1958, he was an Assistant Professor of Pharmacology at the University of Bern, Switzerland. In 1958, he moved to the Laboratory of Chemical Pharmacology at the National Heart Institute, NIH. After a short tenure as Head of the Department of Pharmacology at the Wellcome Research Laboratories, in Tuckahoe, NY, in 1965, he became Professor of Pharmacology and Psychiatry at Vanderbilt University School of Medicine, in Nashville and then Director of the Tennessee Neuropsychiatric Institute. He was interviewed in Nashville, Tennessee on May 9, 1997.

I ever met, and this was Karl Jaspers, the philosopher. He was a physician and a professor of philosophy at the university. He was one of the best known existential philosophers in the German speaking world. Jaspers came from Germany because he had problems in his homeland. His wife was Jewish and, at that time, as you know, the Germans did not like that Germans marry Jews. He left Germany in 1948 and came to Switzerland. It just happened at that time that the professor of philosophy retired at the university, and Karl Jaspers got his Chair. As a medical student, I attended his lectures that triggered my life-long fascination with existential philosophy. This was a man with a vision and a perspective and a sense of history. And, he was a trained psychiatrist. Yes, he was a psychiatrist before he jumped into existential philosophy. He was enormously critical of psychoanalysis, but he liked Freud. And, when I graduated, I came away with the feeling that psychoanalysis, that was predominant at that time, was not what I wanted to do. So, I went to see professor Bleuler in Zurich and solicited his advice about my future education.

LH: Was this Manfred?

FS: Yes, Manfred. And, after I worked in his hospital for about three weeks, he called me into his office. We had a serious talk behind closed doors, and he said, "Look, Dr. Sulser, I think this is not for you. I would not recommend that you go for a residency in psychiatry." I asked him why, and, then, he said, "Well, number one, you don't listen." Listening is apparently important in psychiatry. And, the second thing Bleuler mentioned was that I was too experimentally minded. Interesting. That's a good clinician, a good assessment I thought. So I took his advice and his recommendation that I should do something else than psychiatry, and work in an experimental area that is more to my liking. So, I went to see people in pharmacology in Basel and I got a job there.

LH: In pharmacology?

FS: In pharmacology. It was with Franz Gross, who worked on hypertension at Ciba and with Rolf Meyer at the University of Basel. And, then, after two years or so, I became an Assistant Professor at the University of Bern and I started to work on cardiac function and the effect of digitalis on ion transport.

LH: Well, what you did was quite a role removed from Karl Jaspers.

FS: Yes. Then I read, in the journal Science the article by Pletscher, Shore and Brodie, on the Effect of Reserpine on the Endogenous Levels of Serotonin in Brain. I knew from my hypertension research that a certain percentage of patients treated with reserpine developed depressive

symptoms. So, I said, ah ha, there's a connection! I wrote a letter to Bernard B. Brodie at the NIH indicating that I would like to come for a year or so to the United States to work in his laboratory.

LH: Did you know Pletscher before?

FS: I knew Pletscher from studies we did at CIBA. And while in medical school, we had him and other people from the pharmaceutical industry visiting with us. We also went to visit Hoffmann-LaRoche, where Alfred Pletscher was Director of Research.

LH: When you were still a student?

FS: Yes, when I was still a postdoctoral student. I went to see Pletscher and told him about my interest in his paper. He had just returned from Brodie's lab, and, he said, "Why don't you go to Brodie, it's a great place to be." He told me that there are also other brilliant people there, like Sidney Udenfriend, Park Shore, and Julie Axelrod. And he said, "You should apply for a Fellowship to go there." So, I applied for a Fellowship to the Swiss Academy of Medical Sciences and I got it. I got \$3,000.00. I thought, this was a lot of money and I told my wife that we are going to the United States, presumably for one year.

LH: But, didn't you write to Brodie first?

FS: Oh, yes, before applying for a Fellowship I wrote to Brodie, and Brodie wrote me back that he will take me if I bring my own money!

LH: So, you went to the Swiss Academy after Brodie accepted you to come.

FS: That's correct. I went to the United States just with a suitcase. My wife was to join me later. It was in October 1958 when I showed up at NIH and walked into Building 10. There was a Symposium in progress on catecholamines. Arvid Carlsson talked about dopamine. He had developed a method to distinguish dopamine from noradrenaline.

LH: That was just discovered in those days.

FS: Yes. He reported that he found very high concentrations of dopamine, but not norepinephrine, in the striatum. So, he concluded that dopamine is not just a precursor of noradrenaline but is a transmitter in its own right. And, then, my career began.

LH: So, you were there when Carlsson was there.

FS: No, Carlsson was already gone. He was just there for the Catecholamine Symposium and after its conclusion, he went back to Sweden.

LH: So, you started your work with Brodie. Unfortunately, Brodie isn't with us anymore, and I'm always interested to find out from people who knew him to what kind of person he was. Was he difficult?

FS: I wouldn't have known whether he was or wasn't difficult in the beginning, because I didn't understand English sufficiently well. I had real difficulties, and first of all, I had to learn three things. First, I had to learn English. And Brodie, if you remember, had a very slurred speech that was difficult for me to understand. Second, I had to learn new spectrofluorometric methods. And third, I had to become familiar with new concepts in biochemical neuropharmacology. All I can say, Brodie was very, very nice to my wife and me. He helped us to find a place to live. Mrs. Brodie was driving my wife around in Washington before she learned how to drive. So I have only good things to say.

LH: Did he allow you to pursue your own ideas?

FS: Well, he was very egocentric. He wanted people to work on problems he had an interest in. I remember, once I ran into a little problem with him. I wanted to study something I was interested in and was working on it in the late afternoon. As always he came to the lab in the late afternoon and when he saw what I was doing he asked, "Why are you doing this?" And I said, "Because it's interesting, Dr. Brodie." Then, he said, "Well, if you want to do this, why did you come to work with me?" So, I switched to work on a problem he had an interest in. The problem he was interested in was related to imipramine. And, then, when he saw that I was working on what he was interested in, he became very nice, cordial and said, "Well, imipramine is an interesting drug. People say it works, but I don't believe it." So, I asked him, "Why don't you believe that it works?" And he said, "It doesn't block monoamine oxidase." He also told me that psychiatrists can't quantitate things, and if one gives them orange juice they will find that it works. So, I felt that I have to work on the problem with imipramine but didn't know what to do in the beginning, because imipramine did not block monoamine oxidase and behaved in many pharmacological tests like a weak phenothiazine-like compound. Then, Brodie said, "Well, maybe, we should have a model of depression." We were sitting together like you and I, and I said, "Why don't we set up the reserpine model as a model of depression. Mimo Costa and Silvio Garattini had previously shown that imipramine antagonized some of the symptoms elicited by reserpine. So, we reserpinized rats and studied the action of imipramine in those animals. And, sure enough, when we pretreated reserpinized animals with imipramine, the trophotropic syndrome became ergotropic. Instead of closed eyes,

the animals had wide-open eyes, instead of miosis, they had mydriasis, instead of being motionless, and they showed increased motor activity.....

LH: I don't know if people who will look at this tape will know what the ergotropic and trophotropic syndromes are. Didn't this terminology come from W.R. Hess?

FS: Yes, it was W.R. Hess who coined this terminology.

LH: That's another Swiss.

FS: Yes, that's another Swiss. To put it in a nutshell, the trophotropic syndrome is a syndrome that is characterized by increased parasympathetic activity and decreased sympathetic activity. And this was what reserpine was doing. It induced a trophotropic syndrome.

LH: Does the name trophotropic come from tropho, to repair.

FS: Yes. Imipramine worked like a monoamine oxidase inhibitor when injected prior to reserpine. Instead of miosis, there was mydriasis, instead of ptosis, exophthalmus, instead of decreased locomotor activity, increased locomotor activity, instead of hypotension, hypertension, and instead of decreased body temperature, increased body temperature. And, then, we asked how was the drug doing this? We knew that it didn't block monoamine oxidase, but we had not the slightest idea how the drug without inhibiting monoamine oxidase "reversed" reserpine's effects. And later on, we found that imipramine also "reversed" the effects of tetrabenazine which is a benzoquinolizine compound that has a similar action to reserpine but works a little faster. And, then, Brodie said, gee, this is interesting, maybe, the drug works on brain serotonin, because, at that time, he had the idea, based on the findings by Pletscher and Shore that reserpine's behavioral effects result from depletion of serotonin. So, Marcel Bickel, another Swiss who was there, and I treated animals with o-methyltyrosine, which blocks tyrosine hydroxylase, the rate limiting step in the biosynthesis of catecholamines. It depleted norepinephrine and dopamine in the brains of the animals while it left serotonin untouched. This was the first depletion experiment done long before the Yale group started doing depletion experiments in humans. We found that after the norepinephrine was depleted, imipramine failed to antagonize the effects of reserpine. So, we learned that the availability of norepinephrine was crucial for the action of imipramine. It did not take very long, however, to find out why norepinephrine was needed for imipramine's action. George Hertting, who was a post-doc of Julie Axelrod, came to our lab and said "We can explain all of your data. Tricyclic antidepressants block the uptake of norepinephrine." So, everything became clear. Monoamine oxidase inhibitors and the tricyclic antidepressants increased the

availability of norepinephrine, but by different mechanisms, one by blocking the metabolism of norepinephrine, and the other by blocking its reuptake. And, then, of course, the rest is history; as you know, people started screening for drugs which block the uptake of norepinephrine.

LH: Did Brodie's laboratory identify desipramine?

FS: Yes, well, what happened is another little story. Brodie had the idea at the beginning, that the reason for the need of giving imipramine chronically before it "reverses" the effects of reserpine was that, in time, the drug accumulates somewhere in the brain. James Gillette had developed a method that could detect imipramine by fluorimetric means in the brain. And Gillette had a graduate student, Jim Dingell; Jim and I got together and we decided to look and see what actually happens. So we treated animals chronically with imipramine, and then, we anticipated to measure the accumulation of imipramine in brain. But we couldn't. Instead, we found a compound in the buffer phase with fluorescence similar to those of imipramine. And that turned out to be desipramine (DMI).

LH: It had a different peak from imipramine.

FS: It had a different peak and it was extracted into the buffer phase whereas imipramine remained in the heptane phase. Using paper and gas chromatography, we were able to identify the substance in the buffer phase as DMI. This was the discovery of the first selective norepinephrine reuptake inhibitor. And after that, we used DMI as a tool in our research.

LH: Well, wasn't Brodie the first guy to put out the idea that there were pro-drugs and sometimes they were the metabolites that acted?

FS: Well, he was thinking that way, even about imipramine. He thought imipramine is a pro-drug, and the active compound is the demethylated metabolite. This is true with regards to norepinephrine function, because DMI is much more potent on the noradrenergic system than imipramine, that is more potent on the serotonergic system. So, in many ways, imipramine was a pro-drug in making a noradrenergic drug from a serotonergic drug. The important discovery in Brodie's laboratory was the demonstration that DMI-like antidepressants need norepinephrine to work. The importance of the availability of norepinephrine in the action of DMI-like antidepressants became also evident at Vanderbilt, in our research on the down regulation of the beta adrenoceptor mediated cyclic AMP second messenger cascade.

LH: I think most people have the idea that Brodie had invested heavily on serotonin, but from what you told me, you and the rest of people, had a pretty good idea that norepinephrine was very important. How did Brodie, Pletscher and Shore measure serotonin?

FS: They measured serotonin using spectrofluorimetric methodology that had just been developed by Bowman and Udenfriend.

LH: Yeah, the introduction of the spectrofluorimetric method was a tremendous improvement.

FS: Yes, the one who really put lots of work into developing a methodology for measuring monoamines was Sidney Udenfriend, who was at NIH before he went to the Roche Institute. And it was an enormous advance that one could measure quantitatively small amounts of monoamines in different areas of the brain. In our experiments, after extraction into heptane, imipramine stayed in the heptane phase, and DMI was returned to an aqueous phase. The compounds were then measured fluorimetrically. Jim Dingell, who was instrumental in identifying desipramine, made his doctoral dissertation in this area. Jim and I learned from each other. He was teaching me methodologies in drug metabolism, and I tried to teach him pharmacology. You know Jim Dingell; you interviewed him.

LH: Yes, I know Jim. He is a very modest man.

FS: Yes, he came to Vanderbilt where we continued to collaborate. You asked me before to say something about Brodie. One thing that is of interest is that he used to tell his postdoctoral fellows that there are three things that are necessary to become a successful scientist. First you have to have an idea, second you have to be able to develop methods to test the idea, and third, you have to be lucky. And, I think he has been right.

LH: Well, methodology is tremendously important. I was thinking the other day that a sizable number of Nobel Prizes have been given to people for developing methods.

FS: Brodie's philosophy was that if you want to find new things, you have to be able to develop new methods. With new methods, you will be able to open up new fields.

LH: Well, when he was at Ward's Island in New York, trying to develop new antimalarial agents, I guess, he had to develop new methods. He was also very much in colorimetric methods in those years.

FS: Yes, that's correct. He also told the people in his laboratory how important it is to measure something quantitatively. If you just have qualitative measurements, he used to say, "Forget it, you have to be able to quantitate." And this is what he had done, and what everybody in his lab had

done. They used quantitative methodology and this is why the Brodie School opened up so many new fields.

LH: Well, he has opened up the whole field of pharmacokinetics.

FS: Pharmacokinetics was opened up entirely by Brodie.

LH: Of course, he was into drug metabolism.

FS: Look, Brodie's fantasy was sometimes a little bit ahead of the data he had, and as you know, there were a lot of people who faulted him for this. But it was his demonstration that psychoactive drugs can change the levels of monoamines in the brain, and the development of histofluorescence techniques that helped to catalyze the birth of biochemical neuropsychopharmacology and biological psychiatry.

LH: This was than done by Fuxe. Didn't he develop the histochemical method?

FS: Fuxe and Hillarp.

LH: And, Annica.....

FS: Annica Dahlstrom. They were the ones who developed histofluorescence microscopy. And they mapped, using these techniques, the distribution of noreadrenergic neurons, their terminals, and their cell bodies, the serotonergic terminals in the raphe nuclei, the dopaminergic terminals, and so on. The origin of the idea of working on systems, like the noradrenergic, serotonergic or other systems was deeply rooted in the teachings of W.R. Hess, who emphasized that one has to work on functional systems because if a finding cannot be related to function, it has no relevance to the central nervous system. And, this functional orientation is something that, today, is lost. I remember Hess, when we were looking at a slide of tissue culture under the microscope, asking, "What do you think you will learn from such studies, why you fall in love with a girl?" And in a way Brodie did look at things in the same way. It was absolutely amazing what happened in his laboratory. And, of course, many people went to work with him. His laboratory was a Mecca of psychopharmacology in the 1960s. There was Brodie himself, and there was Axelrod, Udenfriend, Shore, Bogdanski, Pletscher, and Carlsson. There were the Germans, Norbert Matussek, Eric Westermann, Hans Dengler and Karl Netter. There were the Italians, Mimo Costa and Luigi Gessa. Marcel Bickel from Switzerland, who later on became Chairman of Pharmacology in Bern, was there. It was a wonderful stimulating environment.

LH: How long were you there?

FS: I was there from 1958 to 1962.

LH: '58 to '62?

FS: 4 years.

LH: So, that was sort of the high point of your life?

FS: And, if I could have been employed by the NIH, I would have stayed at the NIH, but I couldn't.

LH: Because you were not a citizen?

FS: I wasn't a citizen, and I was on a student exchange visa. I was supposed to go back to Switzerland for two years, and then apply for a permanent visa. But, then, the politicians helped me to fix the problem. Jim Dingell's brother was in Congress, and his mother was Swiss. So, immediately, we established a very good communication He helped me, and Congress passed a private bill to change my exchange visa and get me a green card.

LH: Now, I gather that you were at the International Congress in Moscow where Marshall Nirenberg presented his findings on the genetic code.

FS: No, I was not there.

LH: You were not?

FS: No, I was not there, but I was at NIH when Matthaei and Nirenberg discovered the genetic code. That was in 1961 or 1962. They were just around the corner of me. After I became an immigrant, I went to work for two and a half years at Burroughs Wellcome in Tuckahoe, New York, as head of their pharmacology department. But, as you can imagine, working in industry was not for me. It's not my life style. So when Dan Efron came and told me that Allan Bass at Vanderbilt was entertaining the development of a Psychopharmacology Research Center at Vanderbilt, I thought that's a good opportunity for me to go back to academia and get a little closer to psychiatry. This was in 1965.

LH: You know, sometimes I think we underestimate the influence administrators have, because Dan was nothing but a scientific administrator. But he was the one who encouraged Allan to start the Tennessee Neuropsychiatric Institute (TNI) and to get you.

FS: Administrators, if they're smart, can do a lot by channeling things in the right direction. I actually think that top administrators, who are also scientists, should have membership in the ACNP, as real members, and not just as administrative members. I think some of them have made tremendous contributions to the field.

LH: And, you know, for a very long period of time, in this country, nobody employed by industry could ever hope to be president of the Pharmacology Society. I think John Burns was one of the very first people from industry to be asked.

FS: Well, in 1958, when I came to this country, you could not even become a member of the Pharmacology Society if you were working in industry.

LH: That's never been a bias in the ACNP. Len Cook and Larry Stein were both connected with industry while they were presidents, and, well, one of the guys running for president this year, is also connected with industry. I don't think we've had any biases in that respect.

FS: No, I don't think so, either.

LH: So, after you left Burroughs Wellcome you went down to Tennessee?

FS: Yes, I went to Tennessee.

LH: That was what year did you say?

FS: 1965. And, then, I could develop my own research. In industry, I could not do it. And at NIH I worked with Brodie. So, this was a tremendous opportunity for me.

LH: And, you had to come down here, take a vacant space of some sort, and make it into a laboratory?

FS: Well, the vacant space at the State Hospital had to be turned into labs at the beginning. We got a center grant from NIMH with the enthusiastic support of Dan Efron. And also, the State of Tennessee gave us some money to renovate the place. So we had good space, and, we got good people to come to work with us in the Institute. Just look at my post docs like Elaine Sanders-Bush, Susan Robinson, Dorothy Gallagher, and Phil Mobley. All these people went through TNI. Then, Jerzy Vetulani came from Poland and Janowsky.....

LH: Dave Janowsky from San Diego?

FS: Not that Janowsky, the other one from Oregon, Aaron Janowsky. We developed a very effective basic research group.

LH: Didn't Jerzy Vetulani go back to Poland?

FS: Yes, he went back to Poland.

LH: Is he a Chair somewhere?

FS: He is the Scientific Director of the Polish Academy of Sciences in Krakow.

LH: What did you start on doing when you came down here?

FS: Well, the first thing we did was asking the question why antidepressant drugs take so long to work. I was convinced that norepinephrine uptake inhibition per se had probably nothing to do with the therapeutic activity of these drugs, because uptake inhibition and the reversal of the reserpine syndrome take place rapidly. I had actually one of my graduate students during my first-year at Vanderbilt looking at how fast uptake inhibition *in vivo* happens. We gave the drug imipramine, and a few minutes later, the uptake of norepinephrine was blocked. So, I concluded, that this could not be directly responsible for the therapeutic activity.

LH: Also, uptake into the nerves is especially fast.

FS: Yes. We thought we have to look for other mechanisms that take a little bit longer to take effect. And this is when Earl Sutherland, another one of my heroes, with his cyclic AMP-second messenger concept, came into the picture.

LH: And, of course, he'd done most of his work on cyclic AMP at Case Reserve in Cleveland, didn't he?

FS: Yes, that's correct. He was a man with a vision. It was Earl who first talked to me about cascades in the CNS, in which the interaction of a transmitter with receptors is only the first step, the step that activates these cascades. And this was before G proteins. We didn't know about the G proteins at that time. And while Earl was here at Vanderbilt, he actually put the receptor for norepinephrine on the enzyme adenylyl cyclase.

LH: So, nobody knew about G proteins, then?

FS: No, nothing was known about G proteins at that time. The pivotal role of G proteins in signal transduction was discovered later by Rodbell and Gilman. And, then, in a conversation one evening, over Jack Daniels, with a fire burning in the fireplace, Earl said, well, you know, if I would be you, I would look beyond the synapse, I would look at these cascades and the role they play in the action of antidepressants. And, one of them, obviously his favorite one, was the cyclic AMP cascade.

LH: At that time, cyclic AMP was the only second messenger, wasn't it?

FS: Yes, it was the only one, and it was difficult to measure the activity of the second messenger system. As you know, we didn't have a radioimmunoassay; so we had to use enzymatic reactions to measure cyclic AMP. It was very, very complicated and time consuming. Alan Robinson was involved in that. And then, we discovered that if we gave antidepressants chronically on a clinically relevant time basis, there was an adaptation going on at the level of the beta adrenoceptor-coupled

adenylate cyclase systems. This was in 1975, 25 years ago. It was a tremendously interesting discovery. The sensitivity of a receptor to an agonist was measured by the activation of adenylate cyclase. We found that the number of receptors in the membrane was changed after the chronic administration of antidepressants. Prior to this, as you know, Lefkowitz and others discovered that receptor sensitivity was regulated by phosphorylation.

LH: So you had shown that the number of receptors decreased.

FS: Yes.

LH: But, the decreased number of receptors was not the consequence of the decreased sensitivity.

FS: It was not the consequence of the decreased sensitivity, rather the decreased sensitivity of the adenylate cyclase system was the consequence of the decreased number of receptors. So the first thing we found at Vanderbilt was that the number of receptors decreased. And this led to the receptor regulation hypothesis and all kind of other research. Importantly, we discovered that antidepressant treatments (tricyclics, MAO inhibitors and ECT) given on a clinically relevant time basis, reduced the responsiveness of the beta adrenoceptor-coupled adenylate cyclase system to norepinephrine in limbic and cortical structures of the rat brain, and that chronic but not acute treatment with noradrenergic antidepressants down-regulated the biologically active form of the transcription factor CREB (CREB-P) in the frontal cortex of the rat, thus indicating a net deamplification of the beta adrenoceptor-cyclic AMP cascade. Conceptually, these studies switched the emphasis on the mode of action of antidepressants and on the pathophysiology of affective disorders from acute presynaptic, to delayed postsynaptic second messenger mediated cascades, and opened up the gateway for subsequent studies of events beyond the receptors, including changes in programs of gene expression. And, then, a little later, when Phil Mobley joined our lab, we realized that we have to incorporate the glucocorticoids in some way in our work, because, as you know better than I do, stressful life events can precipitate depressive reactions. So we started to look at glucocorticoids, and sure enough, we found that changes in glucocorticoids are changing the sensitivity of the receptor system to catecholamines. That, then, led to the norepinephrine-glucocorticoid link-hypothesis of affective disorders. The role of serotonin, we did not understand for a long time. That changed when Berridge demonstrated that serotonin through serotonin receptors, that we now know are 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, activates phospholipase C, generating 2 second messengers, inositol-triphosphate (IP3), that mobilizes calcium and diacylglycerol, which activates protein kinase C.

LH: That was in the late 1960's?

FS: Yes, in the late '60's. And then, Elaine Sanders-Bush, who worked with me, started looking at serotonin and serotonin receptors. I took care of the catecholamines and she took care of the indols. Now, what we found was that the two systems, the noradrenergic and the serotonergic systems, converged after the receptors. And that was absolutely fascinating. Norepinephrine, through the adenylate cyclase system activated protein kinase A, that initially phosphorylates the receptor in the membrane, and causes desensitization of the system. Serotonin, through phospholipase C activation, made IP<sub>3</sub> and diacylglycerol, which activates protein kinase C, and, we found that protein kinase C and protein kinase A have a cross talk with each other. Moreover, we found in human fibroblasts, using the transcription factor CREB as a target, that both the activation of the cyclic AMP-protein kinase A pathway by the beta agonist isoproterenol, and the activation of protein kinase C pathway by the phorbol ester PMA, caused phosphorylation of nuclear CREB, and that this phosphorylation is additive in nature.

LH: So you linked the activity of the serotonin system with the norepinephrine system?

FS: Yes. We're trying, now, to see what all this means. Paul Greengard at Rockefeller, who was previously at Yale, has clearly shown that the final common pathway of signal transduction is the phosphorylation process, and the question now is, what is phosphorylated, and what is less phosphorylated after desensitization, and what are the consequences of all this in the next compartment of the cell, in the nucleus. Presently, we're looking into this. Paul Rossby and I developed the hypothesis that behavior is put together by programs of gene expression. It's a large program, it's like a huge orchestra in which there are twenty thousand players (genes) and there are first violins, first cellos, the horns, and so on. This all is well coordinated in "normal" people like you and me. Now, if the horn comes on at the wrong time, you have dissonance. And we feel what happens is that in depressed people, because of stress or whatever, the plasticity of the system is lost in response to an increased input, and what the drugs do, is help to adapt by restoring the plasticity at the level of gene expression. At the present time, we are trying to develop methods to identify the first violins and the second cellos. In other words, what we are doing now is developing methodology to measure programs of gene expression, programs that are activated by transcription factors which are phosphorylated by the kinases. Hopefully, one of these days, we can understand what's going on. The work with these transcription factors is new and people don't really talk about it yet, because it is very complicated. There are about two thousand gene specific

eukaryotic transcription factors. Once translocated to the nucleus, they will affect only genes that have responsive elements in the promoter area (nuclear receptors).

LH: Now, are c-fos and c-jun genes further down the line?

FS: Yes, they are further down the line. A transcription factor, like CREB, turns genes with CRE elements in their promoter region on via the beta adrenoceptor-cyclic AMP cascade. One will always turn on groups of genes, in other words, the first violins, the second violins etc. And the question is what are these genes and, importantly, what are their products doing? That's not so easy to find out. Again, we need new methodology; but I think this is where the field is going. And, finally, you can envision the development of drugs that will affect or restore faulty programs of gene expression.

LH: So we got away from the synapses.

FS: Oh yes, all the way to the nucleus. And there's already some fascinating work in this area from Michael Greenberg's lab at Harvard. Michael Greenberg has shown that fos-b, which is a transcription factor like fos-c and jun-c, is very important for the complex behavior of nurturing in animals. Normal animals (this was done in mice), after they give birth, collect their off-spring, put them in the nest, put their body over them to keep them warm, and nurture them. If you knock out just one transcription factor, fos-b, they don't do those things anymore, because nurturing behavior is interrupted. I think this is absolutely fascinating. By knocking out one transcription factor, the olfactory stimulus of smelling the pups doesn't work any longer.

LH: This knock out gene technique is fantastic. Who is the Japanese fellow....I don't remember his name, who is using the knock out gene technique in studying behavior. He is the one who won the Nobel Prize.

FS: I don't remember his name either. The task in the future is to apply these sophisticated techniques in an intelligent way to behavioral problems.

LH: His name was Tonegawa.

FS: Yes, Tonegawa. So, this is where the field is moving, Leo. We moved from presynaptic events in the '60's, to membrane receptors in the '70's, to second messenger mediated activation of protein kinases in the '80's, and now, we are moving to the last compartment, the nucleus. That's where the action is now.

LH: That's an enormous amount of progress that had been made and you've been part of all of it.

FS: Well, it is enormous progress if you think about it. At the time I entered the field there was nothing known about cascades. When I was at the NIH, in the late Fifties, we were still grinding up whole brains of rats, just to measure serotonin or norepinephrine in the whole brain. There was nothing known about presynaptic events such as uptake, receptors, receptor subtypes. There was little or nothing known about protein kinases, G proteins, transcription factors, not to speak about the organization of the genes and how they're turned on and off.

LH: And, we still don't know anything about the gene products.

FS: That research will not be easy to do because those products are proteins, and the functions of proteins are difficult to study.

LH: Now, you're still at the Tennessee Neuropsychiatric Institute?

FS: No, I'm in the Department of Psychiatry at Vanderbilt University. I have my laboratories there, and my grant was still renewed this fall for another five years.

LH: Oh, it should be easy for you to get grant support.

FS: I think so, too, but, you know, I had to go away for a year, because I realized that the "old pharmacology" is not helping me any longer. It boxed me in with old techniques. So, I went for a year on a sabbatical to the Roche Institute of Molecular Biology.

LH: So, that's how you became interested in molecular biology.

FS: Yes. When I came back and had to renew my grants, I thought, gee, this time I will have problems, because members of the study section will say, how the hell, at age 60 that fellow wants to move into a new area of research. Well, I sent the grant in and, guess what happened? They liked it? They liked it, so much, that instead of five years, they approved it for ten.

LH: Wonderful.

FS: So that's how it worked, I've been very lucky. The number three ingredient for successful research, Leo, is luck, as Brodie said.

LH: Well, I think for all of us, who are in this field, no matter where we are, it's just a great joy for having been so lucky to be able to do the things we like, which gives us pleasure, and may even be helping patients.

FS: Oh, yes. Well, this is one thing, Leo, I sometimes miss, the patients. You remember I wanted to go into medicine because of the patients. And the problem, if you get involved in basic research, is that you have to work with new methods, and you simply have no time for patients. The developing and learning of new methodologies is so demanding, Leo, that you cannot see patients.

LH: Well, when you get to be my age, then, you can go back to that Swiss town and do general practice. One of the regrets I have, and I'm sure you must have, too, that you don't have enough lives to do all the creative legacies. You know, I much would have preferred to do more basic research, but I also feel that I have not spent as much time with patients as I would have liked.

FS: Yes. The last patient I have seen was in the Swiss Army. It was before I left Switzerland. You know, I was in the Swiss Army?

LH: You had to do your military service.

FS: Yes, after I finished medical school, I was in the Medical Corps, and that was the only place where I saw patients. And after that, I saw only rats and tissue cultures.

LH: Well, we have to settle for the blessings of the day.

FS: Yes, and I always think, that in some ways, I made it up. I helped to develop two classes of drugs for affective disorders. I contributed something to psychiatry with my work on the development of the secondary amine tricyclic antidepressant, DMI. And I also helped develop bupropion while I was at Burroughs Wellcome.

LH: Bupropion is a very valuable antidepressant.

FS: It's a noradrenergic antidepressant like DMI.

LH: Doesn't it have dopaminergic activity?

FS: Yes, in the rat. In man, bupropion gets metabolized to hydroxybupropion and hydroxybupropion is a norepinephrine reuptake inhibitor.

LH: Well, I must say, Fridolin, I've always considered you to be one of the most creative people in the field, as well as one of the nicest.

FS: Well, I don't know. I think the most important discoveries are yet to be made, when we get to know these subsets of instruments, the first violins and the second cellos and the horns and so on. We're working on this now, trying to develop methods to identify specific differentially expressed genes. I am very fortunate being able to interact with Peng Liang who, while a postdoctoral fellow with Arthur Pardee at Harvard, invented the differential display technology for cloning differentially expressed genes. This methodology makes it possible to display about 96 % of all the genes expressed in a particular cell type and subsequently to be recovered from polyacrylamide gels. I am looking forward to the discovery of novel genes involved in or providing a predisposition to psychiatric illnesses. And, of course, my dream would be to eventually develop drugs that would selectively turn on or off those sets of genes that are important for certain

behaviors. I consider these transcription factors, activated by second messenger mediated cascades, important as light switches. If you can't turn them on because the light switch is broken, it doesn't matter how much electricity goes in, it does not turn on the light and it remains dark...

LH: It's only as strong as its' weakest link.

FS: That's correct.

LH: Thank you, Fridolin.

### 31. STEPHEN I. SZÀRA

LH: Today is April 16, 1997, and we're in Washington, doing interviews on the project of the History of Early Years of Psychopharmacology sponsored by the American College of Neuropsychopharmacology. Our guest this morning is Dr. Stephen Szàra.\* Welcome, Stephen.

SS: Thank you.

LH: It's been a long time. That's the trouble when you retire, you get lost. Tell us, Steve, I think you have an interesting history of being educated and raised in Hungary, and then, making a career in the United States. How did this come about?

SS: Well, to start at the beginning, I got my first training in chemistry. I did my D.Sc. work in chemistry, physics and mathematics in Budapest. Then while I was doing my thesis work in organic chemistry, across the hall—across the garden, really—of the campus of the University of Budapest, there was the Institute of Biochemistry of the Medical School, which was headed by Albert Szent-Györgyi, I don't know if you remember his name.

LH: Oh, yes, of course. He was one the greatest scientists of that time.

SS: I think he got the Nobel Prize in '37 for his work on Vitamin C and oxidative metabolism in the muscle.

LH: Muscle metabolism, yeah.

SS: I was quite interested in biochemistry at that time, and while I was still working on my organic chemistry thesis, I actually took some biochemistry courses. We were allowed to cross over to another Institute. And I was really interested in it, but I haven't been involved in biochemistry until, I think, 1950. Let's go back for a moment. This was during the war, World War II, and at the end of the war, I started to take courses in medicine. I didn't really want to become a physician, a practicing physician. I wanted to do research from the beginning. So I thought I am going to take a few courses in biochemistry, and maybe pharmacology, and maybe anatomy.

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\* Stephen Szàra was born in Budapest, Hungary in 1923. He received his PhD in chemistry at the University of Budapest in 1950, followed by a medical degree in 1951. In 1956, during the uprising, he left Hungary, ending up at NIMH in 1958. He joined the Center for Studies of Narcotic and Drug Abuse in 1971, which became the National Institute on Drug Abuse in 1974. He retired in 1990. He was interviewed at Washington, District of Columbia on April 16, 1997.

And then I started to get really involved, and I decided that I might as well just go through the whole thing, so that's how I got into medicine.

LH: With no intention of being a medical practitioner?

SS: No, no intention. I was primarily interested in biochemical research, and after my thesis work I got a position in the Department of Microbiology and Immunology of the Medical School. There were problems at the time that had to do with political issues, and eventually, the Communist Party had taken control over many of the organizations at the universities, and that particular Institute was kind of disbanded, the professor disappeared, some people went to jail, and I was transferred to the Department of Biochemistry. That was back in 1950; I was still in medical school in my last year. I got my medical degree in '51. It was in 1950, when I shifted over to the biochemistry department as assistant professor.

LH: In medical school, did you have separate institutes of different disciplines, or was it all combined?

SS: No, there was a separate institute for each separate discipline.

LH: Biochemistry and all?

SS: In that particular campus that I was in, pre-medical subjects were taught in the departments of biochemistry and physiology, and the medical students came to study chemistry, physics, etc.

LH: Now, did you do any clinical work at all?

SS: Well, I did some later on. When I was in my last year in medical school, I did one year of internship, and during the internship, I met a young fellow who was already working in a mental hospital in the outskirts of Budapest. He came to me one day and said that the hospital was very much interested in doing research in the biochemistry of mental illness, and they were interested in organizing a laboratory in the hospital. He asked me whether I would be interested in starting there.

LH: Until that time you had no training in psychiatry?

SS: No, I had no training in psychiatry. I just had my year of internship.

LH: So you considered yourself a biochemist?

SS: Yes. I went to see the Director, and asked her, "What should we do in the biochemistry of mental illness?" "You know," I told her, "mental illness is somewhere up in your brain, there." And we didn't know much about the chemistry of the brain at that time. But, as it turned out, there

was a publication a year before that by Hoffer, Osmond, and Smythies. I don't know whether you remember it. They had two papers I think in the *Journal of Mental Science*, in which they were proposing a biochemical hypothesis, the adrenochrome hypothesis, of schizophrenia.

LH: Hoffer, Osmond, and Smythies were popular in those days.

SS: Very popular. Later on, I got involved in the issue whether adrenochrome is present in the blood.

LH: I assume, by that time, in Budapest, you were able to get hands on the world literature?

SS: Yes, we had subscriptions to a lot of the prominent English and American journals.

LH: At that time, were you able to read English?

SS: Yes, I could read English, but I couldn't speak it. As a matter of fact, I studied internal medicine from an English textbook. So, in 1953, I decided to accept the job in the psychiatric hospital and to start some research related to the biochemistry of schizophrenia. I got involved with the work and became interested in LSD. We knew about LSD since Stoll, in 1947, published the first paper on the experience of Hofmann with the substance. The story had been picked up in relationship to the indole hypothesis of schizophrenia. I was thinking to do some research in that area and decided to try to get some LSD. So, I wrote a letter to Sandoz, the company that made LSD, and I got back a letter essentially saying: "we are unable to send you any LSD." Well, I understood what the reasons were. This was during the peak of the Cold War, and there were some allegations of brainwashing with hallucinogens, so they were reluctant to send any LSD behind the Iron Curtain. In my desperation, I was asking myself, "oh, what can I do for which I don't need LSD?" As it happened, while keeping up with the literature, I saw, in 1955, in the *Journal of the American Chemical Society*, an article published by Fish, Johnson, and Horning about the chemical content of cohoba, the snuff, used by the native Indians in South America for religious purposes. Chemical analysis had identified four compounds in it: dimethyltryptamine, bufotenine, dimethyltryptamine-N-oxide, and bufotenine-N-oxide. Bufotenine had been claimed to be psychoactive; Fabing had done some work with it, but nobody knew much about dimethyltryptamine (DMT).

LH: Who wrote that article?

SS: Fish, Johnson, and Horning.

LH: I thought it might have been Dick Botnish from Harvard.

SS: Are you referring to Dick Schultes.

LH: Dick Schultes.

SS: But going back to Fish, Johnson, and Horning, they identified bufotenine and said that it was probably the active ingredient. However, the Fabing report wasn't very convincing. Others who tested bufotenine reported on flushing of the face and a lot of other primarily vegetative effects with the substance. So, I was not sure whether it was really bufotamine, the active ingredient. There was nothing about DMT in the literature, so, I decided to go back to my old institute where I did my thesis work and ask them whether they could synthesize some DMT, because I would like to test it and find out what it does. This was at the end of 1955, beginning of '56, and to make a long story short, with the help of my old friend, Miomir Mészáros, I synthesized a few grams of DMT. When I tested it in animals (first, on rats, then on mice, and ultimately on cats), it turned out to be active biologically and pharmacologically. From these data, I guessed what would be approximately the active dose for DMT in humans. I thought it would be interesting to see whether it has hallucinogenic effects. DMT has some effects in animals, but who knows whether they're hallucinating. You can't ask them! I decided to take DMT myself first. I started with a very small amount, like the amount Hofmann took from LSD; I used, a quarter of a milligram. So, I started very carefully with a quarter of a milligram. I waited for a few hours and since it had no effect on me, I took half a milligram, then 1 milligram without any effect. And, so, I went up to, I think, 100 milligrams orally. It had no effect at all. At this point I became discouraged. The substance seems to be active in animals, but it doesn't do anything to me. I knew what to expect from a hallucinogen because half a year before taking DMT, I was inspired by Huxley's book, *The Doors of Perception* and took mescaline. But I did not get it from the oral doses of DMT. Someone in the hospital made a suggestion that maybe I should try to inject it.

LH: Yes, it was given to the animals by injection.

SS: I was hoping that, maybe, I could avoid giving the injection, but apparently, I couldn't avoid it, so I went down to the pharmacist in the hospital and asked him to make a preparation of DMT that could be given by injection. After the preparation was ready, I started injecting it into myself, intramuscularly. Starting with a small dose, a quarter of a milligram per kg, it was inactive, I felt no noticeable effect. After increasing the dose to half a milligram per kg, I thought I saw something that started to look like visual, perceptual distortions. At the next test, I injected three quarter milligram per kg; as I weighed about 75 kg at that time, it was a total of about 55 milligrams. Two minutes after the injection I was up in the seventh heaven. It was amazing. It came very fast; I

could hardly keep my eyes open; everything started to move around; the faces had become distorted, in just the same as with mescaline or LSD.

LH: So, that was your first real hallucinogenic experience...?

SS: Yes, my first hallucinogenic experience with DMT. Yet, half an hour later, everything was gone. Everything was gone. I also tested DMT in a colleague of mine, who was assisting me in the hospital, when he told me that he would like to try it. Then, the word got around. At the time, there was no drug control, the kind we have today. It was just pure science. So, the word got around and several other people volunteered. We eventually collected 36 or 37 experiences from 30 volunteers. Everyone got about 1 milligram per kg. Although this was not a scientifically designed dose-response study, it did establish in a large population that DMT was unequivocally hallucinogenic in people. This research was done in 1956. By the end of the summer, we decided that we would write it up and send it in for publication, because DMT seemed to be a very interesting new type of hallucinogen. Its effect doesn't last for 12 hours as of mescaline's, or 6 or 8 hours as of LSD's. It was obviously a different kind of hallucinogen and I thought it would be interesting to do more work with it. I thought that it was appropriate to write up our findings as a preliminary report and get it published. So I sent the report to *Experientia*, a Swiss journal. They accepted it and the paper was published the same year, I think it was published in November. But in November 1956, things were disorganized in Hungary. There was a revolution in October, and after October, the Russian troops came in and suppressed the revolution. They decided to bring back the old communist rule. At that point in time, I realized that I don't have a future there. I wasn't a member of the Communist Party. As a matter of fact, I found a secret report on me when, during the revolution, the communist party archive was opened up. According to the report, my main crime was that I was western oriented; I was reading western literature and sent my paper on DMT for publication to a western journal. As a matter of fact, I had sent a paper before this to *Biochimica Biophysica Acta* in '51 or '52. So, I was western oriented that was my major crime in the eyes of the communist party.

LH: So, this was, essentially, a political crusade against you?

SS: It was, Leo. I was Chief of the Laboratory in the psychiatric hospital and didn't have any chance for advancement. I had a small laboratory with 4 or 5 people working with me. During the short period of time I was working in the hospital, I got involved with some clinical work and not only with human volunteers, but also with patients. Dr. Böszörökéyi whom I was working with,

had suggested that we should try DMT in some of our alcoholic patients and in some schizophrenic patients. We began testing the drug and we found out that it was also active in those populations. It did not have as pronounced effect as in normals, but it was a noticeable effect as measured by the questionnaires we used.

LH: You were still using DMT?

SS: Yes, dimethyltryptamine. I also synthesized some 13 different derivatives of it. I had the diethyl, dipropyl, dibutyl and several other homologues. The dibutyl was inactive, while the dimethyl, diethyl and dipropyl were active in animals. In humans, we had only tested the dimethyl and the diethyl derivatives at that point. Then I left Hungary, escaped illegally. I had to, you know. There were two hundred thousand people who voted with their feet and left Hungary after the revolution, mostly through Austria. I did get out and got into Austria. Once in Austria, I went to Vienna to see Dr. Hoff. Do you remember Dr. Hoff?

LH: Oh, he was head of pharmacology.

SS: No, he was head of psychiatry. He was professor of psychiatry.

LH: Oh, Hoff, oh yes.

SS: H-o-f-f:

LH: Yes.

SS: He was professor of psychiatry in Vienna; I knew him only by name. I also met H. O. Arnold and G. Hofmann who were in Hoff's Institute. You may remember their names. They were publishing some interesting stuff at the time. They had done some work on LSD as well. So I decided that I'd get in touch with them. As a matter of fact, they were very kind to me. When I told them I was a refugee, they said, "there is a room here, which we use for psychotherapy, and at night, if you want to, you can sleep in there, but by 7:00 o'clock in the morning, you'll have to clear out." But, they were nice, you know. They gave me a little shelter over my head. And while pulling out a little bottle from my pocket, I said, "I have a little dimethyltryptamine here with me, you know, if you are interested."

LH: You were a pusher.

SS: Then I asked them, "Could you give me some LSD, to try it, I would be very curious to see how it would compare with my experience with mescaline, dimethyltryptamine and diethyltryptamine." They said, "We have a protocol here. You have to go through it and you can get tested." So I got LSD while I was in there as a refugee, and it was a very interesting experience.

LH: Was it similar to dimethyltryptamine, but longer lived?

SS: It was similar, but longer-lived. I took the LSD early in the morning, like 9:00 o'clock, and at 4:00 o'clock in the afternoon, they said, by now it should be all over and you may go home. I decided to walk to a large hall where the evening meal was served for refugees in Vienna at that time and sat down for dinner. By then, it was 7:00 or 8:00 o'clock in the evening. There was a huge mural painted on the wall and as I looked at it I said, those darn things, those figures are moving.

LH: That's a late onset.

SS: Yeah, for a while they moved, and then they quieted down and everything was back to normal. The effects of LSD are longer lasting than the effects of DMT, and they come back in waves.

LH: How much had you taken?

SS: One hundred micrograms. That's a small dose, a relatively small dose.

LH: That's a rather modest dose.

SS: So, that was my experience with LSD. Then I decided to go to stay with my sister, who lived in Berlin, which, at that time, was still surrounded by East Germany and Russian troops. So the only way for me to get there, as a refugee, was to fly over the Eastern Zone to Berlin. Once I was there, I got in touch with the people at the local Free University of Berlin. It happened that I met Hanns Hippius, who was working there at that time. They had a lab at the University and they said, "You are welcome to come here and do some work if you are interested." And I started to learn German. We had German in the school back in Hungary. For eight years, we learned German. So, the German came back pretty fast and, as a matter of fact, in a few months I gave a seminar in German about the kind of effects I had experienced with hallucinogens.

LH: I take it that you were able to speak and understand German by then?

SS: Yes. I was there for almost a year. I didn't realize that if you are a refugee and once you resettle from the first country, which was Austria, in a second country that was in my case Germany, I was not considered to be a refugee any more. However, I wanted to come to the United States; that was my final goal. I knew that this is the place where much of the action is in the particular area I was interested in. So, I wanted to come here, but I had no chance or very little chance to come here, because I was settled down in a second country already. But I was still interested. I started correspondence with people whom I knew from the scientific literature and I

did eventually get three offers: one from Bob Heath down in New Orleans, who had been looking for a psychiatrist. The second, I forgot the name of the scientist who offered me a job, was in Philadelphia. And the third was from Joel Elkes at the NIMH, who was organizing a laboratory at St. Elizabeth's Hospital. As I was kind thinking over which offer should I take, I saw a film in Berlin, which at that time was a new film with Marlon Brando. It was *A Streetcar Named Desire*, based on a Tennessee Williams play. I don't know if you're familiar with it, but the movie takes place in New Orleans. And my impression of New Orleans was so bad that I didn't want to live there. Marlon Brando was playing a bum, and everything was dirty, hot and sweaty there. So, I said, "I do not want to go to New Orleans; Pennsylvania would be nice, but the NIMH is more prestigious." I decided I'd take the job with Joel Elkes. So that's how I got to Washington.

LH: And, you picked a place, too, where there were many more disciplines involved. Bob Heath was kind of a loner. He worked his own path and had very innovative ideas, but no one else around would interchange with him; whereas, at St. Elizabeth's, I guess Joel Elkes had a more interdisciplinary team.

SS: I was very lucky, that I came here. The laboratories, however, were not ready as yet. They were converting the fifth and the ground floor in the William White building into laboratories and offices, and the laboratories were not ready yet. And Joel Elkes said, "Listen, Stephen, there's some very interesting work going on in Building 10, at NIH, in Julie Axelrod's lab. I talked to him and you can probably stay there, and work with Julie until these labs are ready." So I went there and Julie was nice and very accommodating. He said, "Stephen, if you are interested in applying biochemistry to pharmacology and psychiatry, this is a good place to work on that." A lot of people worked on that. Among many others, Danny Freedman was there.

LH: Now, we're talking about late 1950s?

SS: Actually, it was late 1957. In '57, I did go into Axelrod's lab and, as a matter of fact, I stayed there for about two years, because I liked it there. He's a very, very innovative guy in terms of developing new methodologies. When I told him that I was interested in the metabolism of dimethyltryptamine, he immediately told me that I could study the metabolism of DMT very easily and suggested some methodologies I may want to use. He also told me the way how to detect metabolites in the blood and in the urine, so I could work out the details. I understood from him that I could probably collaborate with some people on the second floor of the NIMH; that there is a normal volunteer group there on whom they were testing new drugs, and some hypotheses, and

that they also have a large chronic schizophrenic population. I teamed up with people there and studied the rate of metabolism of diethyltryptamine (DET) in normal volunteers and schizophrenic patients. We had some very interesting results that we presented at the Third World Congress of Psychiatry in Canada, in 1961. While I was in Julie's laboratory, Hoffer published a paper claiming that he detected adrenochrome in the blood of schizophrenic patients and he made a big claim that adrenochrome is, therefore, the schizotoxin which produces schizophrenia. Seymour Kety got involved in the discussion, and he said, "Listen, this is a very interesting and a very important finding. If it is true, it may be a breakthrough in psychiatry." But, Julie said that there was some deficiency in Hoffer's methodology and there is no proof about the presence of adrenochrome at all in the laboratory tests. There are no controls, so who knows what he is measuring. So, Julie said that we should check it out. I don't know exactly how Julie managed, but he got eventually two milligrams of adrenochrome and told me how to go on and develop the methodology using that two milligrams. Then I got busy and developed a spectrophotofluorometric methodology with proper controls. To prove that it was a sensitive and specific methodology, I showed that we could recover as little as 0.02 microgram of adrenochrome added to plasma and we could measure it. And, I said, "let us try some blood from schizophrenics and see if there's indeed something to Hoffer's claims that there is adrenochrome in their blood." We tested about six or seven schizophrenic patients at the Clinical Center; we collaborated with Irv Kopin who helped us to draw some blood, and then, we tested the blood samples. They were all completely negative. I don't know exactly how it was, but we got feedback from Hoffer, saying that only those schizophrenics have adrenochrome in their blood who are acutely hallucinating. As it happened all the patients at the NIMH were chronic patients who were barely hallucinating any more. Dr Kopin found out that across the street at the Naval Hospital they had a few acutely hallucinating schizophrenic patients, so we drove over and we drew some blood from them. We drove back to NIH and ran the samples through the test and they were also all negative. We were quite disappointed and thought, this is probably going to go nowhere, and were ready to drop the whole project, when our lab director, Seymour Kety, said to me, you know, Stephen, this is a very important finding, even though it is a negative finding, because it is important to make a statement and to publish a short note that there is no evidence that adrenochrome is present in the blood of schizophrenics. He said, it's an important negative finding that can prevent people going up a blind alley in a wrong direction and it should be published. So we published the paper in '58 in the

*American Journal of Psychiatry*. It was a one-page paper, and Hoffer reacted to it strongly. He was outraged. He wrote a letter to the editor of the *American Journal of Psychiatry* and we answered it defending our data. Subsequently, in the late '50's, in the pages of *Psychosomatic Medicine*, our paper and Hoffer's reaction spawned an open debate between John D. Benjamin and Abram Hoffer. Benjamin pointed out that the way "Szàra and Axelrod approached the problem of adrenochrome in the blood was the way to do research in this area," using careful controls and proper methodologies. It was a big debate but eventually it quieted down.

LH: Well, I think one of Hoffer's contentions was that it was a very fragile molecule and could be easily reduced.

SS: It forms spontaneously when an epinephrine solution is exposed to light for an extended period of time.

LH: By oxidation.

SS: It is an oxidation product. Julie Axelrod, at that time, was involved with mapping all the catecholamine metabolism pathways, identifying all the metabolites, and he said that there was no room for metabolism to any other substance, at least in the amounts, that Hoffer was claiming. Julie said that he could account for about 98 percent of the metabolites for epinephrine, so there's no room for adrenochrome. Anyway, the paper was published and that was probably the end of the adrenochrome hypothesis.

LH: Well, Abe Hoffer was an interesting person, wasn't he? He'd get an idea, a wild one, and think it was real. But one of the interesting things about Abe's career is that his most important discovery had nothing to do with psychopharmacology. It was that nicotinic acid reduces cholesterol levels.

SS: I knew that he was using nicotinic acid.

LH: He was using nicotinic acid in those schizophrenics and in the process they were doing a lot of chemical measuring and it turned out that cholesterol would go down and that was the birth of nicotinic acid as a treatment for hypercholesterolemia, which is still being done.

SS: That's interesting.

LH: It's a very effective agent, so, that's a paradox in his career. Now, you were doing all this work while you were at St. Elizabeth's, you had a nice building there where they had laboratories on the first and top floor and the wards in between. Did you run across Tony Hordern at that time, the Australian?

SS: No, I don't think so.

LH: Well, he was a clinician, so you might not have, but didn't you write a book with Weil-Malherbe?

SS: Weil-Malherbe, yes. That was at the end of my stay at St. Elizabeth's in the late 1960s that he asked me to collaborate with him. He was very much into the catecholamine business and he asked me if I want to join him in a book, which was entitled *The Biochemistry of Functional and Experimental Psychoses*. He reviewed the functional side of it, focusing on the biochemical aspects of psychoses.

LH: It was a review of almost all the biochemical aspects.

SS: It was a very nice book. I wrote a chapter in it on the experimental psychoses, produced by drugs such as LSD and DMT and reviewed that literature. Now, you would think if you write a review book like this, it becomes just another publication in the literature and then people forget it. You know, we also forgot about it until about the end of the 1980s. In the meantime eventually some of the ideas which were discussed in that book apparently inspired David Wong. I don't know if you know him, from Eli Lilly. He is one of the pharmacologists at Eli Lilly, who had developed Prozac (fluoxetine). He apparently did give credit for the inspiration that he got from that book for the development of Prozac several times in his publications, but we didn't know about it until the middle of November 1990. When Dr Wong was giving a lecture at the NIH about developing new drugs and, at the beginning, he had the cover of a book on the screen for several minutes while explaining how important that book had been in inspiring him to work on new selective serotonin reuptake inhibitors such as Prozac. I didn't know about this at that time; I wasn't there, but people from the institute would come back and tell me that your name was on the cover of the book, and you were credited for the inspiration in the development of Prozac.

LH: Did they have any idea of the importance of serotonin?

SS: The importance of serotonin is an interesting question, because most of the medical literature in psychiatry at that time was focusing on the catecholamines, while the serotonin was kind of pushed into the background, and our review that we have done with Hans Weil-Malherbe was covering both sides. Hans tried to make a very balanced review of the involvement of both serotonin and catecholamines, and he made a point that transmitters probably don't act just alone, but are interacting with each other, and serotonin may be just as important as catecholamines. He also reviewed some of the early biochemical findings in depression and in schizophrenia. So, he

gave a balanced picture and Wong apparently picked up on this, you know, because I think it was a very interesting statement in Hans Weil-Malherbe's chapters, that the metabolism of tryptamine was reported as changed in depression.

LH: I think the reason you probably didn't follow the line with emphasis on catecholamines was because in Europe, there was much more interest in serotonin, and both of you were primarily transplanted. I think that gave you a broader perspective than if the book had been written by a purely American author.

SS: I think you are right about the European emphasis on serotonin. It was Garattini, who was interested in serotonin. He invited me to present my paper on dimethyltryptamine in '57 in an international meeting in Milano. I don't know if you were there. That was a symposium organized by Silvio Garattini on psychotropic drugs. It was published in a monograph form. It was the success of the Milan meeting that led to the founding of the CINP, the Collegium Internationale Neuro-Psycho-Pharmacologicum.

LH: This was about in?

SS: 1957, in May 1957. Garattini invited me to present my dimethyltryptamine work, and I had chosen to talk about myself experiments with the four hallucinogens: mescaline, LSD, dMT, and diethyltryptamine. I made a comparison, as concise as possible, on the basis of my personal experiences. And I think it was in that meeting that I met somebody from Joel Elkes' lab who interviewed me, and, based on that particular interaction, Joel Elkes hired me without actually seeing me.

LH: Somewhere along the line you learned English.

SS: When I was in Berlin, I had a girlfriend, a German girlfriend, who could speak English, and we went over my paper that was written in English, so that I could learn how to pronounce the words. So, eventually, I gave my paper in Milan in English, but I learned to speak English only after I came here. Obviously, you don't learn a language that late, I was thirty-something, without keeping your accent.

LH: I always remember Dan Efron's famous statement, "The international language of science is broken English."

SS: That's very true.

LH: How long did you stay at that laboratory?

SS: About ten years.

LH: So, that would be '58 to '68.

SS: About '69.

LH: And, did you continue, during that time, mostly your work on hallucinogens?

SS: Mostly hallucinogens. We did some very interesting clinical work, as well. I don't know if you want to hear about that, but we tried to test the effect of diethyltryptamine on alcoholic patients. There was in the literature a claim that LSD and the so-called psychedelic drugs could be very useful in treating alcoholics.

LH: Again, Abe Hoffer and a couple of other Canadians...

SS: A number of claims had been made, so we decided to test to see what our drug could do. We set up a team that consisted of a psychotherapist whose his name was Vourlekis, and another fellow who came to work with me, whom you knew very well, because he has also worked with you, Lou Faillace. We decided to do a double blind study on alcoholics, using what we called an active placebo. The substance we used was a derivative of diethyltryptamine, namely 6-fluoro-diethyltryptamine, in which we substituted the 6<sup>th</sup> position of the indole ring with fluorine. It turned out to be a substance which wasn't hallucinogenic any more, but still produced some autonomic effects so the patients felt that they received something. We had, I think, maybe a dozen patients who were chronic alcoholics for about four to ten years, and the psychotherapist, Vourlekis was involved with the patients until the effects of the drug wore over. He also conducted most of the tests and followed up the patients. We thought we did see some improvements, but they were, unfortunately, only temporary, lasting for about six months. We did a follow up two years later, and those patients who received DMT did not differ significantly from any other alcoholic patients in their drinking habits.

LH: It's surprising that you mentioned Lou Faillace. I'd never heard of him until I did some work with STP (2,5-dimethoxy-4-methylamphetamine), the amphetamine homologue. Sol Snyder was working on it as well at the same time. When I visited Sol in Baltimore, and said, well, there's no use publishing our papers separately, at least for the preliminary report; why don't we combine them? So, the paper came out, Synder, Faillace and Hollister. I didn't know who this Faillace guy was. I guess he was a fellow at that time, doing the clinical work. And as luck would have it, in 1986, when I decided to leave California and come to Houston, Faillace became my boss. He was the Chairman of the Department I joined there. So, I guess the moral of the story is, treat all of the young people gently. You never know when they'll wind up as your boss.

SS: I met him again recently. NIDA organized a meeting on hallucinogens and Lou was invited and I saw him at the meeting. That's when I last saw him.

LH: Well, I was made interested in LSD in alcoholics through a group led by a guy, who was essentially an engineer, named Hubbard (not Ron.) They were going around the country charging people \$600.00 a pop for one session with LSD, with the idea that one session would cure you. So Jack Shelton and I did a study; and Joe Levine and Arnold Ludwig did a study; and perhaps it was your group, I don't know, it was a third group; all independently. None of us knew that the other was doing it. We all came to ultimately the same conclusion, and that was: although there might have been a transitory effect, it was not long lasting. And I think that sort of finished the idea off, but it's amazing, the story with hallucinogens, how they captured the imagination, and I guess it's coming back now, isn't it?

SS: Yes, unfortunately, I read in the newspaper, LSD is very easily available, and people take it without a second thought; they are there for the experience. It's unfortunate, but I hope that these drugs eventually may prove to be useful. They are very powerful drugs, as they do produce something in our brain that affects our mind and this interaction between the brain and mind is a fascinating phenomenon. I have a preoccupation about it, because I think that their major and most important effect is probably losing the ego boundaries. After you take LSD, you feel that you are one with the whole world, with the whole universe. When your ego boundary disappears, you feel one with your fellow beings, so there's a very interesting social facilitating effect there, which is probably there all the time, but we are not aware of it. The hallucinogens give us a key for getting into that particular part of our brain/mind relationship that establishes in our mind a certain boundary; of how far our ego is extended. When you drive an automobile, your ego includes the whole automobile and you are driving together.

LH: Another intriguing thing about LSD was that it would produce these profound mental effects in relatively minor, small doses. You know, 2 micrograms per kilogram was more than enough for a pretty good experience and, when you think of it, there aren't too many substances that have that potent physiological effect. I suppose that Vitamin B12 is one of those substances; 1 microgram per day makes a difference between having a normal blood count and having pernicious anemia. Another example is botulinum toxin, but there aren't too many compounds that are that potent. I think that LSD had the big attraction because it made feasible to consider that something like that, equally potent or, perhaps, even more so, could be produced endogenously and make people

schizophrenic. However, the endogenous psychotogen idea fell into disrepute and hasn't been followed up very much. A new interesting story I learned much later in life, Ernest Rutland, the Sandoz pharmacologist, had come by in Palo Alto and was visiting me, and he said, after Hofmann had his inadvertent experience with LSD, he decided he ought to take it again just to prove that it was that substance. He discussed with Rutland what the dose should be. Hofmann wanted to take about 200 micrograms and Rutland, being a cautious pharmacologist, said, oh, I think I'd only take 30 or 50. Well, Hofmann ignored Rutland's advice and, of course, he had a whopping reaction.

SS: I hear that Hofmann took 250 micrograms.

LH: If he'd taken the dose Rutland recommended he might have missed LSD's psychomimetic effect.

SS: Talking about LSD, a few years ago, in 1993, there was a meeting in Lugano organized by Sandoz to celebrate the 50<sup>th</sup> anniversary of the discovery of LSD and Hofmann. I think he was 86 at that time. He was still very alert and very up to date with work involving LSD and the ergot alkaloids, and he showed us a film about how he discovered LSD and what his experience was. It was very interesting to hear it from him on a first hand basis, you know, of how it was that he experienced it.

LH: Did you ever study psilocybin?

SS: No, I never got around to studying psilocybin.

LH: But, you did some studies with mescaline?

SS: The only study that I had done with mescaline was taking it and experiencing it. That was the only work I did with mescaline.

LH: Because they're all really a part of the same group, clinically, and virtually indistinguishable; although, the dose is different by orders of magnitude. The only person I know who is doing some work currently with hallucinogens, and we're sending him grant support, is a fellow named Rick Strassman in New Mexico or Arizona.

SS: Well, he was in New Mexico up to, I think, a year ago, and he moved to either Seattle or some other place. But at that time, I was in touch with him. He had called me up a number of times, because he's the only one who is following the DMT story in a very systematic fashion. He got around the bureaucratic red-tape that involves the use of these drugs, and eventually he established a good research group.

LH: So, after you finished at St. Elizabeth's in '68, what did you do then?

SS: Well, at that time, I was kind of pushed out of the laboratory. I don't want to name names, but it was a kind of difficult situation.

LH: Had Joel left by that time?

SS: Joel had left at that time, and other people also had to go. It was a difficult time, and I had to decide what to do now. A position opened up at that time at the Extramural Branch of NIMH. They had a Drug Abuse Center; the exact name was Center for Studies of Narcotics and Drug Abuse. Bob Peterson was involved in recruiting new people, and he thought that I could be useful to organize some new work there, so I decided to accept it, and I made the switch at that time. It was a forced switch, but I don't think that I have regrets because I got involved with some very interesting stuff. It was not only new subjects and new drugs. I had an opportunity to meet with a variety of scientists working in that area. I became first Chief of the Clinical Studies Section and, then, in 1974, when the Center was enlarged to become the new National Institute on Drug Abuse, I became the Chief of the Biomedical Branch. In the Clinical Studies section, which I first had, the main question, the main thrust, was to do some controlled clinical studies with THC (tetrahydrocannabinol) and marijuana. That was the first project I was involved in, and I remember reading in one of your books, which you had written at the time, that marijuana is probably one of the only drugs in which more experimentation had been done in humans first, rather than animals, or something like that. So, that was probably part of the impetus, among others, to do some more clinical studies and more controlled studies, because all the experimentations you referred to involved people taking drugs on their own, without knowing how much they were taking, without any controls. The main point was, you ought to do some controlled clinical trials and that was my first job. In the first year when I got involved with organizing the program, I was actually sending out RFPs, Requests for Proposal, to contract. We had contract money and we decided to do a number of studies. We got a group going at UCLA, Sid Cohen was the first principal investigator on that, and then, we had the San Francisco group with Reese Jones, and we also organized overseas studies, in which we decided to study the health effects of marijuana in long-term users in Jamaica, Costa Rica and also in Greece. So we had a number of studies.

LH: Epidemiological studies in Jamaica and Greece.

SS: Yes, epidemiological studies including the study of medical histories and health effects, if any, as a result of the chronic use. We have also supported a number of other grantees studying marijuana and THC and, eventually, we organized a meeting, I think it was in '75, held in

Savannah, Georgia, where we invited all the people who were involved in these studies, including you. You may not have been able to make it, but you sent in a paper, and we included that, indeed, in the meeting proceedings, as you were one of the first ones who studied THC. So, it was important to have a kind of documentation of what was known at that time about THC. This was also necessary, because in my capacity at NIDA, I was responsible for sending over to the FDA reports about basic laboratory studies on THC for the Master File that FDA has to keep for any drug that is being tested for potential therapeutic use. Eventually, THC has gotten an approval, in a capsule form, to treat nausea in cancer patients on chemotherapy; so that was the only medically relevant and important result of this particular study. We also had a grantee at UCLA, Donald Tashkin, who has done some very good work about the effects of marijuana and tobacco, separately and together, on the lung of chronic smokers.

LH: I think we can generalize and say, any time you take smoke in your lungs, it's bad for you.

SS: Yeah, that's it. Actually it is that simple, and it's costing us millions of dollars to document it, you know, and this is the result. So that was my role in the THC studies at NIDA that I had to follow very closely. It was very important to visit all of the sites occasionally.

LH: Well, the therapeutic use of THC or marijuana is becoming a very politically sensitive issue now in states that conduct plebiscites to approve its use without any scientific basis. It's rather remarkable that in spite of all the studies on the therapeutic uses, nobody has tried to assess smoked marijuana vs. orally administered THC.

SS: Maybe they have done that in our study at UCLA, in which Frank was involved.

LH: Who did it?

SS: Ira Frank. Ira Frank became the Project Director of the UCLA project.

LH: Years ago Ira incidentally found that THC lowered intraocular pressure.

SS: That was part of a study that compared smoked marijuana with smoked placebo and oral THC.

LH: I think glaucoma is a dead issue as far as therapeutic use of THC is concerned.

SS: Sounds like it is.

LH: Most people who have glaucoma are old, and I can't see old people wanting to be stoned all day while controlling their eye pressure.

SS: Yes, as a matter of fact, it is a very unpleasant side effect for those people.

LH: Traditionally, glaucoma has been treated with local instillation, and there are now a great variety of different drugs to treat it. Besides, I think THC is not much different from alcohol in terms of the reduction of intraocular pressure, but, again, who wants to be drunk all day, so I consider that a dead issue. The only three therapeutic issues I think that need to be resolved are smoked marijuana vs. oral THC in nausea and vomiting for people on cancer chemotherapy, smoked marijuana vs. oral in terms of appetite stimulation and weight preservation in people who have the wasting syndrome of AIDS, and possibly more studies, because there aren't very many, on its effect on spasticity, say, neurological diseases like multiple sclerosis or other diseases where you have muscle spasms. But, all the other indications, I think have died out by now, or are totally unrealistic. But, there could be a lot more done in that area.

SS: The only hitch is the FDA's resistance to having a drug that cannot be well standardized. To standardize a smoke is almost impossible, and the FDA is very reluctant to even consider a smoked drug to be used in any context, so that's the end.

LH: Okay, let's just go to some other area.

SS: I understand you want to have some discussion about all the drugs that I have been involved in. At NIDA, in the early '70s, the opiates came into focus, mostly as a result of Bill Martin's initiative that there are probably more than one type of opiate receptors. But at that time, there was no known isolated opiate receptor, not even a direct demonstration that opiates are binding onto specific receptors. In '71, we organized at the Center for the Study of Narcotics and Drug Abuse, a meeting with some, I think, 50 or so people attending. I don't know if you were present at that meeting, because it was all related, primarily to opiates. We had rounds of discussion for three days, on the questions of where should the Institute put its money, in terms of opiate research? How should we proceed? Some of the conclusions were that obviously the molecular aspects of the receptors would have to be worked out in a more detailed fashion and some money should be put in that area. And this is what happened. We did establish, I think it was in 1971, eight Drug Abuse Research Centers. Some of them were almost exclusively oriented to research on opiates, like Avram Goldstein's group and a few others, Sol Snyder's group, in the beginning, was not into opiates. They were into amphetamines, primarily, and into catecholamines.

LH: I was talking yesterday to Candace Pert.

SS: I saw her recently and I was reminded that she was working with Sol as a student at that time.

LH: She said after she'd been working on the problem for a couple of months and hadn't gotten any results, Sol got impatient and said, "Well, let's go onto something else."

SS: And, once they identified the opiate receptor with a reasonable certainty, using specific binding of radioactive labeled naloxone with very high specific activity, they managed to measure more reliably the localization and density of specific binding sites in the brain. That, apparently, eluded Avram Goldstein, who started this strategy of research earlier.

LH: Well, you know, there were so many people in the story of the opiate receptor and the endogenous ligands that it's hard to say who deserves the most credit, but I really think that Avram Goldstein was very fundamental in it, because he had started the research on the opiate receptor as early as 1971. He gave a paper at the IUPHAR meeting, in which the problem he had was distinguishing non-specific binding from a specific binding, but that was because he didn't have ligand with high enough specific activity. And, then, a year or two later, he came up and described something called a pituitary opioid-like material, which eventually turned out to be dynorphin, so he was right in the forefront, both in the receptor and the ligand area. But, almost simultaneously with Candace's work, along came Terenius and Eric Simon. And, of course, Kosterlitz and Hughes came in '75, I guess, with the endogenous ligand. He must have been involved in the beginnings with LAAM, L-acetyl methadol.

SS: Yes, Avram was very instrumental in pushing LAAM for the treatment of heroin addiction.

LH: Isn't it incredible, it took 18 years before it got accepted?

SS: There were a number of stumbling blocks as you are clearly aware. LAAM was not a clean drug in some sense, but everybody was willing to go along without any hesitation, until, eventually it became accepted. So, in 1975 and '76, NIDA was discussing, how we should acknowledge these people's contribution to drug abuse research and they established an award. I was asked to suggest who would be the appropriate persons to get an award, and we, apparently, settled on six of these leaders of research groups who were involved.

LH: The Pacesetter Award.

SS: Yes, it became known as The Pacesetter Award. Avram Goldstein, Sol Snyder, Eric Simon, John Hughes, Hans Kosterlitz and Lars Terenius, were the people who eventually got this award. It is obvious that Candace Pert was very upset, that she was left out of this group, and we did, indeed, have some serious discussion about it, but she was still a graduate student at that time.

LH: I remember the time when the older Governor Brown was governor of California. He made a famous statement in which he said, "Every time I appoint a judge, I make 99 enemies and one ingrate" and I think that's sometimes the way awards work, so you can't win. Well, you've had a long career both in clinical and laboratory research, as well as administration. What do you think we should do about the war on drugs? Are we going to win it, or are we losing it, or should we change our tactics?

SS: It depends on who you ask. If you ask me as a medical scientist, I would prefer that most of the available money would go to research on treatment and prevention. That would be probably better spent than putting all this money on airplanes and spraying the fields.

LH: So you would prefer treatment vs. interdictions?

SS: I would prefer that more money would be put in the treatment area.

LH: And, what's the evidence for the effectiveness of these treatments? Is it all that good, once you get past methadone?

SS: Probably not, but at least it makes some people, not everybody obviously, well enough to make a contribution to society, to take a job and be a useful citizen, even though they are on methadone or continuing methadone, but they are still more respected citizens than those who are just keeping on injecting illegal stuff.

LH: Naltrexone is an ideal drug for opiate dependence. It specifically blocks the receptor. It's orally active, fairly long lasting and you don't get high on it. Nobody ever gets addicted to it. So it's a perfect drug for treating it, but nobody wants to take it. The only people who benefit from it are the high-class opiate dependent people like physicians, nurses, lawyers, and people in general, who have a lot to lose if they lose their license. But if you don't have a lot to lose and you have only a very little motivation, as most of the opiate addicts do, it doesn't work.

SS: It doesn't give them a buzz, I think.

LH: What was it?

SS: Doesn't give them a buzz that they can get from methadone.

LH: Well, that's the beauty of methadone. Once you've got them hooked, they've got to stay with it, but the other problem is that as prevention, do you think a whole bunch of advertisements directed at kids are going to change the pattern?

SS: It depends on how it is being handled, I think. Some of the advertisements may provide some education, perhaps making these people aware of the dangers, especially if you have a child

involved, because they feel, themselves, as being invincible and think they'll live forever, so they don't care much about the dangers. But I think if the message is carefully worded and organized, it could be helpful for some people. It may not solve their personal problems, but it could benefit some people. I don't have too much hope for anything that would be spectacular in terms of cutting back on drug abuse. In a free society there is no way to have it policed effectively.

LH: The serious area of hope I think is with smoking cigarettes. There has been a gradual, but slow, decline in the number of smokers and, of course, in part, that's due to the fact that it'll kill you and you've got a constant attrition; but aside from that, I think the social pressures that have been put on smokers have had a very positive effect in either reducing the number of smokers or reducing the amounts they smoke. But that's taken a whole generation.

SS: What's interesting, I don't know if you were aware of it, but the situation you just described is probably valid only in the United States, and it may be completely different in other parts of the world. I can only speak from personal experience about the social attitude on smoking in Europe. When you go to Europe, there's cigarette smoking everywhere, and I really can get sick; I just go to a restaurant, and practically everybody is smoking around me, and I can't even smell the food. So society, in general, would have to recognize the potential problems, and I don't know what kind of public education would be the best, but apparently, some of those that have been effective in the United States could be tried. The social acceptance of smoking is still prevalent in Europe, and we're not even talking about China and some of the other countries, where people are still smoking heavily.

LH: I guess Japanese men have the highest rate of smoking of anybody and, yes, societal attitudes play a big role, but it works so slowly that one can't get very enthusiastic. Well, you had a very interesting career, spanning several countries and several languages. I think it's very remarkable, obviously. Now, when you left Hungary, you left by yourself and no other family? SS: Yes, I left Hungary by myself and I got married here in the States. LH: Do you still have family there?

SS: I have a sister, who stayed back in Hungary. As a matter of fact, there were five children in our family and every one of us is ended up living in a different country. My older sister is still back in Hungary. My second sister is in Berlin, Germany. My third sister is in England. Unfortunately, she had a stroke, but she's still alive. My brother is in Switzerland, and I'm in the United States.

LH: The Szàras are worldwide. Well, I think you can be proud of what you did, and I hope that you will keep active and interested in the field from now on.

SS: I'm trying to keep up with the research literature. In my spare time, I have a little computer and I'm trying to work out a model for the brain/mind.

LH: If you had to do it over again, would you do the same career? You might have a few qualifications, but on the whole, what do you think?

SS: On the whole, I'm not dissatisfied with the way things have turned out. First, I was really fretting and I was very distraught, that I had to give up laboratory research, myself, back in 1970, but then, going into the administrative position, it gave me a slightly different perspective and a different way of leaving at least some of my footprints on the field. It was quite different than what, as a scientist, I would have been able to do. So, that's different. Eventually, I kind of settled down and made peace with myself that I did accomplish something in my life, and I think the field is now moving in almost breakneck pace, which is tremendous. The only problem is that we are now deluged in a sea of data, and we need some guiding principles or new tools, which would be more relevant, more appropriate and more effective in trying to bridge the gap between where the drugs act at the chemical level and, eventually, they give rise to a behavioral response or subjective experience. How this gap could be bridged is going to be a major problem in the near future in our field, so we really need some bright ideas of how a drug acts on a receptor as a chemical, how it is translated or transformed into thinking, feeling, and eventually action and behavior. So this is a major gap, which is still needed to be bridged. There are major advances in the area of brain imaging, like the PET scan and fMRI, where we can actually look into the brain and see the areas that are lighting up as a sign of increased blood flow, presumably as a result of increased neuronal activity. These are very interesting new tools for getting a handle on what's happening in our brain when we give a drug, but there is still no connection, from the chemical level to the more global, neuronal population level, so these gaps would have to be eventually worked out before we can begin really making a major push forward.

LH: Well, maybe molecular biology is the answer.

SS: That's probably part of the answer, but not the total answer.

LH: Thank you.

SS: Leo, it was a pleasure. Thank you very much for spending the time with me.

LH: Yeah, I don't know where time goes, you know.

SS: We may meet some other place and bump into each other as we did in the past, in Copenhagen or in Quebec, all kinds of interesting places.

LH: Well, I'll probably go to the CPDD (College of Problems of Drug Dependence) meeting in Nashville this year. I've been cursed with poor health for the last three years and I had to miss the last two meetings, but I'll go this time, maybe.

SS: Well, I will not be attending, but I will probably go to the ACNP meeting in Hawaii.

LH: Well, if we'd known you were going to be in Hawaii next year, we'd have done this interview over there.

## 32. OLDRICH VINAR

LH: I am Leo Hollister and the date is the thirteenth of December 1995 and I am interviewing Oldrich Vinar\* from Czechoslovakia. Oldrich, you have had so many different jobs that I have lost track of them. Can you tell us what your jobs are right now?

OV: Well, I am a clinician but, nevertheless, my main duty now is to head the Joint Laboratory of the Czechoslovak Academy of Sciences and the State Institute for Drug Control. My duty has been to choose among the compounds which were synthesized in the Institutes of the Academy and identify those which might be developed for clinical use as drugs. But to tell the truth, the time I spend in the laboratory is not the largest amount of time of my working hours because not many compounds synthesized could be considered as putative drugs. I spend most of my working time in the Prague Psychiatric Hospital where I am a consultant and where I see patients. And recently I started to work in my private practice for outpatients.

LH: Well, you have started from the ground from seeing patients with being a clinician, to having something to do with laboratory medicine.

OV: I have tried, yes. I have even done some work with experimental animals and on isolated organs, but my main activity has been always with patients.

LH: Now you are an MD, a Medical Doctor?

OV: Yes. I am a Medical Doctor.

LH: And, you are also a Psychiatrist?

OV: I am also a Psychiatrist, yes.

LH: So, where did you get your training?

OV: I graduated from medical school in 1949. At that time Czechoslovakia did not have many medical doctors, because during the 2nd World War the universities were closed by the Nazis. Czechoslovakia was occupied by Germany. And, so, when I had graduated at The Charles University,

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\* Oldrich Vinar was born in Brno, Czechoslovakia in 1925. He graduated from medical school at Charles University in Prague in 1949. Fortunately for psychopharmacology He worked in the Postgraduate Institute of Medicine in Prague in the Department of Psychiatry in collaboration with the Institute of Pharmacy and Biochemistry as well as the Czechoslovakian Pharmaceutical Industry. Dr. Vinar spent half a year in the Biometric Laboratory at George Washington University, in collaboration with NIMH. He was interviewed in San Juan, Puerto Rico on December 13, 1995.

I got a letter from the Ministry of Health that I have to work in a Hospital for Brain Diseases which was about seventy kilometers north of Prague, in a village Kosmonosy. When I came there, I met the Director of the Hospital who told me that there are about one thousand psychiatric patients and the only Doctor to take care of them is only himself, the director. At that time, there were only forty psychiatrists left in the country with fifteen million inhabitants before the war. It was so, because before the war the majority of psychiatrists in the country were Jews, and many of the others were left-wing intellectuals and communists. So during the war, the majority of them perished in concentration camps. This was the reason why I was sent by the Ministry of Health to the psychiatric hospital in Kosmonosy. During my studies, I wished to become a neurologist, so coming to the Hospital for Brain Diseases, I thought there would be neurological patients. It was a surprise to find out that I had to treat psychiatric patients. My first feeling was that this is terrible. What could two doctors, including one who just graduated from medical school and has no experience in psychiatry, do with one thousand patients. I remember that all that we could do was to move through noisy wards and select the most violent and most aggressive patients for ECT. We had to care for the somatic conditions of the patients, like a practitioner somewhere in remote mountains, and I had to do also x-ray examination and dentistry.

LH: Dentistry!

OV: Dentistry, yes, and I even had to help some of the patients give birth to their babies. In those years some of the female patients delivered their babies right on the wards.

LH: You were their primary care physician!

OV: Yes, something, like that. Well, this was the beginning.

LH: Well, I suppose it was your feeling that ECT at the time, was so traumatic that you would have liked to have a better way to treat them?

OV: Oh well, I had that feeling. Fortunately, soon the conditions improved; new colleagues arrived, we were allowed to invite consultants, and ECT could be done under general anesthesia.

LH: And, you knew, you no longer needed to worry about fractures of the spine and all of that.

Yeah. And, then, what was your first contact with psychopharmacology?

OV: Well, for some three to five years, we had to treat our patients with bromides and caffeine to comply with "Pavlovian medicine," forcibly introduced in Czechoslovakia in a doctrinaire,

Stalinist way. According to Soviet propaganda, “protective inhibition” by sleep is the best treatment in all branches of medicine, so, we used sleep therapy. It was a different kind of sleep therapy from the sleep therapy in Switzerland used by Klaesi in severe psychomotor agitation. His was like a long-term “narcosis”, whereas our patients were put to sleep for sixteen to eighteen hours a day. Early, we discovered that we could combine bromides and barbiturates with some antihistamines and that helped to keep patients sleeping. So, it was not such a big surprise to us when we learned about antihistamines being effective in the treatment of schizophrenia. So, this was my first contact with the new drugs.

LH: With chlorpromazine?

OV: First, with promethazine, and then, with chlorpromazine. It came to Czechoslovakia after a certain delay in 1954, especially because some of our pharmacologists thought that it was just a new kind of sedative, and that there is no qualitative difference between the old sedatives and this new drug. And by arguing with the results of the work of French psychiatrists, some of the Swiss psychiatrists, and then with the work of the Americans, we tried to persuade our authorities to import chlorpromazine and other phenothiazines. We had little success because of lack of money, and especially, because of ideological reasons. The trouble was that chlorpromazine and other neuroleptics or major tranquilizers, acted on the sub-cortex, and according to Pavlov the site of the mind was in the cortex, in the phylogenetically youngest and “progressive” part of the brain. Nowadays, it may sound ridiculous, but according to dialectical and historical materialism, the leading role of the working class is analogous to the leading role of the cortex in the brain. So a drug acting on the sub-cortex could not have a decisive role in the treatment of mental diseases. So we argued to find a solution that the cause of the disease is in the phylogenetically old sub-cortex, and we need to block this “bad boy” so that the cortex could win. I became more active in these negotiations when I moved from Kosmonosy to Prague and began to work in the Department of Psychiatry of the Postgraduate Medical Institute. I could also begin to collaborate with the pharmacologists at the Institute of Pharmacy and Biochemistry, which belonged to the Czechoslovak Pharmaceutical Industry. They were in the team of Mirek Protiva who synthesized tens of putative psychotropic drugs.

LH: Yeah, and were they all phenothiazines?

OV: The first ones were phenothiazines. I think it worked well for our pharmacologists and maybe even for clinicians that we had to study and become familiar with, so called “higher nervous

activity" and with "conditioned reflexes." So they were well prepared for behavioral testing of new compounds; perhaps better than in other parts of the world. I remember that when we compared the effects of promazine and chlorpromazine, we realized that addition of one atom, a chlorine element to a molecule, could enhance so much the action of a minor tranquilizer that it becomes a drug that has robust antipsychotic effects. So, I asked Protiva whether a second chlorine atom could be added and he synthesized dichlorpromazine. Then, to our surprise we noted that dichlorpromazine had the effect of a minor tranquilizer. We got scientific evidence for that when we performed one of our first double-blind multi-center clinical trials in Europe in which the clinical effects of dichlorpromazine and chlordiazepoxide were compared.

LH: Was it that the extra chlorine decreased the effects?

OV: Yes, and it didn't work at all in psychotic patients. Well, it had some effect in neurotic patients.

LH: I suppose reserpine did not play much of a role in psychiatry in Czechoslovakia?

OV: Quite the opposite, reserpine played an important role. For at least eight years, it was believed that that its therapeutic action was comparable to phenothiazines. The chairman of the psychiatry department at the Charles University Medical School believed that phenothiazines would go and reserpine would stay. He argued that reserpine is an alkaloid and pharmacologists know how to study alkaloids. He said that phenothiazines induced jaundice and allergic dermatitis, whereas reserpine does not cause such adverse effects. Reserpine played a significant role in my research. In the mid-1960s, we could work with LSD. It was synthesized in the Institute of Pharmacy and Biochemistry in Prague. We were too dependent on the import of LSD from Switzerland. I thought that the LSD-induced state was a good model for schizophrenia. I thought we can test new drugs using that model. If a newly synthesized compound blocked the effect of LSD it should be useful, based on that model, in the treatment of schizophrenia. Zdenek Votava, a pharmacologist, tested putative antipsychotics using the LSD model in experimental animals and I tested phenothiazines in healthy volunteers. Chlorpromazine worked best. It often blocked LSD effects. I thought, that if chlorpromazine given prior to LSD, would prevent the effects of LSD, it means that it would be effective as a prophylactic treatment in the prevention of relapse. I tried reserpine in the model and was disappointed. Reserpine did not block and did not prevent LSD-induced symptoms. My healthy volunteers and some of the nurses of my department participating in these experiments

were very unhappy. Some of them developed severe anxiety and depression that continued for three to four days.

LH: Well, from what we know now, its ability to release serotonin, you might have predicted that result.

OV: Yes, now this is well understood.

LH: Did you get your chlorpromazine from Rhone Poulenc or did your own Institute synthesize it?

OV: At first, we got it from Rhone Poulenc, but later we bought it in Hungary where they produced it commercially.

LH: Well, that was a revelation then from ECT to chlorpromazine, wasn't it?

OV: Well, yes, it was. I always have in mind my early experience about psychiatric patients who suffered very much before chlorpromazine.

LH: Well, it has been around now close to forty years, I guess, since you started with chlorpromazine. Have we progressed as far as you hoped?

OV: Well, I must say I think that we have progressed more than I hoped.

LH: More?

OV: Yes, more than I hoped. First, I did not expect that clinical experience would induce such a progress in understanding the mechanism of action of psychotropic drugs, which in turn, will teach us more about the activity of the human brain and lead to progress we have seen in the basic sciences. Also I did not expect that we would have drugs which could prevent relapse in a periodic disorder, like bipolar disease. And I did not expect that one of the most successful ways to understand the mechanism of action of chlorpromazine would be through its side effects.

LH: For a while there was a belief that you couldn't get the therapeutic effect until you got the extrapyramidal syndrome.

OV: In Europe, we have the concept of neuroleptic threshold of a German professor in Düsseldorf, Haase. According to his theory, you cannot have therapeutic antipsychotic effect unless the patient does not write in larger letters.

LH: Changes in handwriting.

OV: Yes. The patient tries to overcome extrapyramidal rigidity and writes larger letters.

LH: Now, what drugs came after phenothiazine in Czechoslovakia?

OV: The first drugs after chlorpromazine were not neuroleptics but antidepressants, for example, amitriptyline and nortriptyline. And, then, chlorinated amitriptyline was synthesized. Commercially, dosulepine or dothiepine, under the trade name Prothiaden has been most successful.

LH: And still used widely in Britain, I think, isn't it?

OV: Yes, the pharmaceutical company, Boots, bought the license and thanks to their marketing it is still around in many countries. One of the directions of my research was to investigate the clinical effects of new drugs. But, I think that what has been more important for me, are the by-products of this endeavor, namely that I was able to develop some new clinical methods. I was lucky that I could work with compounds synthesized by Protiva which were studied pharmacologically by Zdenek Votava.

LH: Now you mention Votava. Is he still alive?

OV: Unfortunately, he died about five years ago.

LH: Oh, I am sorry to hear that. He used to send the most wonderful Christmas cards with his enormous family.

OV: Oh yes!

LH: He was a fine man. He was the head of the Pharmacological Institute?

OV: He was not the Director of the Institute, but Head of the group working with CNS drugs.

LH: Now, how long did that Institute exist and when did it come into existence?

OV: Well, this institute was founded immediately after the war. It belonged to the Czechoslovak Pharmaceutical Industry. Votava worked part time at the university and part time in this Institute for Pharmacy and Biochemistry. So he often did both basic science, and the development of new drugs.

LH: I understand that the war and political situation had an important influence and Czechoslovakia has had its' share, first the Nazis and then the Communists, with a little brief episode of freedom. How do you weather these changes?

OV: Unfortunately, the influence on my work and my career was a great one. I spent about half of a year of my pre-graduate studies in Paris, at Sorbonne. In 1948, I wanted to stay in Paris and finish my studies of medicine there. Leaving Czechoslovakia for France, I did not formally end my University study in Brno where I had begun to study. My father was angry with me for this reason and refused to send me money to Paris, if I did not come back and settle the formalities. So

I came back. It was in February 1948. I left my things in the dormitory of Cité Universitaire and thought, well, I will come back in two weeks, but I ended up coming back after eleven years. In February of 1948, there was the Communist coup d'état and I couldn't cross the border for about eleven years.

LH: So, you were kind of a prisoner in your own country for a while?

OV: Well, this was the feeling I shared with the majority of Czechoslovak citizens.

LH: Now, that you mentioned you came to the meeting of the CINP in Washington in 1966, was that your first trip to the United States?

OV: Yes, it was my first trip to the United States. I still consider it as one of the most important events in my life, and a happy one. The opportunity to leave Czechoslovakia was due to the fact, that already in 1966, some sort of liberalization of the Communist regime could be felt. I also fulfilled one condition which facilitated the permission to go to the USA. I had the history of traveling to the Congresses in the Soviet Union, Hungary, Poland and other Soviet Satellites. The authorities just counted how many times you went to the East and how many times you went to the West. So, I could manage to come to this CINP meeting in Washington in nineteen sixty six. Here, I could meet you, Nathan Kline, Heinz Lehmann, Tom Ban and other colleagues. I got several invitations to lecture in some psychiatric research institutions and some psychiatric University Departments. I could spend about six weeks after the congress in the United States. I went to Boston on an invitation from Jonathan Cole, to Miami being invited by Burton Goldstein, to Minnesota having an invitation of Bertram Schiele.

LH: Minneapolis.

OV: Minneapolis, yes. I went also to California and spent some time in Palo Alto. So like that, I could learn much about the activities of people involved in psychopharmacology in the United States. Do you know what helped me to travel so much? I couldn't get enough dollars exchanged. As other Czechoslovak doctors, if I wished to participate in a Congress in a Western country, I had to produce an invitation with a statement, that the expenses would be covered by the organizers or with an honorarium. So I had to have such invitations already before going to the United States. This was another condition to get a stamp in my passport allowing me to leave Czechoslovakia. The honorariums stated in the invitations, ranged between twenty five and one hundred dollars. The problem was that after my lecture, I expected to get the money. I was asked

the number of my account in the bank. And, of course, it was not allowed to a Czechoslovak citizen to have a bank account in dollars.

LH: No, no, no!

OV: But, by chance, I was very lucky that I could buy a US airline ticket from Delta Airlines before my trip, in Prague, and pay for it in Czechoslovak crowns. This special air ticket entitled me to fly around the United States, wherever and whenever I wished for two months. So, when I left without money, I went to the nearest airport, and I ate on the airplane flying across the Rocky Mountains. Often I even had to sleep on the plane.

LH: I heard of people doing this on the subway, but not on the airline!

OV: Well. As you see, the airlines are more generous and more hospitable. Well, I must tell you that sometimes the colleagues, who invited me, loaned me the money when it could be arranged that the honorarium was deposited in their bank account.

LH: I guess the airlines still have those offers for visitors from abroad that you can buy an unlimited ticket for a while. Wow, that's interesting. Now, I know that you have had numerous offers to come to the United States permanently, but you have since actually stayed with Czechoslovakia. Is that because of your family?

OV: Yes, to a certain extent. But perhaps the reason was more my naivete and optimism and hope that political situation in Czechoslovakia would change to the better. I believed that the democratic tradition of the Masaryk's country would gradually overcome the Communist dictatorship. Even after the Soviet occupation of Czechoslovakia, when the W.H.O. organized a seminar in Belgrade in 1969, do you remember? We met at the seminar.

LH: I remember.

OV: It was about the methods of clinical psychopharmacology. I was invited perhaps because I published together with Zdenek Votava and Milan Horvath probably the first book on the Methods of Psychopharmacology. It was published by Pergamon Press in 1961. So, I came to the W.H.O. seminar. Some very important people participated, Michael Shephard from Maudsley, Jerry Levine, you, Max Hamilton, and also a representative of the World Health organization who—at that time—was a Russian colleague, Boris Lebedev. And, perhaps, because he had some guilty feelings because of the occupation of Czechoslovakia, he and you with Donald Klein and Jerry Levine helped me to get an invitation to work in NIMH in 1969. So, I spent about half a

year in Washington D.C. in the Biometric Laboratory of the George Washington University; which cooperated with the Psychopharmacology Branch of the NIMH.

LH: What was your duty in the Laboratory?

OV: Well, the laboratory had to develop a package of methods or techniques which would facilitate the analysis of data obtained during clinical trials. At that time, this was the same task I was working on in Prague. I developed the first version of a comparable package for Czechoslovakia in 1961. We had used it in several multicenter clinical trials organized according the model of the Veterans Administration clinical trials.

LH: Didn't you have a psychopharmacological institute organization in Czechoslovakia? They used to have a mid-winter meeting, as I recall.

OV: Yes. These were annual meetings. The first one took place in January 1959. The official organizers were the psychopharmacological sections of the Czechoslovak Psychiatric Society, of the Society for the Study of Higher Nervous Activity and of the Czechoslovak Pharmacological Society. All these societies were members of the Czechoslovak Medical Society J.E. Purkyne. Thanks to the different interests of the organizing societies, our meetings have been interdisciplinary. The meetings have taken place in Jeseník — Graefenberg, as the Germans call it, which is a spa and ski resort. We always organized the sessions in the morning beginning at eight o'clock and the afternoons were free, and then we had evening meetings beginning at five o'clock until ten o'clock P.M. But, do you know what also helped me to organize multi-site clinical trials in many psychiatric institutions which treated psychotic patients in Czechoslovakia? One of the conditions of the feasibility and success of the program was that the train going from Prague to Jeseník went very slowly and it took, at that time, about six hours. Now, it takes three hours by bus. Nearly all psychiatrists interested in psychopharmacology were on this train. And, as Jonathan Cole had to travel from one institution to the other in the United States to get in contact with the colleagues cooperating in the trial, I could do it on the train, and they couldn't escape. And so, I could say to a colleague, you promised to have at least 10 patients on drug A, B, or C and you have sent data on only about seven. What is wrong? Can I expect the missing data? There was also another fact which helped very much in research and which was unfortunate for routine practice. The supply of antipsychotic drugs, especially of those imported from the West was not reliable. Often, the doses had to be decreased or the treatment stopped, because the drugs were not there. But, if you wished to do something more for your patients, you could be sure to have the

drugs, if you got involved in clinical research and agreed to work according to the design of the study. The inclusion criteria were broad; usually it was sufficient that the diagnosis was among those for which the drug was indicated. Only patients with contraindications, e.g. hepatitis or Parkinsonism were excluded. As president of the Psychopharmacology Society, I had even an influence on the decision of which hospitals got the drugs irrespective of whether the drugs would be used for patients included in the trials. Nobody asked for any payment for participating in the multi-center clinical trials. They also were glad to be able to come to Prague or another city where training in the use of the rating scales was done. Also, they had their say when designing the trial and discussing the inclusion criteria, the appropriate rating scale, the forms to be filled in, etc.

LH: And, you could supervise the multi-center clinical trials from Prague?

OV: Well, I was not the only policeman. Chairmen of the University departments, senior consultants of the hospitals, and later my postgraduate students helped. Usually, they became authors of separate papers or co-authors of the final paper. Usually, its text was also discussed in the Annual Meeting in Jeseník.

LH: I know in recent years you have been active in pulling together a list of drugs that are available in other countries that are not yet available in the United States, and for various reasons, I guess. Do you think that we are missing out on anything that is very important or something that we really should have?

OV: Well, I do not think that it is very important, but it might be important for some patients. I am still surprised that you get the new drugs which were synthesized in Europe with a long delay which seems to me not to be necessary—even if I know about the “safety first rule” of the FDA. In the meantime, there are thousands of patients that can be treated in Europe and in other parts of the world. I think that the patients in the USA could profit from these drugs. Also, I understand that I got the invitation as somebody who knows much about European drugs, not only about the West European, but also about the Eastern European drugs. I came in 1990, oh no, it was in November of 1989 when I came to NIMH just to work. I came with a list of drugs which I thought would be important for American psychiatric patients and which had not been available for them.

LH: Well, the competition, you know, financial is so great in the United States. Unless you can come up with a drug that would sell one hundred million dollars worth, then, most companies just do not have an interest anymore.

OV: Yes, I understand that. If the FDA wishes to have the drug also tested in the United States, it is very expensive for companies. For European companies, there is a minor risk that if they do not get the drug registered by the FDA, then the drug might lose face in Europe. I think that this is the reason that it operates so slowly.

LH: Well, for instance, sulpiride, which has been around for quite a while, I think that this has been offered to almost every major pharmaceutical company in the United States and nobody has picked it up. I think that is largely because they just didn't see enough of a market for it.

OV: Yes. I know the opportunity to do clinical trials is easier when the drug is approved as an investigational one. I do not know whether it could help with the aim of introducing the drug to the market when the industry is not interested.

LH: How did Czechoslovakia deal with clozapine?

OV: At least twenty years ago, we had made some clozapine trials. I compared it in a double blind trial with chlorpromazine. The interest in clozapine subsided when it turned out that the risk of agranulocytosis was high. Nevertheless, it remained attractive because of the lack of the extrapyramidal side effects. European psychiatrists did not find that it worked in pharmacoresistant patients suffering from schizophrenia. Even the advantage of the lack of extrapyramidal adverse effects, could be questioned. No statistically significant difference in their intensity or frequency was found in my double-blind trial when compared to chlorpromazine. Other clinical investigators compared clozapine to haloperidol — and there, the difference has been found. Now, with the revival of interest in clozapine, it might help to introduce a compound synthesized in Czechoslovakia, isofloxythepine. It is a tricyclic with a five atom middle ring. It has antipsychotic effects with no extrapyramidal adverse effects. As far as I know, about five years ago, a Japanese company bought the license to develop it further — to my knowledge, they did not work with it, but developed their own original neuroleptic. So the development of isofloxythepine was delayed by these negotiations with Japan. Now we are trying to introduce it, but the synthesis is very complicated. Therefore, it would be expensive to produce; especially expensive, if it is produced only for Czechoslovakia. Our pharmaceutical industry is already in private hands, so the financial aspects are much more important than before our "Velvet revolution."

LH: I see. The other atypical that is catching on in this country is risperdal.

OV: We, and especially myself personally, have had some experience in the way risperidone has been developed. We got from Paul Janssen ritanserine, which is a specific 5HT2 antagonist. We have worked for about two years with this compound and found that when combined with haloperidol in doses up to 3-4 milligrams, the combination did not induce extrapyramidal side effects and it has good therapeutic effects in negative symptoms. I have been enthusiastic in recommending treating patients with this combination, increasing the dose of haloperidol in patients with predominantly positive symptoms and increasing the dose of ritanserine in patients with negative symptoms. I still think that it could have a certain advantage in comparison to risperidone, where the equilibrium of the 5HT<sub>2</sub> antagonist and D<sub>2</sub> dopamine antagonist action is fixed.

LH: To mimic the dual action of the Risperdal.

OV: Yes, of Risperdal, titrating the doses of ritanserine and haloperidol according to the amount or intensity of negative and positive symptoms. Now, we have everything in one molecule. I wished to organize another double blind trial comparing this combination with Risperdal. Not being in charge of an inpatient department and not having found colleagues who would perform the trial, I cannot tell whether the combination is really better.

LH: No, that is the first time that I have heard of combining ritanserine which is a HT<sub>2</sub> antagonist with haloperidol, which is relatively pure dopamine antagonist. Well, I suppose that your optimism that things have moved along the last forty years is justified, especially with the prospect that clozapine may, over the course of time, allow better re-socialization in schizophrenics than the other drugs. And, it does reduce the extrapyramidal reaction, but other than that, it has been hard to see a great deal of progress compared to what I think that most of us hoped for forty years ago.

OV: Well, maybe here I discuss some views of the perspectives in finding new drugs. My major concern is that we should find ways to treat patients with drugs we already have with better knowledge about the differences among them. I believe that there is more than a quantitative difference among antipsychotic drugs, and even more, that we still ignore the differences in the individual reactivity of the patients. Here it always is more art than scientific knowledge, when choosing the right drug for the right patient.

LH: That's tough! I have spent a rather unproductive decade looking for that!

OV: I know. I learned much from you, from Sol Goldberg and other American colleagues. I spent about twenty years trying to find the answer. I do not consider it a waste of time. The

experience taught me that we have to concentrate not only on the diagnosis, especially when the diagnosis has not been made reliably—even operationally defined in schizophrenia. I thought that symptoms, well defined in a rating scale, are more reliable. I used the data obtained during the operation of the system of continuous controlled trial. The main feature of the system was that all patients admitted to the ward were treated under strict double-blind conditions. At admission, every patient signed an informed consent, that he would be treated under double-blind conditions. Assuming that the affinity of an antipsychotic to a certain receptor is in relation to its therapeutic effects, I calculated the correlation coefficients between the effects of a range of six antipsychotics on symptoms, defined as items of our rating scale FKP, to the affinities of these drugs to different receptors: norepinephrine alpha 1, alpha 2, dopamine D<sub>2</sub>, histamine H<sub>1</sub> and acetylcholine receptors. I had expected that the higher is the affinity to the receptor whose ligand is in relation to the pathogenesis of the symptom, the better should be the therapeutic effect against this symptom. Data from more than 700 patients treated with six antipsychotics were used. From 70 coefficients, 22 were found as significant with P < .01. I was surprised, that high affinity to the D<sub>2</sub> receptors correlated negatively with the therapeutic effects in incoherent thinking, disorientation, dissimulation, the neglect for one's own appearance, and in blunted affectivity. Then, I realized, that the symptoms with high correlation are negative symptoms of schizophrenia, where the blockade of dopamine receptors is in the cortico-striatal pathways. This is just one example of the use of data obtained in the course of the operation of the continuous controlled trial. One of its advantages was that we haven't had any differences between research patients and other patients in one ward, as all patients that were admitted had to be treated under double-blind conditions. And, this worked for about more than twelve to fourteen years. Like that, I had data on about eight to nine hundred schizophrenic patients and for about six to seven hundred depressed patients treated under these double-blind conditions. We always published our data on one drug which was tested under these conditions. I intended to do a general comparison among the effects of all drugs only when having enough of the data. For example, I tested how the system works by introducing one of the drugs after ten years again, and I could see the results were quite comparable.

LH: Yeah, well, we couldn't do that in this country.

OV: Well, it could have been very difficult to introduce such a system in a research institute in the USA, but in the USA, what happened in 1978 to me could not happen. My boss, the director

of the Institute, used all his political power and I was thrown out of the institute and I had to work as a doorman in a hotel for a short time. And even worse, all our data were lost. The data was left in the Institute, and somebody just destroyed it.

LH: What a pity, what a pity! Well, considering the political situation in Czechoslovakia you have done pretty well. I remember a doctor got on the wrong side of the authorities and was sent up into the mountains to a tuberculosis sanitarium.

OV: Yes, yes.

LH: Wasn't it one of the pharmacologists who had to treat tuberculosis patients?

OV: Yes, it was Professor Zdenek Votava, a leading Czechoslovak pharmacologist, a good friend of mine who cooperated with me frequently. Fortunately, the sanatorium in the High Tatra Mountains was built for patients with tuberculosis in the twenties and they were mostly patients with asthma in the eighties, so Votava could not catch tuberculosis.

LH: You were working under some handicaps but; although, I must say that your universal double-blind child, I would have loved to have that going.

OV: I still think that maybe I find the possibilities to resuscitate... to revive in some sort this system.

LH: What are your plans? Are you going to continue?

OV: I would like to use, not my own data, but the data from the literature, to calculate the correlation of the effects of the drugs on the neurotransmitter system to the effects of the symptoms. What I have done, just for six neuroleptic drugs, I would like to do now with more drugs with more different drugs. I would like to use data about the effects of different psychotropic drugs on symptoms as defined in the rating scales. FDA has such data; our Institute for the Drug Control has the data which are part of the registration documentation. Having this data, I would like to correlate the ranges of drugs arranged according to the magnitude of the decrease of the scores in individual items with their ranges arranged according to their affinities to the receptors of different neurotransmitters. This approach based on the effects on symptoms enables me to avoid nosological diagnoses. I do not believe that we will find the best drug for schizophrenia. I believe that a best antipsychotic drug exists for the treatment of patients with a certain pattern of symptoms and another antipsychotic drug is the best one for another pattern of symptoms. This could help also in understanding the role of different neurotransmitters in the pathogenesis of the symptoms.

LH: Well, what you are talking about, essentially, would be a new kind of new nosology where you would find the constellation of neurotransmitter's involved in the pathogenesis of the disorder in each patient and treat that rather than what the name of the illness is called.

OV: You have discovered my hope... or at least my dream.

LH: Is that your door?

OV: My ideology is behind that. Because, I think that in about twenty years we shall not have the nosological entities as e.g. depression or schizophrenia. Instead, we should have, perhaps, some dopaminergic, serotonergic or GABAergic disorder. I know it will be much more complicated. Nevertheless, I do not think that we are more clever than Kraepelin or Bleuler when trying to elaborate nosology of mental disorders. We should use what these psychiatrists did not have: the knowledge about the therapeutic effects of drugs. We can go back from the knowledge about their mechanism of action to the hypotheses about the pathogenesis of the symptoms... and hopefully from the patterns of symptoms to nosological entities. Imagine my thoughts....

LH: There is no question that the DSM and the ICD classifications have clarified our concepts, but they are still the old concepts and they don't break any new ground. What you are talking about would be rather a total departure.

OV: Such a new classification could be better than the old ones. There have been always discussions about what is schizophrenia. Now, we have a consensus about operational definitions. It means progress but now we have to go a step farther.

LH: Well, that will keep you busy for a while!

OV: Well, I am not sure whether I can get the data from the FDA or from our Institute.

LH: Any other thoughts you have about your career?

OV: I never have thought about my career... I was... too involved in the questions I wished to find an answer.

LH: Has it been satisfying?

OV: I think so. I am just curious; so curious that it has become my handicap. I am happy to present a paper or a poster in a Congress. And I stop there. I am lazy to prepare properly a paper because I read something new in *Science*, *Nature*, or in *Neuropsychopharmacology* and having new ideas, I begin to use the new knowledge in my clinical work. I was not lucky with politics, and perhaps, this has been good luck for me, that I have not lost much time with administrative work of a director or chairman of a large department. On the other hand, I was able to organize some work in

cooperation with many colleagues in my country. Unfortunately, Czechoslovakia doesn't exist anymore. We have the Czech Republic and the Slovak one, and I am afraid that to plan common projects will be more difficult. For example, we just have changed the name of Czechoslovak Psychopharmacological Society to the Czech and Slovak Psychopharmacological Society and we ignore the separation.

LH: You didn't split.

OV: No, we didn't split.

LH: Well, that is sort of ridiculous to take a small country like that and split it.

OV: Yes, it was not a good political decision.

LH: Yeah, that's too bad!

OV: Yeah.

LH: Well, I wish you.....

OV: Well, we remained friends.

LH: Well, I wish you luck with your new classification of illnesses, because I think that that is the way to go, and we need that kind of approach. Let me think back, Prague hosted the CINP in 1972?

OV: 1970.

LH: Yeah. Are you going to do it again soon?

OV: Well, we had a regional CINP meeting the last year in Prague. I am not sure whether the very large congress serves well the purpose they should. It's become more of a social event now.

LH: Yeah.

OV: The very big congresses could be good experiences for young colleagues just to get acquainted with the great stars. But, for me, the ACNP has still been the best meeting bringing the new scientific findings which can be discussed and keeping the social events at the margin.

LH: It is a doctor at his limit or capacity though.

OV: Even our Czech and Slovak Annual Meetings in Jesenik (Graefenberg) have been becoming a bit too big. Therefore, I am thinking of organizing a meeting for two to three hundred participants just to discuss the possibilities of how to distinguish between responders and non- responders in order to analyze the results of the trials according to this distinction. I am not sure whether we will find a sponsor for this meeting. It seems that the pharmaceutical industry is not much interested.

LH: No!

OV: But, we just wish to discuss the criteria of the outcome, who is and who is not a responder.  
So, this is what I wish to do in the next half year.

LH: You tackle seemingly simple problems that are more complex, the more you go into them.

OV: Yes, I know I do.

LH: But, they are necessary. Well, it has been nice talking to you and I am so happy that you can travel freely now and come to these meetings. Will I see you in Melbourne?

OV: Well, I am not sure! But, I would like to come again to the meeting of the American College.

LH: Well, you have an honorary membership anyway, don't you?

OV: Well, I am a foreign corresponding member.

LH: Well, OK.

OV: Thank you.

### 33. DAVID WHEATLEY

LH: We're in Waikoloa, Hawaii for the 36th Annual Meeting of the American College of Neuropsychopharmacology. The college decided some time ago to trace back the history of psychopharmacology and one of the media that are being used are videotapes with pioneers and old timers in the field. Today, one of these pioneers and old timers is David Wheatley\* from England, who has long been in our field. Welcome to Hawaii, David. You're no stranger.

DW: And, a very welcome is to be here, after England.

LH: Obviously, your English, I always think of that wonderful saying of Shaw's that every time an Englishman opens his mouth, another one despises him, but I don't think they have to worry about your accent. Were you born in England?

DW: Yes, I was born down in the west of England in Devonshire in a place called Exeter, and that's where I was brought up before I went to Cambridge. I went to Cambridge for the university and, then, to Guys Hospital in London, and I stayed in London ever since.

LH: So, you graduated from Guys Hospital Medical School?

DW: Yes, that's right, yes.

LH: And, then, what did you do?

DW: Then, I went into general practice and I was in general practice for a number of years, but I soon found that it was not really what I wanted to do. I was interested in research and particularly, the effects of drugs, and so, there was a chance meeting. So much in life happens through chance, doesn't it?

LH: You're right.

DW: Well, I met up with Kenneth Carter and he was, then, working with Smith Kline and French, I think he was, and he asked me if I could do some studies in my own practice. Well, it soon became clear that I was limited by the number of patients I saw, and so, I conceived the idea to get a number of other GP's involved in order to increase the number of patients in our studies. So,

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\* David Wheatley was born in Exeter, Devon, England in 1919. After training at Cambridge University and Guy's Hospital he became a general practitioner in London. He developed a consortium of 500 family doctors from all over Britain whose interests tended towards psychopharmacology, the first national collaborative enterprise of its kind in the world. This group became the only NCDEU research center outside North America, directed by a British general practitioner, and funded by NIMH for 12 years. Wheatley died in 2007. He was interviewed in Waikoloa, Hawaii on December 12, 1997.

I set up this group of GP's all over the country. At one time, I had 500.

LH: Good grief!

DW: And, we were doing clinical trials.

LH: Well, that was the very first concept of the multi-clinic study in general practice.

DW: Yes, yes, I think it was. But, of course, this was in all areas of pharmacotherapy; and it wasn't until I had, again, through Kenneth Carter, who's quite an influence in my life, an introduction to Jonathan Cole, who had suggested some studies with psychotropics, because at that time it was difficult to do such studies in general practice in the states. I don't think GP's were interested. There could have been problems; whereas, in England regulations were fairly lax at that time. A doctor working on his own, particularly in general practice, could more or less do what he liked. There were no ethics committees, no need to get permission from anybody and so that was how we got started.

LH: How many years had you been in this general practice group before you switched from drugs for hypertension to psychotropic drugs?

DW: I think I'd been doing that about 8 years. I can't give you a date, but it was around about 1960 that I switched over to the psychotropics, and then, changed the name of the group, which was called the General Practitioner Research Group, to the Psychopharmacology Research Group. And then, I was fortunate enough to get grants from the NIMH, which continued for 12 years.

LH: So, you switched entirely to Psychopharmacology?

DW: Yes, I switched, but not entirely. I still kept some of the other studies going and that's quite useful, because you got insight into other drugs that might have psychotropic effects like beta blockers, for example. I felt that it was worth keeping that connection, but my personal interest was in psychopharmacology.

LH: Well, in a general practice setting, the kind of drugs you could study would be those that are for conditions you see in general practice. You wouldn't have done any studies with antipsychotics, but you did some antidepressants, I suppose?

DW: Yes.

LH: And, a whole lot of anti-anxiety drugs?

DW: Yes, this was the main area. I can remember one of the first studies I did, and at that time, of course, many of the modern drugs were not available; we had barbiturates and we had

amphetamines, and I can remember doing a study with Drinamyl, a popular drug in England, known as "purple hearts."

LH: Well, that was dexamyl in this country.

DW: Yes, a combination of barbiturate with amphetamine, which seemed illogical, and one of the first studies I did was a double-blind comparison of Drinamyl, comparing it to its components in patients with depression and in patients with anxiety. By that time, I had met Max Hamilton, but didn't even know that he had a scale for assessing changes. That, all came, later. So, I was ready to do studies at a pretty early stage, there. By the way, amphetamine worked quite well.....

LH: I think they've been largely underrated.

DW: Yes, I couldn't agree with you more. I feel we could get over this problem of the lag period of two to three weeks before the antidepressants work with amphetamines, and we could use them just for that period to get an immediate effect.

LH: To get them moving.

DW: To get them moving. Yes, you put it so succinctly.

LH: When you did that study of amphetamines, barbiturates and a combination, how did it turn out?

DW: Oh, it turned out as one would expect it. The amphetamine was really better to terminate depression and the barbiturate to terminate anxiety, but from a marketing point of view, it was much easier to market a blanket preparation for all forms of anxiety and depression and to hell with the diagnosis.

LH: Well, I think, later on, Hanna Steinberg came up with a notion that the combination had some peculiar properties, but you didn't see that?

DW: I don't remember that we did. You must remember our methodology was pretty crude in those days.

LH: So, that was a good beginning. What was the first, what we call modern psychotropic drug you worked with?

DW: There was a monoamine oxidase inhibitor made by ICI which was never marketed. I don't remember the name of it. There were various tricyclics we studied. Trimipramine was probably one of the earliest ones I worked with. The barbiturates were on their way out. I was doing studies with the first benzodiazepines. In England, Librium (chlordiazepoxide) seemed to be the more popular; whereas, over here, Valium (diazepam), but, of course, they were both available. So, I

did studies with those. I did some sleep studies. They were still churning out barbiturates for sleep and I remember doing one sleep study with a barbiturate and we found it quite useful. We worked with a rather crude methodology. We didn't have polysomnographs in those days.

LH: No polysomnographs.

DW: Not in our pockets, anyway. Then, it progressed from there, I suppose. I worked with nearly all the new antidepressants as they came along and new hypnotics, too. In particular, I worked with the new benzodiazepine hypnotics. We go around in cycles, don't we? First, we have barbiturates and, then, they're out. Then, we have the benzodiazepines, and then, they are out. Now, we have the non-benzodiazepine hypnotics and they're not without problems. So, I was working with all of that type of drug. I was looking at various sorts of fringe areas, like premenstrual syndrome and assessing the effects of most of the antidepressants on that. I remember doing some studies on the menopause with tricyclic antidepressants and we had quite reasonable results; everybody seemed quite happy with them. So, I have got to the present time, where, now, I've just completed a study in Alzheimer's with donepezil. We have a problem with donepezil in England; it is too expensive.

LH: So, it's on the market in England?

DW: Yes, it's been on the market since April, but the government is doing its best to deter doctors from prescribing it because of the cost, saying, oh, its efficacy is not proven yet. It is proven and, certainly, the results of the study we did, which has now been analyzed, confirmed exactly what the American study showed. It gives you about an extra three years of functioning at the same level you were before deterioration takes place, and that surely is worth having. But, there's a big battle going on in England over the cost of it.

LH: Well, that's becoming an increasing issue everywhere, the high initial cost of drugs vs. the long term possible savings. There are these new so-called, pharmaco-economic studies.

DW: That was something we never had in the old days, did we?

LH: No, and the techniques are somewhat questionable.

DW: Yes, certainly. One of the adverse changes I have seen and maybe you have, too, is the amount of documentation that's necessary now in studies. Everything has to be checked and rechecked to ridiculous extent. Why do I have to write my name twice on the same form? Well, you know it. But, in these days I have an assistant, who sits beside me, and she fills in all the

headers and says, oh, you forgot to do this, Dr. Wheatley, and she remembers to get the blood test done and she remembers to give the patient the next appointment.

LH: She's a walking computer.

DW: That's exactly what she is, yes, but she looks all the better than a computer.

LH: Well, am I correct that you joined John Feighner's international group now?

DW: Yes, part time, in advisory capacity, yes. But, I still do a lot of independent work, myself.

LH: But, on occasion, you do studies with him?

DW: Oh yes, I'm doing studies with them. Not only do they provide all extra facilities, but they find the patients, too. We now have Andrea Shorts over there. I don't know whether you know her. She's full of fun. And, I don't have to bother about trying to find patients. They're just queuing up. They've already been partially screened over the telephone, so one gets very few rejects, and it really does make life a lot easier. It's like the old days.

LH: The old days used to be good.

DW: Why are the old days always better than the present days? They always are, or they seem so to people like myself.

LH: I suppose that the data you generated through your general practice group is perfectly okay for approval by the U.S. Food and Drug Administration?

DW: Oh yes.

LH: You follow the rules of the British equivalent?

DW: Yes, exactly. We have an Association of the British Pharmaceutical Industry and they lay down guidelines for trials, and so, all trials must be done according to those guidelines, which are very similar to FDA requirements over here. But, in fact, most trials in England are done to FDA standards anyway, because the US is the largest market and they're always looking to this as their main market, so they want to get it right as the word, goes.

LH: I used to study drugs, but these days it doesn't look to be very attractive, because the drug companies provide you with the protocol.

DW: Yes, right.

LH: And, then, you gather the data and they get it, so you never had a chance to look at it, yourself, in the aggregate.

DW: I couldn't agree with you more. In the old days, I did all my own analysis.

LH: What is done now, takes some of the fun out of doing trials.

DW: You see, sometimes I wonder that this is supposed to be independently analyzed, but it's a company statistician who's doing it and all you get is his results. He doesn't even provide you with his data sheet.

LH: And then, some of the companies in the US, at least, after the data is analyzed, will farm it out to some professional writing firm, and they'll come up with a final manuscript.

DW: Oh, yes. I try to resist that. As far as anything that appears under my name, I've written it.

LH: That's good.

DW: But, the pressure is strong, and sometimes, they say, well, we just like to alter the phraseology so it will fit in better with the other papers, or something like this. But, I do try and preserve that piece of integrity for papers that got my name on. And, I still try and do a bit of research of my own, but, of course, one is dependent these days on pharmaceutical grants. The poster I did here was something I devised completely, and then, I happened to mention it to a company, I won't mention the name, saying I was looking for some travel funds. And they, very generously, I must say, offered me the funds, but then, they said, well, could you put in a little bit about our drug. It wasn't that I couldn't put in a little bit about their drug, because, in fact, it's a good drug, but that was my poster. I never read a paper that's been written by somebody else.

LH: Well, I used to be on the road a lot giving talks and usually the local pharmaceutical representative would tell me his problems on the way to the lecture, and my reply always was, you can't rely on me to talk about your drug. I'm not going to do it. I'm going to talk about your drug in connection with the whole field, but I'm not going to single your drug out for any special preference, and the best you can hope for is some general good feeling if I make a hit, and if I don't, you're stuck.

DW: Well, fortunately, the two antidepressants I happened to be involved in, recently, they both have advantages, and so, I'm quite happy to talk about them.

LH: Which are they?

DW: Mirtazapine, which for most depressed patients is useful, because most depressed patients have a sleep problem and off their food and so they lose weight. Well, of course, it corrects both of those. But, it's not so good if you have a rather large patient, particularly if she's a lady, because she will complain bitterly of putting on weight, and it's not so good for somebody who's at work and falls asleep over her desk, which have had happen. So, I think you have to choose your patients fairly carefully. But, for the majority of patients it's good and it doesn't seem to

disturb sexual functioning, which is very important. With the SSRI's, I get a lot of complaints about that. In fact, people sometimes won't go on with them because of that. And, the other drug is hypericum perforatum, St. John's Wort, which has been in Germany for about the last 10 years, and I heard that in Germany it outsells Prozac. Now, when I hear a statement like that, I think there must be a reason for this, so I took part in a study that was done with FDA standards. And it did come out as good as the control drug, which was amitriptyline; there was no placebo in the study I was involved. But placebo studies have been done with it. The beauty of hypericum is, of course that it has no side effects at all and it's very, very easy to get depressed patients to take it. They think it's a natural product, and therefore, safe, but you and I know it's not so at all. Of course, they don't get problems in the first few weeks while they're waiting for the antidepressant effect. So these are two compounds, which I'm quite happy to talk about in positive terms. However, I did have a problem when they launched mirtazapine in England and I got the brunt of all the publicity, when the Sun, which is sort of a rag tabloid in England, I hope I don't get sued by saying this, found me out and said, Dr. Wheatley, can you tell us about this drug that makes you more sexy? And, I said, well, you certainly can't say that I said that; if you're depressed, it may. And, they wanted to run a great headline, you see, the new drug that makes you sexy.

LH: Hardly anything better you can say to sell a drug than that.

DW: No, no. It'll be interesting to see what happens when Sildenafil comes on the market from Pfizer.

LH: Unfortunately, those claims generally are overstated.

DW: Yes, they are.

LH: There's so much hype about all kinds of herbs and natural products these days that you tend to be skeptical, but if you look historically in medicine, many of our most important drugs have come from natural products.

DW: Of course, digitalis, morphine, reserpine and there are many others, too.

LH: For example tamoxifen.....

DW: I think there seems to be a move, now, to look more seriously at natural products and do proper studies as we did. Another one that was around when I went into practice was tincture of valeria that supposed to be a mild tranquilizer and used to help sleep. Well, I went to a meeting recently and somebody was reading a paper on tincture of valeria, reporting findings from a proper double-blind controlled trial with tincture of valeria against placebo, with sleep EEG recording

throughout the night, and showing it produced a selective increase in deep sleep and short wave sleep compared to the placebo. Based on that sort of study, it's good solid evidence that maybe there's something in it after all, and we should look at it and find out what the active ingredient is.

LH: Remember, if it's tincture, it has alcohol.

DW: It was a tincture that has been around, but I think for that study they had put it in the form of a tablet.

LH: I remember, god knows, it was about 60 years ago, when I was working in a drug store, we used to have valeria extracts on the market. We didn't sell that much of it, but it was available.

DW: I didn't use it much, because it did not seem to work, but that doesn't mean to say that it might work if it's given in the correct dose.

LH: Well, of course, most of these natural products don't appeal at all to the pharmaceutical companies, because they're not patentable. But, my guess is that there'll be a great rush if it turns out to say that St. John's Wort, or Gingko Biloba for Alzheimer's work.

DW: Gingko biloba, yes.

LH: They can look and find out what the active ingredient is, and then, synthesize something that's similar.

DW: As you know, one of our various esteemed colleagues is a firm believer in Gingko, to the extent that he's taking it himself. In fact, I thought I'd better start taking it, but, unfortunately, every preparation I've tried upsets my stomach. It gives me awful gut ache.

LH: I guess the trees grow all around, mainly in the US, at least in California. Well, you've seen them come and seen them go over the years.

DW: Hopefully, we'll be around for a little while, anyway, to see some more come and go, as I'm sure they will. I think one of the great tragedies, of course, of research on drugs is that you introduce it and it seems to pass every test, and then, years after, some side effect becomes apparent, it has to be withdrawn. I'm thinking of, I forget what the generic name was, but the trade name was Merital; it was an antidepressant.

LH: Nomifensine.

DW: Nomifensine?

LH: That's an example that things can unexpectedly go wrong.

DW: Exactly, but no amount of very careful testing could foresee that.

LH: They estimated that ten million people had been exposed before the cases with aplastic anemia, or whatever occurred. And, they had no choice. They had to pull it off the market.

DW: Of course they had to pull it back straight away.

LH: I imagine surveys were taken on pulling of fenfluramine.

DW: Yes, they must have done surveys.

LH: God knows how many people have taken it.

DW: I was doing general practice then and I was prescribing it freely all the time and I can't say I ever saw any great problems with it, but, obviously, they existed.

LH: It's a risky business.

DW: It is. And we talk about the good old days when it was so simple.

LH: In your days, have you ever had a drug you had to pull?

DW: No, I've been very lucky but it could easily have happened. I was once planning to do a study on thalidomide, and this was before anything was known about it and that, fortunately, fell through. That was the nearest, I think, I ever came to it.

LH: One of the saddest ways to develop a drug was the way they started to develop thalidomide. I think it was Merrell in this country that started developing thalidomide, and they were giving practitioners five bucks a head for clinical reports on using it as a hypnotic.

DW: Yes. I think that's what we were going to do.

LH: All you had to do is fill out a form about how well the patient slept after they took it and got five bucks.

DW: Well, I believe that for the elderly and, certainly, for male elderly, it was a very useful drug and they used it in old people's homes. It was far better than the barbiturates for calming them down at night and keeping them alert during the day. But, of course, give a drug a bad name, and there's no way to continue using it.

LH: Although, it's coming back as a treatment for, of all kinds of things, including leprosy.

DW: That's interesting.

LH: Well, I guess the closest thing to what you did in England, that I can think of in the US was what Karl Rickels was doing before John Feighner and some other people got involved.

DW: Yes, that's right. In the early days, he had a group of GP's, but they were a local group in his area in Philadelphia, and I think he integrated them with hospital psychiatrists, whereas my group covered every part of the nation in some ways.

LH: How do you keep track of some 500 practicing people?

DW: Well, they weren't all necessarily doing studies at the same time. I don't know how I was able to do it in the early days. There was no e-mail; there was no fax, there was simply, the mail and telephone, but I also think that things went at a more leisurely pace then. Well, we didn't have to fill in so many forms. My original form was a single sheet, which was perforated and all the doctor had to do was make marks on it on the perforations for analysis. The instructions were on the back of the sheet. A lot of my earlier work was done with rather crude methods.

LH: And, it worked. Sometimes I wonder if we're not overly meticulous, because despite all of the care that's taken, and trying to prevent some unexpected reaction, they still occur.

DW: They still occur, yes. I think the most that you can do is to take every precaution, but you're never going to be able to avoid them. I think you will never be able to devise an absolute fail safe method for clinical trials.

LH: And, when you get right down to it, as far as detecting organ toxicity, you're pretty limited clinically. We have the various blood tests, liver function test, urine analysis, but where do you go after that in any kind of reasonable way?

DW: Yes, exactly. Well, there's only one way and that's to study individuals over long periods of time, so you've given them treatment for a long time. Then, there is the question to whom to give the new drug? I suppose from an ethical point of view there can be many cases of drug resistant depression. I think you always have to balance. The old adage isn't that: the good of the patient against leaving the illness untreated.

LH: That's a constant problem, how much risk is acceptable.

DW: Exactly.

LH: Now, there's been a lot of talk about it, but not a whole lot done in this country, about so called Phase IV studies, monitoring patients on already marketed drugs to pick up a real odd ball complication that might not become apparent in the few hundred patients that were studied for the FDA. Have you ever done any work so called Phase IV study?

DW: No, I've never done a Phase IV study, myself. My group of GP's, were more interested in the shorter term studies because we have a reasonable reporting system in England; whereby, all practitioners have a supply of what they call yellow cards for reporting adverse effects and so they pick up quite a lot of information on long-term effects that way.

LH: Well, it's a wonderful way to gather information if you can get people to do it.

DW: This is a problem, yes.

LH: I think they've been more successful in England with the yellow card system than, in our country, the FDA with the adverse reporting system.

DW: Is that so?

LH: They put out a mailing every quarter with the forms, I guess, but I don't know how many replies they ever get.

DW: I think in our country they get quite a good return and it gives you some information.

LH: But, the question is what they do with it. They don't do a damn thing with it to alert the public, you know. If they would publish, periodically, all these reports in the past few years...

DW: Yes, I have a feeling it's put into a filing cabinet somewhere and maybe ten years later, something will be done.

LH: You know, physicians might not make the association between the drug and some clinical side effects they see, but if they know that there's been before a similar effect then they're much more likely to do that.

DW: That's exactly right.

LH: I remember in 1960, the AMA tried to get a reporting system, and I was there in review for those that came in our field and you got reports of Parkinson's from antipsychotics. But, of course you'd get all this drowsiness and coordination problems from somebody who's taken 5 drugs. It was kind of meaningless without some more information

DW: Yes, exactly. It needs someone with medical knowledge to coordinate such a program.

LH: Well, I expect you've been happy with what you've been doing?

DW: Oh, I've spent a wonderful life, yes, and one of the nicest things about it, if I may say so, is traveling, meeting my colleagues, meeting you in various places. I remember once, when we met in Yugoslavia, I know that you will remember that. What I always liked about ACNP meetings in the old days was the informal discussion around the swimming pool from about 2:00 to 4:00 where I always met people and talked to them, where I'd say look, I'm looking for someone to write a chapter in a book, and someone would say, I'm just the guy, and I didn't know about this. I think they got the timing wrong here to finish at 10:30 and, then, not start again until 2:30. It would be much better, I think, to go through to 1:00 o'clock and, then, have the break, and then, an evening session, perhaps at 7:30. But, they have two evenings for posters and then, a late evening session.

LH: Well, some of us old timers, a number of years ago, we sat down over a drink and decided we should try to organize a session the way it used to be, before we had to carry all these formal papers and slides. It was just people talking.

DW: Yes, exactly.

LH: It was just people exchanging opinions about a particular subject. One other thing about the program is the increasing time spent with pure science.

DW: This is what has bothered me most at this meeting. Most of it is beyond me.

LH: Yeah, that's right. You know, we used to have things that would be appealing to sociologists, psychologists.

DW: Exactly, and, now, it's dominated by basic research, and this isn't even research on humans. It's mostly on rats, and admirable though the rat may be, it's not quite the same thing. Yes, I agree with you, but it happens in all of the societies. In our own, BAP, our British Association of Psychopharmacology, exactly the same thing has happened.

LH: But, you haven't had a split off as we have had, with the American College of Clinical Psychopharmacology.

DW: No, I didn't know that.

LH: Oh, Don Klein spun off a new organization called the American College of Clinical Neuropsychopharmacology.

DW: That's most interesting, because when we started our BAP, British Association — we can't use the word, college, because we have the word college in England reserved for organizations that give degrees, so it'd be confusion—it was started by a group of clinicians, including myself, and Anthony Hoerdern, whom you know, and we rather overlooked the basic scientists. There was outcry, of course. And, they came along to us and said, we wouldn't have minded it if you had called it the British Association for Clinical Psychopharmacology. But anyway, we realized the error we made to let them in, but of course, they now dominate it.

LH: I'm not against having disciplines mixed. In fact, that's one of the big educational advantages of these organizations.

DW: You do need some input from basic science.

LH: But, you need a little more balance.

DW: I couldn't agree with you more. It's losing sight of what the objective is. The objective is treating a patient.

LH: It all boils down to that it's a very difficult task to get a balance.

DW: Yes, it's interesting to know what the mechanism of action of these drugs is, and it is certainly important to developing new drugs, but from your point of view and my point of view, when we are sitting with our patients, what we are interested to know how to make them better. We want to know the best ways of doing it.

LH: Well, I'm glad you found your career rewarding, as I think most of us in this organization have, and in your case, I think it's going to be good for some time, yet. You're not ready to become part of history yet.

DW: No, I don't think so. I don't see myself as a historical figure.

LH: Well, I don't know the threshold you have to pass to be that.

DW: I don't either. I'll worry about that when I find it. Meanwhile, I'll go on looking.

LH: Thank you for the interview. It's nice to see you.

DW: It was a pleasure. Thank you.

## 34. JOSEPH WORTIS

LH: Joe,\* I suspect you are the oldest living member of the ACNP, among other distinctions.

JW: Well, how old are you, Leo?

LH: I just turned 74.

JW: You're kidding! I'm 88.

LH: Well, by God, you're going very strong.

JW: I celebrated my 88<sup>th</sup> birthday by running 5 miles, so that I could boast about it for a year.

LH: You make me feel awful with the idea of running.

JW: I also say that at my age I have no difficulty remembering. I just have trouble forgetting.

LH: Well, what we're going to do today is to see what you can remember.

JW: Too much.

LH: You've probably got a lot.

JW: I'm writing my autobiography now and I've swept up all the material I have accumulated in my house and office, and as they say in the business, I'm overwhelmed by an excess of papers and I don't know how to use them all.

LH: Well, speaking of biography, when did you get started in medicine?

JW: Well, I was born in Brooklyn and I got a kind of scholarship that allowed me to go to New York University up at University Heights. I got my bachelor's degree there. Then, in the last year of my college, an English writer named Havelock Ellis brought out a book called *The Dance of Life*; he was a writer with universal interests.

LH: And, he was also famous for his book on sex.

JW: Sex, yes, but he was also a poet, a novelist, a literary critic, and literary historian; he was into everything. H. L. Mencken, the great iconoclast, called Havelock Ellis the most civilized man in England. And Havelock Ellis became one of my heroes. And I liked the fact that he was into

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\* Joseph Wortis was born in New York City, New York in 1906. He graduated in medicine at the University of Vienna in 1932. He trained in psychiatry at Bellevue Hospital in New York, remaining on staff until 1952. He directed the pediatric psychiatry division of Jewish Hospital in Brooklyn until 1968 and did similar work at Maimonides Hospital in Brooklyn until 1972. Until his retirement in 1976, he was chief of the Division on Mental Retardation at the State University of New York, Stony Brook campus. He began the editorship of *Biological Psychiatry* in 1965. Wortis died on February 22, 1995 in White Plains, New York. Interviewed at San Juan, Puerto Rico, December 12–16, 1994.

intending to practice. I was an English major, so it's no accident that I ended up being an editor, everything. I thought, how nice! I said, "I'd like to be a universal man, too." I was, then, majoring in English, so I suddenly switched to pre-med and decided I would be a doctor, too, never because I was always interested in writing and literature.

LH: And you do it very well.

JW: Then, I was admitted to Yale Medical School. They had a new dean there. I think his name was Gildersleeve, and he was insistent that prospective medical college applicants have very broad interests. And when they interviewed me, they liked the fact that I had been an English major. So I was admitted. But then, a schoolteacher of mine, a high school teacher, gave me a gift that allowed me to have my first trip to Europe. And I went to London, Paris and Vienna. And, in Vienna, I met a couple of Americans studying medicine there, who persuaded me to study medicine in Europe. I was adventurous and I followed their advice.

LH: You left Yale for Vienna?

JW: Yes. I sent a letter to Yale, saying, I was staying in Europe and that, maybe, I'd come back next year. And they politely responded, in effect, saying, to hell with you.

LH: They must have told you that.

JW: So, I studied in Vienna, in Munich and in Paris. I picked up foreign languages, which proved to be a useful acquisition. And I got my medical degree in Vienna. It took me five years under the European system, but I finally made it. In those years, students used to say that anybody who registers and doesn't drop dead is going to graduate. You could take examinations over and over again, so, once you were registered, you had it made.

LH: As long as you took the exams. When was it that you graduated?

JW: I graduated in 1932. When I came back to the States I became resident in psychiatry at Bellevue Hospital. Up to then, there was no psychiatric department at Bellevue Hospital or New York University. There was just a so-called, observation ward.

LH: Did you choose psychiatry because you wanted to become a universal man?

JW: Well, I felt that psychiatry was virgin territory. I had an uncle who developed schizophrenia before my eyes. I was raised in the United States by European-born parents. They did not have much formal education, but they liked intellectual pursuits. My mother was trilingual. She came from a French family, attended German schools and spoke English like an American. She was a constant reader and she encouraged us children to read when we were

toddlers. So I became a constant reader. My father's side was more working class than my mother's side, but they got very active in the radical movements of those times, in Socialism and so on. So I was exposed to a lot of stimulating influences. My father was a fine musician and singer. We had a lot of musical evenings at home. We'd have Italian pianists and German singers gather at our home; that was my background. I got accustomed to foreigners and always felt very international. When I elected to go to Europe, it was not out of line with the way I was brought up. I was brought up international and I was accustomed to hearing foreign languages.

LH: In fact, it almost sounds like you're more European than American.

JW: Well, paradoxically, I was raised in a Polish and Italian immigrant neighborhood and the only language my parents spoke to each other was English. I came from one of the few English speaking homes in my neighborhood, and since I read a lot and was articulate, my teachers at school always regarded me as very indigenous American. So, on one hand, I was exposed to international influences, whereas on the other hand, I acquired a great love for the English language, and I was immersed in American literature. I had both these influences.

LH: Now, what did you say, what year did you go to Bellevue?

JW: In 1932, and I was one of the first two residents that was ever hired at Bellevue. The hospital had only an observation ward in my time, where people picked up by the police were left to be observed, and to see whether they should be committed to a state hospital. The doctors who worked in the observation ward were called alienists. It was considered very unattractive work. They got salaries from the city as alienists. Then, the big middle building on 32<sup>nd</sup> Street was built, an 8-story building for a psychiatric institute under the administration of Jimmy Walker. It was a big graft job; they made fortunes on contracts. If they had anything that was expensive they put it into the building. The institute was run by a Napoleonic little figure without any scientific credentials. He was a very aggressive guy, his name was Menus Gregory. When they opened the psychiatric institute, he needed additional help. But since he couldn't pay for any more alienists, he got two young guys to put on white uniforms, Milton Abeles, who had just finished his neurology training at Montpelier, and me. And they called us residents, but they didn't pay us anything. We were the first two residents in a newly created, so called, psychiatric department. And the place was filled with patients. I saw an enormous number of patients. Menus Gregory was eventually fired for being a grafter. Soon after I started at Bellevue, I was awarded a Havelock Ellis and Adolph Meyer

fellowship that allowed me to go back to Europe for a year, where I studied at Queens Square Hospital.

LH: Neurology?

JW: Yes. And then, I went to Vienna to study neuroanatomy. It was then, that I had this exposure to Freud, which was to become the basis of my book on Freud. I kept a diary and published it 20 years afterwards because by that time it was no longer very personal to me.

LH: Isn't it you were analyzed by Freud?

JW: Yes.

LH: So, you were?

JW: Yes.

LH: I thought that was a humorous title for your book.

JW: No, that was the diary of my analysis with Freud, a daily account. I kept notes. Every day I entered notes on my little index cards that I carried with me. And that's the record of what he said and what I said. It is based entirely on index cards I had.

LH: Well, you started off with training in neurology and psychoanalysis?

JW: Yes. Some of the interesting persons then on the staff at Bellevue were Paul Schilder and his wife Lauretta Bender. I was assigned to Lauretta Bender's ward, and I remember the first thing she asked me to do was to draw blood specimens for Wassermann tests on every new patient. And most of the tests came back positive. Apparently, in my ignorance, instead of sterilizing I cleaned each syringe in alcohol after I used it, and as a result, the same red cells were utilized in the tests. So that was my first experience with Lauretta Bender.

LH: I hope nobody got syphilis.

JW: Paul Schilder used to take me around when he saw patients. He was kind of brilliant, but not a very systematic scientist, who tried to combine psychoanalytic insights with his knowledge of neurology. Schilder was a rather peculiar looking guy with a very high-pitched voice, but he used to delight audiences because his lectures were so excellent. While I would trail after him he would dictate notes to me. I picked up a lot of information at Bellevue, but I also brought information back from Vienna, like the news on insulin shock treatment, which I observed when I was there.

LH: You met Sakel?

JW: I translated Sakel's monograph. I introduced the treatment in this country. It hit the newspapers, and here I was in my 20s, thrust into prominence as the herald of this new, first

successful treatment of schizophrenia. And Karl Bowman, who was then chief of a psychiatric hospital, set me up with an insulin ward. People were flocking from all over the country to learn this wonderful new treatment of schizophrenia. And it was, indeed, a wonderful treatment.

LH: So, that was how you got into biological psychiatry?

JW: That's right, and then, Farrar, the editor of the *American Journal of Psychiatry*, asked me to write a chapter on insulin shock treatment in his *Annual Review of Psychiatric Progress*, but I didn't want to be an advocate of one particular treatment, so I suggested that he change the title to "Physiological Treatments." He agreed and for 20 years, I wrote an annual review on physiological treatments. About that time, psychopharmacology started. My reviews were probably among the most comprehensive reviews that appeared on psychopharmacology, because I knew foreign languages. I also developed the new technique of microfilming that fascinated me. So much, that I had a portable microfilming machine set up at the New York Academy of Medicine. I would check everything in the *Index Medicus* that appeared in a weekly basis that interested me. And I had my whole family sitting around the table, and my kids and my wife would slit out everything related to physiological therapies and mount them on index cards. Then, my secretary would go to the Academy of Medicine and she would photograph on microfilm every item I was interested in. So I could sit in front of my machine, turn the crank and review the world's literature in all languages. As a result, I probably had the most comprehensive reviews of these new approaches to treatment. I did that for 20 years. In fact, I just threw out, these past few weeks, the thousands and thousands of index cards left over from that period that I kept because I had hoped that, sometime, I would write a book on physiological methods of treatment in psychiatry. Now, to my amazement, Leo, when George Simpson, my friend, gave his presidential address here a couple of years ago on Treatment of Schizophrenia, he completely omitted any reference to insulin shock treatment that was one of the great historical developments in psychiatry. It was the first successful physiological treatment modality. We had of course Wagner-Jauregg's treatment of general paralysis with fever therapy. But compared to schizophrenia, general paralysis was a relatively rare disease. And George Simpson omitted any reference to its treatment with insulin shock. When I criticized him later for his omission, he said, there were no good controlled studies. But he was wrong! There were some very good controlled studies. It was not a universally accepted treatment but it was a remarkably good treatment that actually induced remissions.

LH: I guess the reason it never caught on too well was that it was fairly labor intensive.

JW: That's right, and because of the introduction of pharmacological treatments, particularly chlorpromazine.

LH: Tell us about that.

JW: At the time chlorpromazine was introduced, I sat on a therapeutic committee of the APA with Heinz Lehmann, who is European born. And he asked me whether I had heard about this new French treatment with Largactil (chlorpromazine), that's what they called chlorpromazine in France. And I said no. So, he said, "look it up, it's very interesting." A guy, a surgeon named Laborit, was developing it. So, I looked up the French literature, and included Largactil (chlorpromazine) in my *Annual Review*. So, believe it or not, the first reference in the English language to chlorpromazine was in my *Annual Review*. And, pretty soon after, I published this, Smith Kline and French got after me; Len Cook visited with me at my hospital to persuade me to use it. I was running a child psychiatric service, so I couldn't use it. But they were recommending Largactil (chlorpromazine) for treatment of nausea in pregnancy and so on. It was, actually, I would say, a very effective sedative, and it had wide applicability in a number of conditions.

LH: It was one of the first effective anti-emetics.

JW: Yes, that's right. I didn't have a big patient population. I had no inpatient service. So I turned the literature over to our chief pediatric resident, a guy named Jerry Schulman, who later became a psychiatrist, a rather well established psychiatrist in Chicago. He looked over the literature and he said, "I don't think much of it," and he wouldn't allow me to use it. But the first English language reference to Largactil (chlorpromazine) was in my *Annual Review*, and then for years I was covering a literature on psychopharmacology.

LH: Was that in about 1953?

JW: From about 1935 to about 1955 I was writing an annual review on physiological treatments. When Braceland took over the editorship, he changed the format of the annual reviews and it was discontinued. So my interest shifted to another area. I had several separate careers in psychiatry. In the years of the *Annual Review* people would look at me and think I was Mr. Physiological Treatment. And, when I was in the field of mental retardation for many years, they would think I was Mr. Mental Retardation. Then, I published a book on Soviet Psychiatry that got me into trouble. It came out in the McCarthy period and I was called before a Congressional

Committee and, they thought I was Mr. Soviet Psychiatry. And, then, I held a Fellowship for sex research and people would think I was Mr. Sex Research. So, I had all these separate careers.

LH: A complete man.

JW: Well, I like to do always a little bit of the out of the way and unexpected. It's more fun.

LH: Did you ever get around to studying chlorpromazine?

JW: Yes, I did some very interesting research with chlorpromazine. I was interested in brain metabolism and had a Warburg respirometer. So, I minced rat brains, added chlorpromazine to the vials, and found that chlorpromazine had a selective action on different parts of the brain. If I remember correctly, and this was many decades ago, it depressed metabolism of the lower structures and enhanced metabolism of the cortical structures. So there you could demonstrate, by metabolic study, its selective action. Also, I found, and I published this stuff but nobody paid any attention to it, that chlorpromazine has a biphasic action. In other words, if I sacrificed the animal at different time intervals after I administered chlorpromazine to it, I found that, at one time, in one phase, it would enhance respiratory activity, whereas in a few days, at another phase, it would depress it. I presented my findings at a meeting in Chicago and published it in the *American Journal of Psychiatry* but the work was never noticed, let alone replicated. But I did fool around with these kinds of studies.

LH: These were the kinds of biochemical studies in the beginning.

JW: Yes. I was in private practice at that time, and in order to pursue this research, I had to have a Park Avenue practice. People used to come in and lie on my couch and throw money at me. I didn't even have to listen to them. But I set up a Warburg respirometer in the laboratory in my office, and the rat man used to come around to deliver rats. I had a great big paper scissor, which I still possess, and used to cut their heads off with it. It was very cruel. I would split the skull and mince the brain. And I would do my work using the Warburg respirometer in my private office.

LH: While the patients were still on the couch?

JW: Yeah. I didn't even have to listen to them.

LH: Well, were you treating any of the patients with chlorpromazine?

JW: I wasn't very actively involved in using it in treatment. Well, I ran the insulin treatment ward, and then, I had something to do with the introduction of convulsive treatment. At first, we used Metrazol (pentetrazol), which in Europe was called Cardiazol. I was one of the very first to introduce convulsive treatment. So, I was in charge of both insulin shock and convulsive treatment.

Chlorpromazine came some years later, and I had my assignment, my ward where I pursued the things that I was doing.

LH: Now, were Metrazol convulsions preferable to electrically induced ones?

JW: Janice Stephens has reviewed Meduna's work currently. Meduna's idea was Pavlovian, although he didn't realize it. He observed, clinically, an incompatibility between epilepsy and schizophrenia. Now, Pavlov, who in the last ten years of his life turned his attention to human psychiatric problems, had reached the conclusion that psychotic states were states of internal inhibition. That was great insight, because the thinking in dreams is actually schizophrenic thinking. In his systematic observations, he observed negativism and other catatonic phenomena at a certain stage when dogs were going into sleep. Although Meduna was not aware of it, he used the Pavlovian paradigm of inhibition versus stimulation when he produced with his powerful stimulant convulsions to relieve psychosis. Now, Janice Stephens has just written an editorial, which I'm about to publish, saying that the most effective treatments of schizophrenia are with analeptics.

LH: Well, most of these drugs will produce seizures.

JW: I called her on the phone and asked, "Are you reviving Pavlov's theories?"

LH: She probably didn't even know it.

JW: Well, she said her library was burned up when her house was burned down, but she was very much interested in and remembered Pavlov's work. So, here we are! We've gone full circle so many years after Pavlov's death. His name is never mentioned any longer, but he has been a great influence in psychiatry. His work needs to be revived.

LH: I think he was the first Nobel Laureate in the field of physiological psychology, wasn't he?

JW: Yes, but he would have great difficulty getting his papers published nowadays. Of course, he didn't have controls and he didn't use statistical methods. He was just a good observer.

LH: Well, I did as many controlled studies as anybody in the world, I guess, but I've always said they cannot replace observations in research.

JW: There is nothing wrong with observations.

LH: Research begins with a good observation.

JW: Darwin's work was all based on observation.

LH: Well, I think the reason that ECT is not used so much anymore is that it's frightfully expensive by the time you have an anesthesiologist, and you have to have a recovery room and all that.

JW: I gave the treatment for decades and I never used an anesthesiologist. You don't need an anesthesiologist.

LH: I know you don't, but they made it the standard to use one.

JW: ECT produces instant anesthesia.

LH: I know.

JW: In fact, it has been used as an anesthetic agent. You know who used it? Walter Freeman. He anesthetized his patients by giving an electroshock, and, then, stick in his ice pick, rotate them through the orbit and produced lobotomies.

LH: That's right. But, as you know, they've raised the standards so high that it's almost impossible to do research.

JW: That's not raising standards. That's just, what I call hyperscience. What we're doing, we're overdoing something and making it incorrect.

LH: For ECT, I'm sure that's a deterrent, because in our hospital we figure, we don't want to do it despite the fact that we had a wonderful ECT machine. By the time you hire all these people, the cost of each treatment is about five hundred bucks.

JW: It's absurd. I used to give the treatment in my private office for 50 cents.

LH: I know.

JW: The patient would come in depressed and walk out normal.

LH: Well, it would be nice if we could get some chemical that would induce seizures that we would get us away from the electrical current.

JW: Well, Indoklon (flurothyl) was used as a convulsive agent. Now, Metrazol was used in Europe as a substitute for camphor. Camphor was used as a cardiac stimulant, but because it was administered in oil base it produced infections. They then developed the water-soluble substitute, which they called Cardiazol (pentetrazol). And, by the time that was done, they hit upon the idea of using this as a convulsive agent. When it came to this country, it was called Metrazol. And, when I started using convulsive treatment, it was Metrazol (pentetrazol) I used first. Then, Cerletti and Bini got the idea from the cattle industry, the butchering industry, to use an electrical current. They used to stun the cattle in the cattle pens with these prods, and then, they'd slit their throat and slaughter them. And many of the animals would go into convulsions after being stunned with the prods. So Cerletti and Bini got the idea of inducing convulsions with an electric prod. What we are using today we owe to the cattle industry. That's how electric shock treatment was developed.

And Kalinowsky and Impastato brought the news about electroconvulsive treatment from Italy, particularly Kalinowsky.

LH: I was going to ask you about him. How does he fit in the time frame we're talking about?

JW: He preceded me by, maybe, a few months in utilizing this treatment, but I was not far behind and so, I became Mr. Shock Treatment. I was pushing insulin shock. Everything was called shock. Well, insulin shock, obviously, is a misnomer, because there's nothing shocking about insulin shock. The term, insulin shock came from the internists, who were afraid of diabetic patients getting an overdose of insulin and going into what they called "shock," and so, that term was used. It was actually hypoglycemic coma. It was more analogous to sleep treatment. Now, I would say to you, Leo, one of the biggest challenges in psychiatry is to find out how insulin shock treatment works.

LH: Or ECT, for that matter.

JW: Or ECT, because if we discover the mechanism it works, we're going to have an insight into the nature of psychosis. But nobody is working on that.

LH: When you were studying in New York, were they using sleep therapy?

JW: Yes.

LH Did you ever use it?

JW: Paul Hogan took it up and used it at Ward's Island. He used protracted sleep treatment. It's very effective and it's cheap.

LH: I guess it's very labor intensive, isn't it?

JW: Well, its chief danger was the susceptibility to pneumonia, but then, with the development of antibiotics, that danger was reduced. It was also very Pavlovian. Pavlov had great confidence in the therapeutic effect of what he called "protective inhibition." Many of the animals, in whom he produced what he called neuroses, we would call them behavioral derangements, recovered if they were exposed to protracted sleep. He had the idea that there was such a thing as exhaustion of the nervous system, and that this could be relieved by protracted sleep.

LH: Goes all the way back to Weir Mitchell.

JW: Yes, Weir Mitchell was also on the trail of a good idea. There were so many valuable things in psychiatry, but people don't know of them.

LH: Well, that's what we're doing right now, preserving them.

JW: The history of psychiatry is full of fascinating ideas and pathways that we need to retrace.

LH: So, you got into biological psychiatry pretty early on in your career.

JW: Well, I don't know what your interest is in pursuing. I suppose your focus is on psychopharmacology. But I got into the field of sex research first, because I had that Havelock Ellis Fellowship. It has a curious history, which I described in my book on Freud. But, let me review the story very briefly. There was a famous and distinguished Harvard professor, Kingsley Porter. He was something of a prodigy and he produced a classic work on medieval architecture when he was still in his twenties. He was a person of great personal wealth, but he was homosexual. In those days, it was impossible for homosexuals to come out of the closet, and he was a very unhappy man. He was married and loved by his wife, who was devoted to him, and he confessed to her that he could not control what he thought was his inborn sexual drive. She was very sympathetic. He knew Havelock Ellis, and Havelock Ellis who was very advanced in his thinking, introduced him to a young man whose name was Allen Campbell. They became lovers and lived together for a short time in Cambridge. When Allen Campbell gave up this relationship, Kingsley Porter became very despondent. He was studying medieval architecture, and all the Gaelic crosses, in Ireland at the time. He owned a castle, Gleanveagh Castle, which he used as a summer home, and he also had a little cottage on an island off the coast of Ireland, where he would spend quietly the weekends, away from this big castle. And one morning, he threw himself from the cliffs. His body was never recovered. His bereaved wife asked Havelock Ellis how she could use some of her money to do something for the cause of homosexuality. She felt they were entitled to their own lives, to pursue their own destiny, because they couldn't help being what they were.

LH: Sounds like an enormously modern view, doesn't it?

JW: And Havelock Ellis told her that the best thing is to invest in a young man. Being the kind of person Havelock Ellis was, he had befriended me. We were corresponding. And I got this Fellowship to study sex research. Since I was at the beginning of my training in psychiatry, I would accept the Fellowship provided it saw me through my training period. Adolf Meyer was drawn in as another sponsor, or monitor. So I accepted this Fellowship under the joint guidance of Havelock Ellis and Adolf Meyer, and I had a long close relationship with both of them. At any rate, it was under the terms of this Fellowship that I went back to Vienna and went through an analytic training period with Freud. When I returned to the United States, I began to publish in the field of homosexuality. One of my first stops when I was returning from Europe was in London, where I called Adrian, the great physiologist. He was very nice to me. I was a young guy in my twenties.

I walked into his laboratory. He talked to me and he said, "Young man, the trouble with research in the field of 'sex' is that people think sex behavior is unconditioned. Well, it is really conditioned behavior." And that gave me the clue to realize when I studied case histories and met patients that, almost invariably, I could find the conditioning influences which created the homosexual pattern. Not only that, but I realized that heterosexual behavior was a learned behavior. Birds can build a nest and sing their songs through a series of chain reflexes, but human beings can't speak English that way. They have to learn it. Human beings can't build a house unless they learn it. And the higher, more complex forms of human behavior, and that includes sex behavior, are learned behaviors.

LH: So we aren't doing what comes natural.

JW: It seems natural, because we're conditioned so early. Well, the point of view I developed was at variance with the wishes and hopes of this widow, who regarded homosexuality as a congenital condition that needed to be treated with respect and forbearance. And, here I was, saying it is learned behavior. How do we raise our children? Do we let them practice incest? No, that's taboo. Do we let them masturbate? No, that's taboo. The whole so-called normal pattern of sex derives from a system of inhibitions, taboos and enticements. And that's how we become normal.

LH: So, being good means not having opportunity.

JW: After I pursued my interest and published on sexual behavior, I got into mental retardation and I developed my own views there as well. Now, we have the big hullabaloo over the bell curves. Well, I learned that Binet and Simon, who were first to measure IQs, never thought that they were measuring innate intelligence. They were tied in with the French educational system and they merely wanted to learn what levels students were at, so they could be approached on the level where they stood. They didn't think that where they were at was a measure of their inborn intelligence. They said explicitly, in their first monograph, that the IQ of people could reflect that they came from Algiers and didn't know the French language, that they had a hearing disability and couldn't learn properly, that they had an inter-current illness and lost time from school. They were quite clear that there are all kinds of reasons why people fall behind. They complained that Terman in this country was using these tests as a measure of inborn intelligence.

LH: So, it was the influence of the Stanford group that turned the IQ into a measure of inborn intelligence.

JW: Yes. It is the American style to measure everything, and to think it is the measure that is everything, without analyzing it. And now we have this book, which was a best seller, with the Bell Curve, imputing that the blacks and the minorities have inferior intelligence because they test low on the IQ scale. The trouble is their poverty and educational neglect. And this has become a serious problem in social policy.

LH: Besides, I'm sure there is a tremendous overlap between two bell curves.

JW: No mental test ever devised, actually follows the Bell-Shaped Curve. Even the best of tests have a bell and then, they have a drop, and then, they have a bump. The bump, I call the bump of pathology, where you find the encephalitis, the brain injury, the obstetrical injuries, and so on. As a result, all these tests are skewed to the right, because there's pathology and there's no balancing hyper-health, so that IQ's need to be interpreted.

LH: Of course, in those days, when you were working with mental retardation, it was still a pretty unknown field.

JW: It was opening up as a scientific field, because the tendency was to regard mental retardation as a kind of stupidity that people were born with. We now know there are a hundred or more conditions that produce mental retardation. I mean, your own son is an example. The reason I'm so friendly with your son is that he's my material. That's what I spent my life with. I like these people.

LH: Well, he's a shining star. Unfortunately, he's handicapped.

JW: He's limited, yes, but he's human and he's appealing.

LH: The trouble is, you can never be sure of the etiologies.

JW: The etiologies we have, probably in most cases are subtle, and they induce impairments. They are either genetic or toxic or birth injuries, but we seldom can make a good etiologic diagnosis. There are a number of specific etiologies but they are relatively rare.

LH: I would say probably 85 or 90 percent of the cases are still sort of idiopathic.

JW: I applied some of the Pavlovian paradigms, unsuccessfully, to see if I could tease out some basic pathophysiology that would explain mental retardation in different cases, but it was very difficult to do, and I don't think we were too successful.

LH: All right, now, we've got you through several careers. How did you get to be an editor?

JW: Well, that, too, is an interesting story. I did brain metabolism studies with Harold Himwich for years, using the technique of jugular puncture. He was then professor of physiology at Albany.

He had something to do with the earliest demonstrations that the brain only metabolizes glucose. Well, when he heard of the insulin shock treatment, he came rushing down from Albany to see if he could do brain metabolic studies on my patients, because, if, indeed, you lowered the blood sugar, then, you had arrested brain metabolic activity.

LH: So, he was puncturing the jugular vein and draining from it?

JW: That's right, and we measured the respiratory quotient and the oxygen uptake. He was one of those scientists who did everything himself. I remember the first day he plunged the syringe into the jugular and drew the barrel back and I was wondering whether it's going to be blue or red. To our great relief it was bright red, which means the blood leaving the brain had its oxygen in it. It hadn't been taken out. Brain metabolism was reduced almost to zero. That was the crucial test. And, then, we pursued that in all kinds of variance. Well, Harold Himwich was one of the first members of the Society of Biological Psychiatry. I joined the Society a few years after it started, just a little bit before he did. At that point, there were maybe 20 members and we would sit around an annual dinner and told dirty stories.

LH: That was the only biological society in psychiatry.

JW: Now, the original members were almost all neurologists, interestingly.

LH: Harold was an MD, though, wasn't he?

JW: Yes, he was an MD. Well, Harold was not one of the charter members. There were, I think, about 10 charter members, Neilson, Thompson, Bailey, Sam Bernard Wortis my cousin, and some others. They were all neurologists. Neilson had the idea that they had to look to neurology to explain mental illness. And, actually, the logo that's used is a neurological logo, based on a sketch that Papez, the neurologist, did from the basic structures of the cortex. That's the logo.

LH: When did the Society first start publishing the Journal?

JW: Well, it started publishing an annual program with abstracts of the presentations first. Then, as the Society got bigger, Henry Stratton of Grune and Stratton suggested that it be published as a volume. Jules Masserman had very close ties with Henry Stratton. Masserman is now dead, so I can now speak ill of him, because he's dead. The Latin motto is that say nothing but good of the dead, but I follow the opposite motto. Once they're dead, you can insult them. Masserman was a great careerist and he was bringing out an annual volume on psychoanalysis published by the newly formed Neo-Freudian group, the American Academy of Psychoanalysis. And he got the bright idea that he would persuade Henry Stratton to publish a volume on *Biological Psychiatry*.

Then he brought out the first volume. And Howard Fabing who was then president of the society did not like Masserman and what he was up to. He didn't like the idea of Masserman straddling two companion publications, one on psychoanalysis, which most of our members were not too sympathetic with. He had just read my Freud book and was enthusiastic about it and, to my surprise, proposed that I take over the editorship. So, for 10 years, I edited this annual volume. And during this time we changed publishers, from Grune and Stratton to Plenum, because Stratton was behaving like a kingmaker and we didn't like that. Plenum Press gave us more attractive conditions, and so, Plenum Press brought out this annual volume, which I edited for 10 years. And then, at one point, they suggested that we should convert it to a journal. Now, some of the old time members, like George Thompson and Bob Heath, didn't like the idea of a journal. They opposed it, because they thought it would run away and be too independent. But a number of the wiser members thought we could obviate that danger by making the officers of the society ex-officio members of the editorial committee, and conversely making the editor ex-officio a member of the executive committee, so that there would be some monitoring and control. And so, I became editor of this new journal and edited it for years until it became so successful that I couldn't keep up with it.

LH: Ending your editorship about 2 or 3 years ago?

JW: Yes.

LH: Well, it was a long period of editorship and it became a preeminent journal under your auspices.

JW: Well, my wife had died soon after I took on the editorship, and I also reached so called retirement age, age 65, almost 30 years ago, and though, I continued my connection at my university, I was not on salary. So I happened, by virtue of these circumstances, to have a lot of free time. There was very little money coming in. People think that it's very charming of me to have handled my correspondence with handwriting. I couldn't afford a secretary.

LH: You were the only journal editor I ever knew.

JW: Well, there was no money for a secretary. I used to do my duplication on a little Minnesota Mining heat processed duplicating machine. I'd run the papers through, a special heat sensitive paper, and that's how I kept my copies. They all turned brown in time.

LH: Are there any careers we've missed?

JW: Well, I have a secret career. I'm now writing my autobiography and I found hundreds and hundreds of letters, to my surprise, between my late wife and me. We met at age 16, and she was a wonderful person. My voice cracks when I talk about her. But, this is a unique record from a time when people didn't use telephones. We corresponded, so I have hundreds of letters of the correspondence between us.

LH: A lost art.

JW: Yes. The correspondence includes a very stormy period, when after years of being together, I fell in love with a German woman while we were in Vienna, and my wife decided to leave me and return to the United States, putting 3,000 miles between us. I had to pursue my medical studies but we continued corresponding. So our marriage began to limp after a while, because I was stuck with my medical studies and was kind of peeved that she ran off without discussing it with me, because mine was a transient infatuation, and quite uncharacteristic of me, the only time I ever did this. Meanwhile, she got involved with a couple of other guys, and when I returned to this country, she was about to marry one of them. I rescued her, to my good fortune, at the last minute. And we had 40 years of a wonderful relationship, all that is in my correspondence and it makes a great love story, a great soap opera.

LH: Sounds to me like your whole life was a soap opera, with many different episodes and a very charming one. Well, it was a pleasure talking to you, Joe.

JW: You didn't ask all of your questions.

LH: Well, hell, we don't go by questions. We go by what people want to talk about.

JW: All right.

LH: But, you gave us a lot of insights.

JW: Well, as I usually say when I finish a talk, I find myself in general agreement with all of the things I said.

LH: Well, I'm sure everybody is, too, and you know, we're so interested in kind of, what we call the pre-history of modern psychopharmacology, and your insights into some of the areas.

JW: I'm glad to be regarded as part of the pre-history.

LH: Pre-historical Joe Wortis.

JW: And as I've often told, I step up to the people here. The meetings are always stratified; the higher hierarchy always speaks to people on their level and, so on. Everything is stratified here, socially. So I would always get a laugh by stepping up to somebody and saying, ah, what can you

do to advance my career? Now, I say, which of you departmental chairman is in the collecting of antiques?

LH: Well, as long you keep running 5 miles on your birthday, I think you'll be around for awhile.

JW: I can boast about it this year, but I don't know about next year. We'll see. Thank you, Leo.

One year at a time.

LH: That's the way to do it.

JW: Okay, did I give you a good time?

### 35. LEO E. HOLLISTER: interviewed by Frank J. Ayd, Jr.

FA: Good day. I'm Dr. Frank J. Ayd, Jr. from Baltimore, Maryland. I'm an active member of the American College of Neuropsychopharmacology. It's my pleasure and my honor to interview this morning an old friend who has been active in psychopharmacology and was, at one time, the president of the American College of Neuropsychopharmacology. Leo Hollister\* is his name. He's been around a long time. Everyone knows who Leo is and everybody is familiar with most of what he's done, but not all, because he's done so much. So, Leo, let's start off with a little background. Where did you go to medical school?

LH: I went to the University of Cincinnati, largely because I couldn't afford to go out of town. I lived in Cincinnati. But the motivation of going to medical school, I think, began during my high school years of reading some of the publications of Paul De Kruif. He was a wonderful journalist, who wrote books called *Men Against Death* and *Microbe Hunters* and other rather inspiring tales of the accomplishments of medical research and medical progress. I think De Kruif probably had much more influence than anyone really believed, because I've talked to a lot of people who say they had the same experience. Did you have that?

FA: No, I personally, didn't, but I know plenty of people did. In fact, the *British Medical Journal* and *Lancet* recently had something about literature and medicine and they gave a lot of credit to De Kruif for, in a sense, converting a lot of people to become medical students, and even to going into certain specialties right from the very beginning.

LH: Yes. Well, that was my motivation. I didn't have a whole lot of money, though, to support my medical career. And it turned out that two jobs I got in the course of getting a medical education, in retrospect, seemed to have had a profound influence on the way my career has developed. During the pre-medical years, I got a job in a chain drug store nearby where I lived. I was kind of a general factotum, but most of the other employees were pharmacy students and

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\* Leo Hollister was born in Cincinnati, Ohio, in 1920, and graduated in medicine from the University of Cincinnati in 1943. He trained in internal medicine at Boston City Hospital and the Veterans Administration Hospital in San Francisco. In 1953, he became chief of the medical service of the Veterans Administration Hospital in Palo Alto, and remained there until taking a post, in 1986, as professor of psychiatry and pharmacology at the University of Texas Medical School in Houston. Hollister died in 2000. He was interviewed by Frank J. Ayd, Jr. at San Juan, Puerto Rico on December 9–13, 1996.

there was a registered pharmacist on duty all the time. So I got interested in drugs through that kind of contact. And then, after I got to medical school, I was running short of funds and word got around to the dean that I was considering dropping out and joining a program for training naval aviators, which, thank God, I didn't get into, because in those days, your life expectancy wasn't very great as a naval aviator. The dean called me in and found out what the problem was and he said, "I'll try to find you a job." He found me a job as a technician in the neuropathology laboratory, where I came under the influence of a very great neurologist, Charles Erin, a neurosurgeon, Joe Evans, and a whole group of people. Al Sabin used to come there and it was an inspiring experience, because the people from internal medicine, from psychiatry and from neurology attended the Neuropathology Conferences in Cincinnati, and that was almost unheard of to have three disciplines like this not only attending the same conference, but also collaborating in research. So, I think that's where I got the influence of the nervous system and the complexity of it and the desire to learn more about it.

FA: Then after you left medical school, what did you do?

LH: Well, after I left medical school, I finally became an internist, and one of the residents in my first year of training in internal medicine was Mort Reiser, who ultimately became Chairman of Psychiatry for many years at Yale. Mort had gotten interested in psychosomatic medicine, but I was interested primarily in general medicine, particularly hypertension. And, again, this was something of a probable influence in my career. Over the years, as an internist, I was trying all kinds of things to treat these hypertensives. In those days hypertension was a very serious matter. We could hardly budge the blood pressure, and sometimes they'd have a malignant hypertension and we knew damn well they were going to be dead within a few months. So I was trying a lot of things to remedy that, and eventually that is what got me into psychopharmacology.

FA: All right, Leo, where was this training going on?

LH: Well, I had an internship in medicine at Boston City Hospital, and then I went back for an assistant residency in medicine at Cincinnati before going into the Navy. Then, after discharge from the Navy, I completed my training in internal medicine at the Veterans Administration (VA) Hospital in San Francisco, which was then affiliated with both University of California San Francisco (UCSF) and Stanford. I got recalled into military service during the Korean War and decided that if we were going to have wars every five years, I would not want to try to establish a practice, but rather go into a salaried position with the VA. It turned out that the initial position I

had, which was in San Francisco, was far from where I lived near Palo Alto, whereas a chap from the Palo Alto VA lived in San Francisco. So we traded jobs and I became an internist in a psychiatric hospital in Menlo Park, California. The previous guy left about 250 unanswered medical consultations, which I tried to liquidate as fast as possible, but during the course of doing that, I learned that most of those who were in the hospital had hypertension. That came in handy, because –I guess this was in 1953 – a detail man from CIBA came and said, “We have a drug that we think is pretty good for hypertension,” and I said, “Gee, I’ve tried them all and nothing seems to work very well; let me try this one.” To give you some idea of how simple matters were in those days, he walked out to his car; he opened the trunk, and pulled out some reserpine and gave it to me. Within three days, I had new patients under treatment. So, about two or three months later, he came by and said, “How’re you doing?” And, I said, “Gee, that’s just fine. It works.” He said, “Well now, we’ve got word that it might be useful in psychiatric patients, this being a psychiatric hospital.” And, I said, “Well, I don’t know anything about psychiatry. I’ll have to find what the psychiatrists think about that.” I went to the Chief of Psychiatry and told him the story and he said, “Leo, we’ve had drugs come and go, and you know, they never amount to much. I wouldn’t waste my time.” So I asked some of the psychiatric staff, some of whom were golfing buddies. They said they wouldn’t mind trying this under my direction, and we said, “Sure, we’ll go ahead.” And that’s how I got into psychopharmacology. It was through reserpine being used as an antihypertensive, and then later on, as an antipsychotic drug.

FA: And, that was 1953?

LH: That was in 1953. In 1954, I became aware of chlorpromazine and, in the same simple manner as I did with reserpine I was able to get hands on that. Now, it turned out that CIBA had some interest in getting studies started with reserpine in California and they sent out a very admirable physician, named Dick Richards. Richards was a big guide in the proper use of reserpine, because I think in the initial studies that Nate Kline did, the dosages were very small, and by that time, they’d come to the conclusion that they should be larger. So we used the larger doses. Right off the bat I figured we should do double-blind controlled trials, which we did with both reserpine and chlorpromazine, using a dosage schedule where the initial doses are given parenterally, and then followed by oral doses. The parenteral dose is sort of loading them up, and then the oral is maintaining them. This worked pretty well. By the end of 1954, they were having the annual meeting of the American Association for the Advancement of Science (AAAS) in

Berkeley, which usually occurred during Christmas week, and I was invited to present my finding at that. That was the very first meeting that I ever attended in this field. I think it was organized by Jon Cole, who was a protégé of Ralph Gerard. That was an interesting meeting. I met a lot of people in the field, John Kinross-Wright, Nate Kline and Murray Jarvik, and a few others whose names escape me now. My initial meeting with Nate was very strange. I was sitting with Dick Richards and Nate came in. Dick got up to greet him, and did so with some difficulty, because he had had polio in one lower extremity and was sort of lame. I got up and we said hello to Nate, but Nate was very high hatted, you know, he didn't give us much heed, and proceeded on up to the front of the auditorium. I turned to Dick and said, "Is that guy going to get the Nobel Prize today, because he used your drug?" Well, it turned out it wasn't a bad hunch, because two years later, he got the Lasker Award for doing just that.

FA: Leo, if you did a controlled trial with chlorpromazine in 1954, it would be nice to know, if you can recall, what month? The reason I ask that is, I had tried to find out recently, for the talk I'm going to give tomorrow night actually, what it was like "back then", when we first started. Who did the first controlled study? And, what I learned was that Joel Elkes did a controlled...

LH: Crossover study.

FA: Yes, that's right.

LH: Joel did a crossover study, but ours was a parallel group design, the kind that is used even today. I started with reserpine. I would say, in the first quarter of 1953, and with chlorpromazine, say, about mid-year, but it's sort of hard to pin these things down, because it wasn't an original idea, by any means. Harry Gold at Cornell had promoted that design for years. The VA and Armed Forces had done a controlled study with anti-tubercular drugs around 1946–47. So it wasn't a novel idea.

FA: No, but it was the beginning of psychopharmacology. That's why I was trying to find out, precisely, who did it and when and where. Joel did his in England, in Birmingham.

LH: Now, as I understand it, his was a crossover study.

FA: That's correct.

LH: A variant of crossover design, he substituted placebo in patients who were already on a drug.

FA: But that was in the spring, as I understand it, of 1954. I'm going to confirm that when I see Joel, at this meeting. All right! Now, you, from the very beginning, got very active, but you started to write somewhat later.

LH: I was incredibly naive in those days. I thought, well, if you published something, it was there forever. It was written in stone and you didn't need to say it again. So, this conference at Berkeley at the end of 1954 was supposed to be published, and ultimately was, with Jon Cole and Ralph Gerard as editors of a book called *Psychopharmacology*, but the book didn't appear until 1957, and I don't imagine there are more than several hundred copies extant. So what I was doing was essentially kept a secret. I continued to do the work and expand the study with both of those drugs. But, I guess around April or May of 1955, the New York Academy of Sciences, under the direction of CIBA, had a second conference on reserpine. Now this time, they focused on the psychiatric aspect. The first one was more on hypertension. I was invited to that program. Nate was on the program. Tony Sainz, whom I've lost track of completely—Do you know whatever happened to him?

FA: Tony is dead. He died several years ago.

LH: And, I think Fritz Freyhan was on the program, and some of the other early people in the field.

FA: I was there. I didn't give a paper, but I was there.

LH: Oh, you were?

FA: Oh, yes, I was there, definitely.

LH: Well, for some reason or other, and I'm not sure just why, the paper I gave attracted the attention of the press and I was interviewed by all kinds of wire services, and the next thing I knew, every newspaper in the country was telling about this wonderful new drug for schizophrenia that Leo Hollister in Palo Alto had. And I was absolutely overwhelmed by the power of the press and how it influenced people with dire illnesses to seek help, because all of a sudden I was getting stacks of mail saying, "Can I bring my son, daughter, father or whatever, out to California and get this drug"? I made a policy of personally responding to every one of them, although some were rather formal letters. I said that there were no secrets in medicine, and I was sure the drug would be available in their locality and they should talk to their local psychiatric chapter and see what they could find. But, it was really quite humbling to see the enormous power that the press had to stimulate interest in possible treatment for a very serious illness. I suppose that still exists today.

FA: Well, I'm fairly certain it does. That happened to me in 1955, when I gave my first paper on chlorpromazine at an American Psychiatric Association (APA) meeting. It was picked up by the press and by the time I got home that evening, it was on the front page of the *Evening Sun* in

Baltimore, and all of a sudden I became a local hero. And the patients kept calling for days afterwards, wanting to make appointments and what not. That's a thing that can generate a lot of professional jealousy.

LH: Well, I think, in that sense, that there was professional jealousy on Nate's part, because he thought that he was going to be the dominant person at that meeting. And when he was totally ignored, and this guy that nobody ever heard of before, Leo Hollister, who was not even a psychiatrist, caught all that publicity, I think that ruffled Nate's feathers. We always had a kind of a rocky relationship after that, sometimes friendly, sometimes a little fractious, but that's the way Nate was with most people.

FA: That's right, yeah. Now, tell me, have you become board certified in anything besides internal medicine?

LH: Well, I was board certified in internal medical in 1950, and then re-certified in 1971. I never did bother to get formal training in psychiatry, but I tried to be self-taught and keep my ears open, go to the conferences and learn things, review records, and the same way with pharmacology. I never had any formal training in either one of them, and sometimes I tell the students—not to brag, but to try to give them a sense of the fact that you can continue your education beyond the formal years—by saying that I'm the only person I know, who's been a professor of pharmacology and psychiatry in two different medical schools who had no formal training in either discipline.

FA: That's right. That's exactly the experience I had. I've had no training, *per se*, in pharmacology, but by attending the meetings, reading, and asking questions, I acquired a considerable knowledge, to the point that many people thought I was trained in pharmacology.

LH: I don't see anything wrong with it, and these days, with all the cross-disciplinary stuff going on, you almost have to do that. Especially in the basic sciences, it's hard to tell who's a biochemist, who's a molecular biologist, who's a structural biologist. What people do is often different from the label they wear.

FA: Now, Leo, you mentioned your early publications. I know you've published many articles and contributed to a number of books, and I believe you may have published one or two books on your own. If you could tell us about that part of your life, I'd like to record that.

LH: Well, just as I did with the conference in Berkeley, I thought the one in New York was going to be published in the *Annals* of the Academy and I didn't need to say anything more about it. That was published, I think, in 1957, and again I don't think the *Annals* had very wide circulation. So

for the first three or four years of my career, I was what you might call a stealth candidate, because I was doing this work but nobody knew about it, other than those attending these two meetings and a few others. As far as written publications were concerned, I was way behind. Over the course of the years, we looked at most of the newer antipsychotic drugs that came along. We looked at Stelazine (trifluoperazine), and again in this case used a design a little bit akin to what we used with chlorpromazine. We treated patients with Stelazine and in some of them, we substituted the Stelazine for phenobarbital as an active placebo, and in some others we discontinued the treatment to see how they did. And of course, the ones who were discontinued had had a higher relapse rate. That told us that Stelazine was doing okay. We looked at prochlorperazine, which at first was thought to be an antipsychotic drug, but by that time Smith Kline & French (SK&F) had both Thorazine (chlorpromazine) and Stelazine, and didn't need another phenothiazine antipsychotic, so they promoted it primarily as an antiemetic.

FA: One of the reasons for that, Leo, I think, for the record, is that prochlorperazine had a capacity to evoke acute dystonic reactions, particularly if it was given in a suppository form, and it was available in that formulation. A lot of people just were shocked because they had not seen this with chlorpromazine.

LH: I remember that quite well. When we first started treating patients with prochlorperazine, as I told you, the technique was to give loading doses parenterally, and then follow it with oral doses. I had three relatively young patients there. I think they were all, certainly, no more than mid-thirties. These are the kind of patients who are most susceptible to dystonic reactions. So we started them off in the morning with shots of prochlorperazine, and by that afternoon, when I was at the nursing desk, writing some orders, one of these patients came up and said, "I-I-I can't talk." I told the nurse, "Well, I don't think he's crazy." I saw it as hysteria, so I just started giving him phenobarbital or something. But then after I got home, my collaborator in the study called me up and she said, "You know, those other two patients we started on that drug today are doing the same thing." And that was my first experience with acute dystonic reaction.

FA: Well, my first experience was with a young girl, who was a manic, and we were trying to keep her out of the hospital. So I kept boosting the dose of chlorpromazine on her, and lo and behold the parents called up and said, "She's twisted like a pretzel; she's twisted like a pretzel!" They brought her over, and it was so dramatic that I called a friend, who was a professional photographer, movie photographer, and he came over and we filmed her. And then, I took it up to

SK&F and showed it to them. They said they'd never seen this before. I said, "Well, here it is." And actually, what I did was I gave that girl phenobarbital also, and that alleviated the problem. But SK&F arranged for me to go down to Atlantic City to the American Neurological Association meeting and they got a group of neurologists together, because they really wanted to know what this was. And I showed this film and the consensus was: hysteria. That was the consensus vote of the neurologists, and they too had not seen this before. So, very early, we learned about some of the potential adverse effects of drugs.

LH: One of the curses of living in a place that's rich in medical literature and has a wonderful medical library is that you can find almost everything that's been happening in the world. So I went over and looked it up and there was a beautiful article in a German neurological journal, the *Nervenarzt*, about Largactil (chlorpromazine) and tardive dyskinesia. They had pictures and everything, and we were told the whole story. I think that article could be written and published today and would show everything you needed to know. "Gosh, the *Nervenarzt* already reported this reaction; there is no need for me to report these three cases", and I never did. Well, ten years later, there were case reports, of course, coming out about dystonic reactions from antipsychotic drugs.

FA: We're still having them come out now, dystonic reactions, with the atypical antipsychotics, you know.

LH: Yeah. It doesn't take much more than four milligrams a day of risperidone to induce a dystonic reaction.

FA: Leo, during the period, when we started off, we had reserpine, and then we got chlorpromazine. Then we got a number of phenothiazines, but we still had the problem of the neurotic patient. And, as you know, the first so-called anxiolytic was meprobamate, and I wonder, did you ever do a study of meprobamate, yourself?

LH: Well, we didn't have very many anxious patients in our hospital, because you don't get hospitalized for anxiety, but we did have some psychotics, so I tried fairly large doses of meprobamate in them, and we did find some calming effect, but not really an antipsychotic effect. We reported that at another New York Academy of Science (NYAS) meeting on meprobamate, but I would have preferred not to have published that one, because I think it created the impression that meprobamate might be useful in psychotic patients; whereas it was essentially acting as a sedative.

FA: As a sedative drug, right.

LH: So that was not one that I was proud of. It was a curious way I got into the field of substance abuse. Sidney Raffel, who was the Chairman of the Department of Microbiology at Stanford and a good friend of ours, said, "We've been looking at drugs for action on microbacteria in tuberculosis and we find that chlorpromazine in concentrations of five micrograms per milliliter kills it." In those days, they didn't have very many antitubercular drugs that would actually kill the bacteria. They'd done some *in vitro* studies, which were ready to be published, so I said, "Let's do a clinical study." In a nearby tuberculosis sanatorium, we added 300 milligrams of chlorpromazine or placebo to the ongoing treatment of about thirty some patients. In those days, you usually followed the tubercular (TB) patients every three months to see their progress in the sputum and the X-ray. After six months went by, we saw really no differences between the two groups, so we decided that either we weren't giving the necessary concentrations of the drug, or something was wrong. We decided to stop, and within twenty-four hours, I think, seven out of the fifteen patients who were on chlorpromazine, experienced nausea, vomiting, jitteryness, sleeplessness, the whole withdrawal reaction.

FA: Withdrawal reaction.

LH: None of the patients on placebo showed this. So in a sense, this was the first demonstration, by using a placebo control, of a withdrawal reaction to a drug; and secondly, it was the first demonstration of what might be called therapeutic dose dependency, that therapeutic doses of drugs could probably produce this kind of dependence. Well, again, with my way of publishing in those days, this was described in about a paragraph or two in the paper in which we published the results of the main study. We never did publish it separately, and of course, it was published in the *American Review of Respiratory Diseases*, which was not a widely read psychiatric journal.

FA: That's for sure.

LH: So that was the first withdrawal reaction we studied. Later, we followed withdrawal reactions to meprobamate, and compared them with a preparation in which meprobamate and promazine were combined. Our hypothesis was that possibly the combination with promazine would mitigate the withdrawal reaction, whereas in fact, it was the opposite, it made it worse.

FA: Because both of them were pretty anticholinergic.

LH: Yes.

FA: Promazine and chlorpromazine are fairly potent anticholinergics.

LH: In 1959, I think it was, just before they launched Librium (chlordiazepoxide), Roche had a private meeting of the investigators at Princeton, New Jersey, and I was invited just as a participant observer, because I had not worked with the drug. And when I heard all the glowing reports about how people brightened up on Librium, I said, "Gee whiz, if this is as good as they say, it's going to be a beaut." Again, they hadn't tried big doses of Librium in psychotic patients, and I decided it would be an excuse to use large doses. So we started treating some psychiatric patients with Librium with doses up from 300 to 600 milligrams a day, and then, under very closely controlled circumstances, but without their knowledge, we switched the patients to placebo, and followed them by recording their electroencephalographs (EEG's), clinical observations, and measuring blood levels. And much to our surprise, when we stopped the Librium, nothing much happened for a day or two, and then about the third day, they began to develop withdrawal reactions, which peaked around the fifth day; two patients had seizures on the eighth day, as compared the second or third day as usual. Well, our blood levels were incomplete, because I had no idea of measuring it at the eighth or ninth day, but it indicated that the half-life would be such that by the eighth day, you'd be down to zero level, and the attenuation of the withdrawal reaction was due to the slow disappearance of the drug. I think that was one of the first withdrawal studies to indicate that the half-life of a drug has a bearing on both the onset and the severity of the reaction. And that concept, I think, has held true over the years. So that's how we got into withdrawal reactions, largely through the anxiolytics.

FA: Right. And that's because the benzodiazepines had become available.

LH: Oh, yes. Of course, they were enormously successful. Then diazepam came out a couple of years later, I guess, in 1963. We were doing a study on diazepam in schizophrenics, as part of a collaborative group that I'd set up, and the Salt Lake City group decided they would goose them all up to the maximum dose of 120 milligrams a day, and suddenly discontinue it. And they had precisely the experience that we had with Librium; that is, delayed onset withdrawal reaction with late seizures.

FA: Late seizures.

LH: So, apparently diazepam was rather similar in that respect to chlordiazepoxide. Well, personally, I thought, with these two studies I was publishing at the same time that the drugs came

out, there would be warnings that this could happen. I fully expected that Roche would have a warning on withdrawal reaction. It was several years later...

FA: One of the reasons was, of course, that the drug has a long half-life and people were not giving the doses that you gave. They are uncommon...

LH: They were giving smaller doses and the drug has a long half-life. I guess, around the 1970s, the issue of benzodiazepine withdrawal became alive again, but I don't think there's ever been a major problem with it.

FA: Well, it depends on the patient, how much he's had in terms of total daily dose, and also how long...

LH: Well, I was looking for patients who were chronically on diazepam, because I wanted to see what it was like in nature. So I sent Hamp (Gillespie), my associate, over to the psychiatric clinic, and I said, "Find out how many patients that are being seen that are on diazepam for several months." He came back and said, "Oh, two or three." I said, "Well, try the medical clinic" and he came back with the same thing. Then we hit a bonanza in the neurosurgical clinic, because they were using diazepam for people with back pain and using substantial doses over long periods of time. So, oddly enough, we had a collaboration then with the neurosurgical group, and we studied over a hundred patients who had been on chronic diazepam for an average of about five years, and on fairly substantial doses. We measured the plasma concentration, and much to our surprise, the plasma concentration withdrawals were lower than they should have been for the dose they were getting, which meant that the patients weren't taking the full dose prescribed. This was more often the case than not, and a few, whose concentrations were high — we found later on —were due to the fact that the proper interval between the last dose and blood drawing hadn't been fulfilled. When we repeated it with the proper time interval, the apparent high levels had disappeared. So there was no evidence of abuse in these patients, who had been exposed to it for a long time. Well, of course, neurosurgical patients might be quite different from anxious patients, so I can't be sure that would apply to all of the anxious patients.

FA: Well, the majority of people who have really abused benzodiazepines were multiple substance abusers.

LH: And possibly finding a benzodiazepine abuser who doesn't use alcohol or other drugs is difficult.

FA: Absolutely, that's right. All right! Now tell me, you've mentioned some of the articles you wrote. You also mentioned that you'd published a book or two.

LH: Well, I didn't publish a book until somewhere in the 1960s, I guess, just a little paperbound volume that reviewed the evidence for the effectiveness of some of the psychotropic drugs from the VA cooperative study. It turned out that one of the drug companies bought a great supply of the book and provided them free, so, it was very widely circulated. I was delighted, because you never make a whole lot of money writing books. And I was delighted to have people come up to me from time to time and say, "I've read your book and it was very helpful to me in learning about the drugs and using them." So that was a fair success. One of the drugs that we studied early, I guess, it was still in the 1950s, was Mellaril (thioridazine), which today, begins to look like the first of the atypical antipsychotics, doesn't it?

FA: Exactly.

LH: A lot of people doubted whether it would be an effective antipsychotic drug, because it had such weak D<sub>2</sub> antagonism, and it also blocks serotonin receptors. Of course, those are probably the most potent anticholinergics. What was interesting is the fact that it was an antipsychotic, and the dystonic reactions and Parkinson syndrome with Mellaril were much, much less than with the other antipsychotics.

FA: That's right.

LH: Regardless, Joe Correll and George Simpson, I think, published a joint letter saying, you can still get tardive dyskinesia with it.

FA: That's correct.

LH: Because the company was making the claim that you couldn't. But, you know, that was an interesting jaunt.

FA: Now, besides the benzodiazepines and meprobamate, and the different phenothiazines, we got into the tricyclic antidepressants. When did you start working with them?

LH: Well, again in the VA population, we didn't have a whole lot of depression, so I didn't have a very great reason to get into that field. We did get iproniazid from Roche, and as luck would have it, I think out of the first ten patients, we had three who had hepatitis, so that cooled me off a little on it. And of course, iproniazid subsequently died because of that; although many people said it was the best antidepressant that we'd ever had. But we didn't follow up on it until later. Now, in 1959, I think it was, the VA decided, since they had the largest number of psychiatric beds in the

U.S., that they'd better get interested in studying these drugs, and that started the VA Cooperative Studies Program. I was not invited to the first organizational meeting, but they invited me to the second, and from there on, I became one of the prime movers in organizing these large scale cooperative trials, which I think were very successful, and which I truly believe have never been given the credit that they deserve, because they were the first, only done by state systems. California did one, New York and, I guess, Delaware. Fritz Freyhan did some. But the VA set the model. And then subsequently we had the National Institute of Mental Health (NIMH) Psychopharmacology Service Center (PSC) there in the field and I was invited by them. But I think they copped off with most of the jewelry, largely because they were financing everything in those days, and you always like to pay attention to the people who have the pocketbook. So one of the stories that I think isn't dealt with enough, is the way the VA started the whole thing. In retrospect, I call this a massive scientific overkill, because even my early controlled trials were not very necessary. All I had to do was give these drugs to a patient and watch him. You knew damn well something was happening. But at that time, the Zeitgeist in psychiatry was such that nobody wanted to believe it. You know, psychoanalysis was dominant, so I think that these controlled studies served a useful purpose, because they overcame the reluctance to accept these drugs. Of course, now, opinion on this has gone completely in the opposite direction. But in the 1950s and early '60s, almost every chairman of a department of psychiatry in the country was an analyst or analytically oriented. Today, it's a biological psychiatrist or a biologically-oriented psychiatrist.

FA: Right. There's been a lot of change in psychiatry.

LH: So the VA cooperative studies were good.

FA: They were very important.

LH: I was able to get funding from the PSC to set up kind of a separate group, along with John Overall, and we studied a series of drugs including antidepressants for the next several years. Working with John was a great pleasure, because he knew a great deal about experimental design, about statistical analysis, psychometric ratings, of which I knew very little, and I knew something about the clinical side and the use of drugs. So we formed a nice joint group, where our expertise kind of complemented each other, and that was a very productive time. We did waste a lot of time, however, because we were then searching for what we might call the right drug for the right patient. The problem was that every time you thought you'd found it, if you checked it back, which we tried to do, we learned that other people couldn't find it. So we were frustrated in that effort. Now

it makes sense that these drugs are acting on a specific kind of psychosis. So that was my early career in psychopharmacology. By that time, of course, I had become fairly well known. I was one of the first members of ACNP, but I never attended a meeting of the ACNP for the first two years, which should have gotten me kicked out, according to the rules. Ted Rothman had to prevail on me to get me to join, because it appeared to me there were enough organizations now, and we didn't need another one, about which I was dead wrong. So I did attend the third one, and as we were checking out of the hotel, I walked over to Ted and I said, "Ted, I was dead wrong. This is a great organization. I'm awfully glad you persuaded me to join." Since then, I've never missed a meeting.

FA: I know that. That was in Washington, that year.

LH: That was the meeting in Washington.

FA: Was that the one where we had the blizzard?

LH: Yes.

FA: I had flown in from Rome for that, and we only had a handful of people there because of the blizzard.

LH: Well, I never attended any of the meetings of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) until 1964, in Birmingham. I remember very well we had lunch together in Birmingham and you were coming from the Vatican, then also.

FA: That's correct.

LH: I told you, my secretary told me last Christmas, "There's a card here from the Vatican", and I said, "Well, that must be from my friend, Frank Ayd, and if there's not a signed picture of the Pope, I'm going to be disappointed." You didn't say a word. The next Christmas, there was that photograph of you and the Pope with your whole family.

FA: The CINP is an organization that you know something about, in terms of its early days, and you also became a president of the CINP, right?

LH: Yes, that was quite a surprise to me. I didn't anticipate it at all. It was at the meeting in Paris, in 1974, and I understand that they had the idea that they should increase their bonds with the ACNP. At that time, I had become ACNP president, so they figured if they had somebody there from the ACNP that would increase their bond. My understanding is that Nate Kline argued fiercely against my being given that job. Of course, in those days, it was given and it still is, I guess. You're really not elected but selected. But they did give it to me anyway, and I became

president. I had a tremendous influence, much more so than usual presidents do, in selecting my successors. I got Arvid Carlsson as one successor; I selected Arvid Carlsson, Paul Janssen, Paul Kielholz and Ole Rafaelsen. I think that getting both Arvid and Paul as presidents was the right thing to do. They're giants in the whole field, far more so than I am, or any other presidents we've ever had.

FA: There were a lot of politics, and if you got the right people behind you, then yes, you had a chance of becoming a president.

LH: Speaking of presidents, though, I really think that you have been slighted. You should have been president of this organization, and you damn well could have been president of the CINP. I was very happy to see your photograph is up with all the presidents, as a founding member, and I think that gives you the same rank.

FA: Oh, I'm pleased. I never aspired politically, you know, and I don't think you have either. If someone had asked me, I would have said yes, because I never said no to any request I've had from the college.

LH: Well, how I became president of the ACNP is kind of a strange thing. The council had a nominating committee, of which Doug Goldman was the Chairman, and Doug had come to me and said, "I'm the Chairman of this nominating committee, and I'd like to see Ted Rothman nominated as president. Do you have any objection?" I said, "No, how could I have any objection, because Ted got me into this organization." Well, he gave his report and the council was upset because they thought he was going to nominate me. So Dick Wittenborn, I think it was, came to me and said, "Say is it true that you don't want to be president of this organization?" I said "No." I told him the story, and eventually got into a little hairy situation, because I was very good friends of both Ted and Doug. And here it looked as though I was trying to intervene over Doug's decision and over Ted's ascendancy, so I didn't feel too good about that. But ultimately Ted was given the Paul Hoche Award, and I think, we all recognized his importance in the founding of this organization.

FA: Oh, yes, absolutely. He was really the man who did the negotiations in the beginning, no question about that. Alright. Now, if somebody asked you, "What was the important thing you did in psychopharmacology?" What would be your answer?

LH: Boy that would be tough, because you know when you look back, you become extremely marred. You say, now really what did I do that's so important? What did I do to change the course?

I suppose I would have to answer, in a more general sense rather than in any specific accomplishment.

FA: The role you played in getting controlled studies done?

LH: Our controlled studies in the 1950s may have not been the first, but at least, set a precedent, and then the VA studies following this. So even though I think they were probably overkill in a way, they did set a pattern by which we know we can get effective drugs and relatively safe ones. We haven't had too many misadventures in this field on the market, and it helped overcome the reluctance of organized psychiatry, at that time, to admit that drugs could be useful. If anything, it was more in this general sense, than any specific thing I did. I still enjoy proving the efficacy of these drugs. Yet, I haven't done that for years, because now most drug companies have in-house people who can write protocols, statistically analyze all the data, and there are professional contract organizations to do clinical trials. All the investigators do is collect data. You know, it's kind of a dull business. It's become formalized, not in the way that I think it should be. I think we ought to experiment with different designs beyond the parallel group controlled trials. And there are other things that we might very well try that might shorten the course of developing the drugs and reduce the tremendous expense.

FA: In the beginning, when you started in psychopharmacology, there was no pharmacokinetics, correct?

LH: Well, I never was a pharmacokineticist; although I would say we did blood levels in the meprobamate withdrawal study, and also in the Librium withdrawal study. But the methods that were available then, were very crude and measured all kinds of metabolites, which in case of benzodiazepines was probably okay. But I never did go into pharmacokinetics.

FA: My point is that pharmacokinetics came sort of late. The trials had already started, and the way of measuring what was really happening was purely clinical, and it had nothing to do with our ability to know how much was absorbed, where it went, and all the other things.

LH: I've never been very keen about measuring plasma concentrations of these drugs in the clinic. You know, first of all, almost every drug had very wide therapeutic ranges. For haloperidol, it could be anywhere from two to twenty milligrams a day. What does a ten-fold range tell you? It doesn't say a damn thing. We did a study some years back that tested that with nortriptyline, because it was the drug that had been widely studied with the plasma concentration related to clinical response. What we did was, we looked at patients treated by the clinician the way they

wanted to, but with half of them, chosen randomly, we fed back the information about where the plasma concentrations were, and the other half, we didn't. And then, the two questions were, did having the knowledge of the plasma concentration result in their staying within the therapeutic range more often than not, and did it make any difference? Both answers were no. So why spend people's money measuring plasma concentrations. It seems they really don't help much.

FA: That's right. Now, in the early days of psychopharmacology, aside from the Rorschach and the Minnesota Multiphasic Personality Inventory (MMPI), and say, the Wechsler intelligence tests and few other tests that would measure organicity, what other assessment instruments did we have? I'm asking that, Leo, because a lot of young people have a very difficult time visualizing what it was like thirty-five years ago.

LH: Well, in our initial studies, we didn't use any rating scales. We just sort of arbitrarily divided the patients into markedly improved, moderately improved, slightly improved, or unimproved. It was all clinical data and I think that worked pretty well. You know, if you watch your patients, you can learn a lot.

FA: By that, are you advising the young people or the young doctors, who may be watching this videotape in the future, to be a clinician and an observant person, and don't worry?

LH: Be a clinician; watch the patients; listen to them. You know, I'd always been mystified by the great concern about negative symptoms and drugs that are specific for negative symptoms, as if the other drugs didn't do a damn thing for them. So, some years back, I went to John Overall and while we had dinner, I said, "Look, John, we've got data all along, and we're showing that negative symptoms respond as well as the positive symptoms." John wasn't interested, and he'd thrown away a lot of the raw data, so he would have had only abstracted data to work from. But early on, I remember calling one of my golfing buddies, who was one of my prime collaborators, and asking him, "Would you like to have some more patients on these new drugs?" And he said, "Leo, I've got so many patients talking to me, who never talked to me before, that it's all I can do to keep up with them, and now you want to talk about negative symptoms." So, you know, there were effects on negative symptoms. Maybe the newer drugs are better, I don't know.

FA: We've had no comparisons yet.

LH: I'm maybe a little too skeptical in that part. But there certainly wasn't an absence of response of negative symptoms, by a long shot. People who were mute—you know, in those days, we had

people who had never talked for years—and in a couple of weeks, they'd be conversing with you. I remember one of our patients I inherited when I first started, was a young chap, an Armenian chap, who would curl up in a fetal position, wouldn't respond to anything, just about the most regressed schizophrenic I've ever seen. And I tried every damn thing. I gave him electroshock, insulin, and other things, and it wouldn't budge him. And when reserpine came along, he perked up a bit, eventually left the hospital. And when Sputnik went up in 1957, in the *Encyclopedia Britannica*, there's a picture of Sputnik by my Armenian friend. He got into photography. He got a good picture and got in the *Encyclopedia Britannica*. Well, twenty- something years later, I was making rounds in the intensive care unit (ICU) of a medical service, and I heard my name. And I looked over and there he was. He'd had a coronary. He knew me, remembered everything, but he had been so crazy. So these were the kinds of things that I think were really quite impressive.

FA: Right. I think that's because in my opinion, we were more interested in the patient as a person, than we were in the disease the patient had. And that, I think, should still be the moving force.

LH: And the other thing is, when I see a patient, I say "Well, here's what we are going to do first." But then, I have the second, third, fourth choices in my mind, or even on paper, as what we do next when the first one doesn't work. You have to plan what your alternatives are, because you're never sure. Each one is so individual. If you're lucky, you hit it well on the first time, but if you're not, then, you have to try other things.

FA: Right.

LH: But, getting back to rating scales, the first popular rating scale, I think, was the Lorr scale, what Morey Lorr came up with in the VA, and called the Inpatient Multidimensional Psychiatric Scale or IMPS. That was a rather detailed scale, used a lot to describe the different domains of psychopathology. And it wasn't a bad scale. Then John Overall and Don Gorham shortened it, condensed it, and came up with a Brief Psychiatric Rating Scale (BPRS.).

FA: When were these scales introduced?

LH: I think the IMPS came out in the mid 1950s. I know we had it for our first VA studies. The BPRS, I think, came out around '59 or '60.

FA: So it was just before we organized ACNP.

LH: And of course, since then there have been scads of scales.

FA: Oh, yes, yes.

LH: In fact, I remember, Jim Clinton and some of the psychometricians in the VA were interested in developing a scale for depression, and they asked a whole lot of questions about what depressives might show. And when they boiled it down, they found only thirty-two discrete statements that you could make about depression. I think that's the extent of it, rather than probably thirty-one scales, based on various combinations of everything.

FA: That's correct.

LH: But you don't need scales, unless you're trying to impress the Food and Drug Administration (FDA). If you know what your patients have been doing and have some sense of their past history, you can tell when they're changing. That's the way you operated, isn't it?

FA: That's exactly how I operated. Yes, it's the only way I could operate. I was in private practice. I was not in an institution and it was observation, knowing the patient, forming a relationship with the patient. I don't know if I ever told you this story, but early with chlorpromazine, I had this elderly woman who was a chronically agitated depressive and she suffered. She really did suffer, and I tried everything. I even, unfortunately, produced a little bromide intoxication in her. Chlorpromazine came along and I started her on it, and she came back two weeks later, walked in and she's jaundiced. I said, "Oh, my God, Mary, how long have you been like this?" She said, "Oh, about ten days." I said, "You stopped your medicine, didn't you?" "No, doctor, you've tried so hard to help me, and I do feel better. I'm not as agitated." So, you learn from that. You could keep up with chlorpromazine, and not necessarily make the jaundice worse.

LH: I published a paper in the *American Journal of Medicine* in 1957, on "Allergy to Chlorpromazine Manifested by Jaundice." I think I reported seventeen cases, and I don't know what internal clock told me that that was enough, because if I'd looked for twenty-five, I would still not have published the paper, because all of a sudden the jaundice in the patients vanished. But that's true; some patients sometimes inadvertently go right through with the drug and still resolve a cholestatic jaundice that they develop. I guess if that had happened today, in today's climate, you get three percent of such patients and you might kill a drug.

FA: Absolutely, sure.

LH: I am not so sure about Sertindol (mesoridazine). It prolongs QT interval and there is sudden death that of course worries me a little bit. But we had the same thing with Mellaril (thioridazine).

FA: All right. Now, another question, Leo. Since you've been in this field for so long, you know who the ballplayers are. Who among the North American psychopharmacologists would you list as those who made major contributions to the advancement of psychopharmacology?

LH: Oh, dear. Well, I think you certainly are on the list. You've been in the field longer than I have, or at least as long, and have produced an enormous amount of information that has been clinically useful. Jon Cole certainly is also one. I suppose before that, Nate Kline was an enormous influence, more on a political level, but he got Congress to provide funding; he established hospitals in other countries, and with his usual flair for publicity, he put psychopharmacology on the map, and we can't deny that he was a major influence. I think Jon Cole, starting the PSC was important in getting things started and funding groups to look at drugs. On the clinical level, I think people who were early in the field, like you and Jon and me. And probably, had he lived long enough, Fritz Freyhan would have certainly been that way, and also, probably Paul Hoch. But as far as the basic pharmacology is concerned, there I haven't been as impressed with the people in North America as I have been with the people in Europe. I think Hornykiewicz, for instance, in showing that dopamine was not only a neurotransmitter but was intimately connected with Parkinson's disease, was a major influence. Levodopa treatment of Parkinson's disease was a major accomplishment. Arvid Carlsson, who established the role of dopamine in schizophrenia, also was a major influence. And, of course, I remember vividly one night at Paul Janssen's house, after a few drinks and coffee, Arvid got Paul talking about how his company got started. I sat in the middle, and I only wished we'd had a tape recorder to get this all on the record, because it was an enormously interesting history. But, you know, he's got the most productive pharmaceutical company in history. It's not only psychotherapeutic drugs, it's the whole field.

FA: The whole field.

LH: Yes, and it's a remarkable institution. He's almost the Henry Ford of psychotherapeutic drug development, because he established a system that goes from chemistry, right up to screening tests, and so on. So he was an important person. I'm trying to think of an American pharmacologist who was important.

FA: Let me throw in the name to see what you think of Gerry Klerman, a clinician.

LH: Oh, Gerry was of course important. I first knew him when he was a Fellow with Jon Cole; a very bright, ambitious fellow full of energy and wonderful personality, always had something to make you laugh. You know, Gerry became quite influential later on. I guess the only reason he

wasn't the president of this organization was that he was the head of the NIMH. He had some big government job, and they figured it a conflict of interest. But he did a remarkable thing. And I remember, shortly after his death, I wrote to Myrna Weissman and told her what an angel she had been in his last years, because he remained very productive right up till the time of his death, and this was largely due to her keeping him going. Again, when I go back to basic pharmacologists, I suppose, Bernard Brodie and Julius Axelrod are the two big guys. It must have broken Brodie's heart when Axelrod got the Nobel Prize and he didn't, because they were both excellent candidates. Axelrod's contribution of the inactivation of neurotransmitters by uptake was a completely new concept. And of course, Brodie was the father of biochemical pharmacology, and established the concept of active metabolites of drugs, and he had a whole lot of other seminal ideas. Mimo Costa, I think, has had a distinguished career in pharmacology and psychopharmacology. Most of the names that come to me are people who were at the National Institutes of Health (NIH) in those early days.

FA: Another one that you haven't mentioned, that's Sol Snyder.

LH: Oh, yes, Sol. I remember, I was at a meeting in Washington, one of the things where I used to go every fortnight, and Milton Jaffe, who was then with the FDA, I think, said, "We've got a problem with a drug out in San Francisco, called STP (2,5-dimethyl-4-methyl- amphetamine), and we don't know what in the hell is going on with it. We've given a contract to Sol Snyder to study it, but he says it's going to be a while before he gets the answer." So, I said, "Milton, have you got some of this stuff?" And he said, "Sure, I've got some in my desk drawer." I said, "Give it to me." This was about two hours before I caught the plane back on a Friday afternoon, and by Tuesday, we had the first subject run, because I had a protocol set up for something that we were going to do with lysergic acid diethylamide (LSD), and just worked this one into it. Within a few weeks, we had the whole answer on STP. It was an amphetamine homologue that had mescaline-like qualities. It was in the same ballpark as mescaline, in terms of potency. You could build up tolerance to it. And Sol had done some things too with it. Sol had a contract with *Science*, so we got our preliminary report published in *Science*. I met Sol first when I visited him in his office at Hopkins. He has been on the forefront of almost everything from the dopamine receptors to the opiate receptors. He was always at a close place in the horse race, even if not a winner. It was the same way with nitric oxide. Sol had an extraordinarily distinguished career. Some years back, a friend got me on the list of people who could nominate Nobel Prize winners. I took advantage of

it for several years, because you can make more than one nomination for it. So I was nominating all of my pharmacologist friends, and I had Paul (Janssen) linked up with Hitchings and Black. I thought that was a wonderful trio. Hitchings and Black made it, but Paul didn't. I talked to him about it and he said that maybe the Nobel Committee figured he was making so much money that he didn't need the prize. But he certainly could have very well had it, with all of his contributions in drug development. I don't think his were as novel as Hitchings or Black's, but his was perhaps the greatest extension of structural activity relationships that's ever been done. So the more I think about it, there are some North American psychopharmacologists, in the basic sciences, which are very important in the field.

FA: Another question, because I want to move on, and that is if you could in a capsule describe for the young doctors who will be seeing this videotape, what was it like in psychiatry when we started with psychopharmacology?

LH: Well, first of all, psychiatry was pretty well dominated by psychoanalytic thinking in those days, I guess *DSM-I* days.

FA: Yes, it was.

LH: They didn't call it schizophrenia; they called it schizophrenic reactions, the idea being that with reactions, there's some set of life circumstances. So advances in psychoanalysis would explain these illnesses. The introduction of biological terms has been a major event. Now, maybe, we've gone too far. My friend Mort Reiser wrote a paper called "The Mindless Brain." We're so focused on the brain that we're not thinking much of the mind. But I don't have any trouble with that. I think mind is an abstraction, like circulation or digestion or respiration. It describes an abstraction of a great many different functions. The second thing was that not a whole lot of attention was paid to diagnosis. I think diagnosis came, really into its own with the *DSM-III*. If you look back, in those early papers in the proceedings of the Berkeley meeting or the NYAS meeting, people were talking about treating a hundred and fifty or two hundred psychiatric patients with no diagnosis at all. Because of my training in internal medicine, I was more likely to specify the diagnosis of the patient than those with a psychiatric background. But now, diagnosis has become important. I'm not sure that we've got diagnosis nailed down, but at least we have a common language, so that people can define their terms, and so as for Alice in Wonderland, the words mean what I want them to mean, so we arbitrarily make our diagnoses. Of course in those days, mental hospitals were barbaric, by today's standards; we had patients in the Palo Alto VA

who had been there for fifty years, since World War I, never left the hospital, stayed there until they died. We had about a thousand patients and most of them were very, very quiet. We had a wonderful social service department, which managed to get many of the patients into local foster care homes and that was a great advance. But even before the drugs came along, I remember a congressional committee came and said, "What's your estimate of how many patients we could get out of here if we had funds for their care outside?" Well, I said, "Well, fifty percent, at least." Ultimately, that became the case. But the mental hospital became a way of life. Hardly a day went by that there wasn't some assault by a patient on a member of the treatment team. I never was assaulted, because I did two things. I always wore a light coat, and I always sat close to the patients, so they did not have enough leverage to hit me very hard. I always nestled up close, and you get outside of a good swing. But there was an ever-present danger. Patients weren't allowed to have any kind of sharp objects, so you ate your food with a spoon. There were no seats on the toilets, because the toilet seats could be ripped up and used as weapons, so you sat on the cold porcelain. Bath days were public occasions, where everybody went in the shower nude and dried off on the ward. It was just unthinkable by today's standards of care. And that was in the VA hospital, which at that time was spending about twice as much per capita as the average state hospital, so you can imagine what it was like in the state hospitals. We don't think any longer in terms of treating patients with schizophrenia for years, but rather for days, and the whole outlook has changed to a much more favorable prognosis. I'm not sure that eliminating mental hospitals entirely was a good idea, because a lot of times we just change the scenario from sitting in front of the television set in the mental hospital to sitting in front of the television set in a skid row hotel. So it might not be a whole lot better for some patients, but by and large, I think things have improved immensely.

FA: Okay, now, predict what you see for the future of psychopharmacology, and also, the ACNP.

LH: Well, the ACNP, in recent years, has become a kind of secondary society for neuroscience, at least, in terms of the program content. Neuroscience advances have been so enormous, especially in molecular pharmacology and all the explicit techniques that are now used for genetic analysis. So as we have your lexicon for psychiatric terms, we need now a lexicon for the terms in molecular biology, and this hurts some of our members. There's been an eclipse in the clinical emphasis. Now, whether this will continue indefinitely or not, I don't know, but I think maybe we, as clinicians, need to try to develop some new approaches of our own in evaluating these drugs and seeing if we can find some ways to reduce the time and the cost of getting them

on the market. What most people don't realize is that these new drugs are terribly expensive. It costs you eight dollars a day to be on Risperdal (risperidone). It'll cost you about eight cents a day to be on haloperidol, a vast difference. Now there are all kinds of pharmaco-economic studies being promoted these days, but they show that they come out even. I had a little trouble believing that, and it doesn't matter anyway, because hospital pharmacies don't have the money to spend on these drugs and patients can't get them, so we've got to find a way to reduce that cost. As far as psychopharmacology itself is concerned, it looks as though we're beginning to move into an era of designer drugs in the true sense of the word. We are looking for drugs for either specific pharmacological profiles, or even more importantly, with structures that would fit different transporters or receptors. So we may be able to have even more specific drugs than we now have. Beyond that, there's a possibility that we can even influence some of the genetic factors that would play a role. It's a terribly exciting time that we're in. It's kind of frustrating to us old timers, who have to learn all the new stuff. I always give up, or I feel depressed about what I don't know, but by the same token, that's a good sign.

FA: It is a very good sign. As a matter of fact, I share with you the belief that this is an extremely exciting time. You know, there is a lot yet to be learned.

LH: I think you would agree with me that we've had a wonderful life.

FA: Oh, yes.

LH: I feel so privileged to have known so many bright, productive people and have become friends with them, acquaintances with them, and to have had the intellectual stimulation of being in this field over the years. I often have wondered what would have happened had I stayed in hypertension, because that's been an exciting area, too. But, you can't change history. History has only one side and you can't tell what the alternative would have been; but nonetheless, it's been a real privilege to be a member of the ACNP and to know the members in it, to be friends with people like you, and I have no regrets.

FA: I have none, either, Leo, and I thank you for letting me be your interviewer.

LH: Well, it was turnabout, fair play.

FA: Fair play, yes. Leo interviewed me, two years ago, wasn't it? Yes, I think it was two years ago. But, actually, on behalf of the ACNP members, I want to thank you for what you did for us; you did for us a lot.

LH: I'll just say, in retrospect, you're not very impressed with what you accomplish, and wish you could have done more, but we do what we can.

FA: That's right. Well, that's it.



### 36. LEO E. HOLLISTER: interviewed by Thomas A. Ban

TB: This will be an interview with Dr. Leo Hollister<sup>9</sup>, one of the pioneers of neuropsychopharmacology. We are in Nashville, Tennessee. It is April 6, 1999. I am Thomas Ban. Tell us where and when you were born, and something about your childhood and early interests.

LH: I was born in Cincinnati, Ohio, in the 1920's. I was educated in that city, which had excellent facilities. I went to one of the first college preparatory high school that was public in the whole country and then to the University of Cincinnati, which was sponsored by the city. Whatever educational attainments I've had, I owe to the city of my birth. My medical school training was about the same as everybody else's. I'm always amazed when people rank medical schools; it's not what the school gives you, but what you put into your education.

TB: Did you always plan to get into medical school?

LH: No, the earliest idea I had was to go into law. My stepfather was a Judge in the city, and I remember, at the age of eight or nine, being placed in the judge's seat, looking over his courtroom, and being impressed by the majesty of the law and what it means to civilization. Later on, I determined lawyers spend time trying to distort the truth and physicians spend time trying to find it out. This was influenced greatly by the books of Paul de Kruif. He was a Dutchman who was a journalist and wrote books about the early adventures of scientific medicine. One was called Microbe Hunters; another was Men against Death, which celebrated the great advances made in the 1900's, elucidating infectious and nutritional diseases and medical progress in general. It seemed a great adventure to make such

wonderful discoveries and have a profound impact on the lives of so many people

TB: When did you graduate from medical school?

LH: I graduated about six months earlier than normally because the war came along and programs were accelerated. Our class was the first to graduate early due to wartime. Actually, I graduated the day before my twenty-third birthday. That gives you some idea of how accelerated things were.

TB: What year are we in?

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<sup>9</sup> Leo E. Hollister was interviewed at Nashville, Tennessee on April 6, 1999.

LH: December 1943. I took an internship in medicine at the Boston City Hospital, and on the way, I was accompanied, as far as New York, by Mort Reiser, who later became Chairman of Psychiatry at Yale. Mort was taking a medical internship at Downstate New York. It was rather peculiar, both of these Cincinnati boys leaving home the first time, ultimately for similar careers. After residency in medicine, I went into the Navy almost simultaneously with the end of the war. I was stationed at a naval hospital in Portsmouth and one of our officers said the war would be over in two weeks. We were still island hopping in the Pacific, so I bet him ten bucks, and he won. He must have had advanced knowledge of the atomic bomb and that changed things drastically. My naval career was totally undistinguished. I was stationed in Hawaii; it was the first vacation I'd had in years, with very little responsibility and a beautiful place to be.

TB: You finished your residency in Internal Medicine?

LH: After military service, I finished residency and started a private practice, but being a member of the Naval Reserve, attached to the Marines, I was summoned back in 1950, when the Korean Conflict broke out. Again, I had a pretty soft posting assigned to the Naval Hospital in Oakland, across the bridge from San Francisco, where I lived.

TB: So, by 1950, you were in San Francisco?

LH: I'd gone there after the war to finish my training; having passed through on the way to Hawaii, it looked too good to pass up. I wound up with a wife, who was a native Californian, and produced four children. That became my home for almost forty years.

TB: Did you go back to practice after the military?

LH: No, having decided that maybe I would be called back to the military every four or five years, I thought I'd play it safe and join the Veterans Administration. There was a chap, who had a job at the V.A. Hospital in Menlo Park, near where I lived, and I had a job in San Francisco, where he lived. We decided to switch; the one he had was internist for a psychiatric hospital, a totally new experience. I thought it would be similar to practicing veterinary medicine, because you couldn't get reliable histories, and we rely on that for diagnosis and treatment. So, it was an interesting experience. While I was there, a detail man from Ciba Geigy said they had a new drug they thought might be good for high blood pressure. Oddly enough, that had been one of my major research interests. I never published, but I'd done a lot of trials with different drugs to treat hypertension and nothing worked. So I said, "I know all the hypertensives in the hospital. If you give me some of the drug, I'll be happy to try it out." Things were so informal in those days that all he had to do

was go to his car, fetch a few cartons of tablets and give them to me. Two days later, the first patient was started on reserpine. It didn't take long for many patients to find out it was the first effective antihypertensive. So I was impressed. When he came back three months later he said, "We now have evidence from a specialist on hypertension in Boston, that this might be good for psychiatric patients, mainly, schizophrenia." I said, "Gosh, let's see what we can do." Not having any training in psychiatry, I didn't feel confident to evaluate a drug in any kind of mental disorder, so I went to the Chief of our Psychiatric Service and told him the story. Somewhat patronizingly he said, "You know, in psychiatry, drugs have come and gone over the years, and they all turned out not to be very effective. I think it would be a waste of time." I had a streak of obstinacy, so I said, "Do you mind if I ask my golfing buddies, who are psychiatrists on staff, if they would take a look and tell me what they think?" He replied, "No, go ahead." So I asked a colleague to send patients to my medical ward; I would begin treatment with reserpine or placebo, randomly, and send them back to him for observation and evaluation.

TB: So, you did a placebo controlled double-blind study?

LH: That's right, the first of its kind in schizophrenia. At first, we didn't know what the proper dose was, because the only paper relating to reserpine in schizophrenia was a short paper by Nate Kline, with not very striking results, using the same doses given for hypertension. It turned out later on that Ciba decided the dose needed to be much higher. They had sent a physician from the East Coast to arrange studies on the West Coast for hypertension and any other indication. Based on the results, I would start patients on five milligrams by intramuscular injection for three days, follow it up by oral doses of the same magnitude for another few days, and then taper it down to three milligrams by mouth before sending them back to their ward on active drug or placebo.

TB: Are we in 1955?

LH: This would be probably late 1953 or early 1954.

TB: So, it is before Heinz Lehmann's paper on chlorpromazine?

LH: I think it was the same time. The first study we did in hypertension was in the latter part of 1953 and was followed by the ones on schizophrenia in early 1954. My friends were saying, "I don't know what the hell you're doing to these patients, but something is going on. They're vastly different from how they've been before." Others seemed to be unchanged. In those days, the American Medical Association annual meeting was a big affair and there was a scientific exhibit on chlorpromazine by Mark Altschuler from Harvard. Altschuler was a professor of medicine. I'd

read stuff he'd written; a nice review on pulmonary edema and other medical topics, but I was curious how he got to study chlorpromazine and schizophrenia. It turned out that, tragically, his wife was afflicted by the illness and that encouraged his scholarly interest. He and one of his residents had an exhibit reporting on two patients treated with chlorpromazine. I remember talking to Altschuler and asking him the details. Again, things were ridiculously simple in those days. I simply contacted Smith, Kline and French (SKF), and said I'd like to have chlorpromazine to try in patients and, in no time at all, I had an adequate supply of both chlorpromazine and placebo.

TB: Didn't you do the first placebo-controlled parallel design studies in schizophrenia, with both reserpine and chlorpromazine?

LH: I think so. Joel Elkes had done, unbeknown to me, the first crossover study, but mine was the first parallel group design ever used blindly.

TB: The psychiatrists who evaluated your patients were totally blind?

LH: Yes.

TB: Before switching to chlorpromazine hadn't you done other studies with reserpine?

LH: Yes, a year or two earlier. Nate Kline, who always had original ideas, some rather far-fetched, decided that if reserpine was good and chlorpromazine was good, the combination would be better, which sounded reasonable.

TB: Am I correct, that you also studied the effect of reserpine in normal subjects?

LH: Yes, along with the studies in schizophrenia, I was curious how it might affect normal people. As I recall, we got nineteen normal subjects. Half got one milligram of reserpine a day for a week and the others got placebo. The placebo people complained of the trivial things you expect with placebo, but the ones who got reserpine felt like they had the flu with mild diarrhea, which was one of the side effects of the drug. But the most striking thing was that seven out of ten developed depressed feelings. I reported that along with the early experiments of reserpine and chlorpromazine in schizophrenics.

TB: People talk a lot about reserpine and depression, but when one looks at the literature, you are one of the few who published findings.

LH: I was curious about that.

TB: It seems what you noted, as you described, was not clear cut depression.

LH: I guess we'd call it dysthymia these days.

TB: Technically, for the psychopathologist, it would have qualified as dysphoria, feeling lousy, and not for dysthymia which is having a depressed mood.

LH: Nonetheless, it was easy to see how reserpine developed a reputation, not only in psychiatric patients, but also in hypertensive patients, of being able to produce depression and there were several case reports of people committing suicide. People who are hypertensive tend to be depressed regardless of what they get.

TB: Reserpine and depression is a tricky issue. In some countries, such as Argentina and Hungary, for example, they even used reserpine in low doses in the treatment of "neurotic depression." Michael Shepherd, I think with Davies, found that in low doses it was an effective treatment for those patients. When did you first publish your findings with chlorpromazine and reserpine?

LH: I got an invitation to the AAAS Meeting, which was held traditionally in Christmas week, and in 1954, was to be held in Berkeley, which was close by. So there was a chance, for the first time, to publicize my work. At the AAAS Meeting, I gave a paper reporting on the studies we did with reserpine and chlorpromazine.

TB: So, you reported on findings in several studies.

LH: In one paper. I always tried to be economical. In those days, I was terribly naïve; I thought I was giving a paper in public and it was going to be published, so that's all I needed to say. So, I made no more mention of it. The paper was given at the end of 1954, and the book that had the paper in it appeared sometime in 1956, about a year and a half later, which is the way books are. And, of course, it wasn't read by many people. I don't know what kind of printing they had, but it couldn't have been very large. If there was a way to keep your "light under a bushel", I was doing it. I think the book was edited by a young chap named Jonathan Cole, who was a protégé of a famous neurophysiologist, Ralph Gerard, from the University of Michigan.

TB: Oh, by Jon Cole and Ralph Gerard?

LH: Gerard was a fascinating guy. He was one of these short pyknic individuals, with a round bald head and cherubic face. He always had a quip, some joke, but he's most famous for the line, "Behind every twisted thought, there's a twisted molecule." It was through his pressure that the Psychopharmacology Service Center was set up as a branch of the National Institute of Mental Health, and Jon Cole became the first Director. I'm not sure of the details but I think that this is generally true.

TB: So you first presented your findings with chlorpromazine and reserpine at the AAAS meeting in Berkeley?

LH: I'd been working in a vacuum, almost totally by myself, until at that meeting I ran into people who were in the field. I remember Dick Roberts from Ciba accompanied me to the Berkeley meeting and he recognized Nate Kline heading toward the podium. So Dick introduced me to Nate. Nate's attitude toward both of us was like we were peasants beseeching the emperor; I was put off by it and remember saying to Dick, "Who in the hell does that son-of-a-bitch think he is? Does he think he's going to get the Nobel Prize for using your drug"? Well, that wasn't so far-fetched. Two years later, he did get the Lasker Award. It may be he wasn't so off the mark, but that was a disagreeable beginning. That was a rocky relationship Nate and I had over several years. Sometimes we were friendly; sometimes we had almost ad hominem arguments. Nate was a strange person. He always had this chip on his shoulder and he'd never miss a chance to get into an argument, even if there was a way to find some resolution. He was, of course, tremendously ambitious, which I guess we all were. That's not to fault him, but he would pick up any little idea and immediately follow it. I remember something came up from someone that copper oxidase enzyme in blood was increased or decreased in schizophrenics and Nate immediately studied it and wrote a report. A year or so later, we found it wasn't changed at all, wrote a report and that was the end of that. Nate was always willing to go out on a limb to be first and that was a manifestation of his great ambition.

TB: Anyone else you would like to mention who participated in that meeting?

LH: I ran into Murray Jarvik, who was there to talk about LSD. Somewhere in the history of psychopharmacology the Abramson Group seems to have been lost. You hardly ever hear of them. Murray was part of the group led by Abramson in New York, which used to get together every Friday night, and after an elegant meal, they all took LSD, did some tests while on it, and on Saturday, they'd write papers on the different effects of LSD on the various tests. There were about seven people in that group and Murray was reporting on that. Nicotine later became his major drug of interest. Another chap at the meeting, who later became a drinking buddy of mine, was an Englishman, named John Kinross-Wright. He wound up in Houston, Texas. John was a really adventurous type. His idea was if a little bit of medicine is good, then a whole lot has got to be better. He set the course record on giving chlorpromazine to people; I believe it was six grams a day. Anyway, John did do a lot of pioneer work and as a result of his aggressive treatment he

probably described the first case of neuroleptic malignant syndrome. But at that time it wasn't recognized as an entity; I think he referred to it as an acute mid-brain syndrome. John was also very imaginative. So, those two people stand out in my memory.

TB: You had done two placebo-controlled studies; in one you found reserpine and in the other chlorpromazine better than placebo. Did you see any difference between the two drugs?

LH: Well, the general feeling seemed to be that chlorpromazine did it a little better, a little more quickly and a little less noxiously. You didn't get that flu like syndrome with chlorpromazine that you did with reserpine although chlorpromazine wasn't easy to take either. Then, of course, there was also the fact that there was no commercial advantage to reserpine. You couldn't patent a natural product, but you could patent chlorpromazine.

TB: How did you get to the idea of giving reserpine to normal subjects?

LH: I was always curious as to what drugs do in the absence of pathology, so that's why. Because of my interest in medicine I was also interested in side effects and I had seen the first cases of acute dystonic reactions in this country. Maybe I didn't see the first ones, but I recognized them. It was my custom at the time to start off with parenteral medication then switch to oral and we were working with the second phenothiazine SK& F had, which was prochlorperazine, (Compazine). I started three young patients on it with an IM injection in the morning and by evening, when I was leaving and while I was at the nursing station, one of the new subjects came up and said, "Ahhhh, I can't talk." I'd never seen this before and nobody else had. I looked at the nurse and I said, "Well, what do you expect? He's crazy." I thought it was some sort of a bizarre hysterical reaction. In those days the all-purpose drug was Phenobarbital, so I ordered it. I called back a couple of hours later after I got home, and said, "How's the guy doing?" She said, "Fine. It's all subsided." So, it seemed definitely to be a reaction to the drug. One of the advantages of being in a medical area, where there's a tremendously good medical library, is you can find out what's been going on if you really want to. So, I went to the Lane Library at Stanford and there was an article in Nervenarzt, the German neurological journal, about a year before, which told the whole story of acute dystonic reactions, covering everything. After I read that, again in my naivety, I thought once it's in the literature it becomes generally known; there's no use reporting anymore, because it's all there. Of course, it wasn't and up until ten years later, there were still case reports of dystonic reactions appearing in the literature. But, it was that sort of thing that would attract me.

TB: When did you work with prochlorperazine?

LH: This was about 1956. SK&F, for commercial reasons, decided to promote that drug as an antiemetic.

TB: In Canada, it was marketed as an antipsychotic. Did you do the same kind of placebo controlled parallel design study with prochlorperazine as you did with chlorpromazine and reserpine?

LH: We were starting, but I don't know we ever finished that study, because when SK&F decided to go the antiemetic route, I abandoned it. It was a perfectly good antipsychotic, but the reason they abandoned it was commercial. They didn't want to compete with their own product, trifluoperazine, which they were developing. Until ten years or so ago, Compazine was a major antiemetic drug. Now, it's been superseded by a number of others.

TB: During those years you picked up and reported on several side effects with psychotropic drugs.

LH: Over the next several years, we had a number of papers on side effects. One of the first was hematemesis and melena, associated with reserpine. And, while one could make a case that reserpine could produce peptic ulcer, because of its parasympathetic activity, my impression was that these were gastric erosions due to increased acid. You could get a good bleed from them, but they were not the kind that continued and gave a lot of trouble. Later on, we had a report on unexpected asphyxiation associated with a number of these drugs. I was called to see one patient in the night and he didn't have any signs of life. The idea that he died of asphyxia was a reasonable one at the time, but later on we realized that it was probably ventricular fibrillation.

TB: Now, in addition to chlorpromazine and reserpine, you were also one of the first in North America to work with Hydergine, an ergot alkaloid, in geriatric patients, sometime in the 1950s.

LH: Oddly enough, my first psychopharmacology paper was on Metrazol in old age. I did a study on oral Metrazol, which was considered to be an analeptic drug. Now we'd call it a GABA antagonist and it didn't work. Then we did a study with Hydergine and had very good results in two patients; the others showed no change. Both of these patients had hypertensive brain disease, which we now call vascular dementia. I've often wondered why people don't think more of treating the vascular component of dementia. It used to be that vascularization accounted for about a third of old age dementias, whereas now, it's only ten or twelve percent because of the better treatment of hypertension. The vascular component is treatable even with anticoagulants or aspirin or any number of antihypertensive drugs. All of these are probably simple, safe, and relatively effective treatments. They're not going to affect a lot of patients, but they might benefit some. I think this

accounts for the occasional anecdotal experience, when somebody says, "Gee, I put my grandmother on Hydergine and she did wonderfully."

TB: Weren't you one of the first who published on Hydergine in old age?

LH: I was, and I felt much more confident to be a judge of the effect of Hydergine on psychosis in the aged than about the effect of reserpine and chlorpromazine in schizophrenia. I don't remember other people working with Hydergine at the time, but I remember several working with chlorpromazine. Yesterday, thinking about this interview, I remembered one of the neglected names in psychopharmacology is Nathaniel Winkelman. He published, in JAMA, the first report on chlorpromazine in schizophrenic patients in the U.S.

TB: Is he alive?

LH: No. I'll tell you the story. Winkelman was son of a prominent Philadelphia neurologist and neuropathologist. He was a straight out psychiatrist of the time; SK&F, when they got chlorpromazine, was just a small company and weren't prepared to do any kind of scientific study. So they decided they'd get a psychiatrist to look at this drug, found Winkelman, and persuaded him to try it because he was local and they could keep their hand in. And, that's how Winkelman got to study chlorpromazine first.

TB: Another early investigator of chlorpromazine in this country was Kinross-Wright.

LH: I don't think he was as early as Winkelman, who had the pressure of SK&F behind him to get published. I don't remember the cause, but Winkelman died very early in life and that's why nobody's ever heard of him; but he left his mark as the first who tried chlorpromazine. SK&F had only one drug. Since 1937, they had dextroamphetamine and they were making a living on just that.

TB: What did they sell it for?

LH: Initially, as an antidepressant, I think. It wasn't too long after, when some pediatrician found it was good for the hyperactive child, so that indication came along pretty early. Appetite suppression also came along quickly. So, there were a number of indications. Gordon Alles, the pharmacologist who rediscovered it, because it was synthesized back in 1898, had a patent on it and became the largest stockholder in SK&F. He was a big philanthropist in Southern California, making all his money on one drug.

TB: In addition to reserpine, chlorpromazine, and Hydergine didn't you also work with meprobamate in the mid-1950s?

LH: I picked that up around 1956. I remember I paid a visit to Frank Berger and heard the whole story; how they were looking for a long lasting form of mephenesin and put two carbonic acids on either end which prolonged its action. I got a little booby trapped by that. I thought it'd have a more specific activity than the barbiturates, but it didn't have anything special.

TB: What population did you use it in?

LH: I decided to try it in schizophrenics; that had become my major interest. We gave as much as forty eight hundred milligrams a day, which puts you at a great risk of dependence. Later on, I did a formal study of meprobamate dependence. We did see improvement, but it was more on the behavioral side. What I saw, and probably misled me, was the same thing we see today when we use benzodiazepines to curb disturbed behavior in schizophrenic patients, while using the antipsychotics to work on the psychosis. It wasn't that meprobamate didn't help, but it was not effective as an antipsychotic.

TB: It wasn't as effective as chlorpromazine or reserpine in that population. Weren't you the first to pick up withdrawal reactions with meprobamate?

LH: We did a study with high doses up to forty eight hundred milligrams. People could not go any higher without becoming ataxic. It turned out meprobamate produced a classical withdrawal reaction, the same thing that had been described by the group in Lexington a few years before, with short acting barbiturates. We were using simple chemical measures for plasma concentrations and calculated the half-life was about eleven hours, which would put it in the same realm as short acting barbiturates. For practical purposes, meprobamate had the same kind of withdrawal reaction as the short acting barbiturates, and we applied about the same increment in dose to produce it. I don't think it ever became a major problem in clinical use because most people thought twelve hundred milligrams was a sizable dose.

TB: Then you became involved with the collaborative Veterans Administration studies, didn't you?

LH: The VA had a history of doing collaborative studies, dating from the end of World War II, when streptomycin and other drugs, like isoniazid and iproniazid, came along for tuberculosis. In those days, there were hospitals diverted to treating tuberculosis patients in a sanatorium. There were hundreds of patients languishing there, sometimes on eighteen months of bed rest. It'd kill me. I don't know how you could do that. So, the VA and the Armed Forces developed a set up around 1946 or 1947 to study these drugs in tuberculosis. They used the double-blind technique,

derived from a clinical pharmacologist at Cornell, called Harry Gold. Cornell used to have wonderful conferences on therapy that Gold produced; they were published periodically and would discuss the treatment of different medical problems. Gold was always harping on the need to do double-blind studies. In those days, he was a voice in the wilderness, because no one cooperated, but with the VA/Armed Forces study of the anti-tuberculosis drugs, that became much more acceptable.

TB: Were you involved in studies with iproniazid?

LH: No. I'd had a little experience with iproniazid, but unfortunately, in the first three patients we treated, we had a case of jaundice, and I did a liver biopsy and showed it was typical parasitical jaundice. I remember Dr. William Middleton, the Chief Medical Director of the VA came by; he was a fascinating man, tremendously interested in every aspect of medicine and he would go into backwater places like ours to find interesting cases. I pulled up a slide and told him the story and he was very fascinated.

TB: So, you were not involved in studies with iproniazid?

LH: No, but the VA decided these drugs were important and needed to be looked at, so they asked every psychiatric hospital to nominate somebody to go to the central office to discuss this. Our administration decided that they'd send the Chief of Psychiatry, the same guy that told me to get lost, as our representative. That didn't work, and the next meeting, a few months later, they specifically asked for me to come and from that point on I became closely allied with the VA collaborative studies on chemotherapy and psychiatry. That was an eye opening experience because even though I had met people like Kinross-Wright and Nate Kline, psychiatrists in the field, I had never been exposed to a great number of other people that were important. For instance, I knew nothing about psychometrics and statistics. All of these things were fairly new, but I got to meet Maury Lorr, who developed one of the first major scales for evaluating psychiatric patients, the inpatient multidimensional scale (IMDS), later refined by John Overall and Don Gorham into a brief psychiatric rating scale (BPRS), which became the most popular rating device in psychiatry. I got to meet a number of biostatisticians. I had contact with one on a follow-up study I was doing on rheumatic fever, a chap from the National Academy of Science (I can't think of his name right now); it wasn't an inferential statistic that we used, but a more descriptive approach. This was something new to learn. At the same time, I had good ideas about design, and as a result, there were a series of large scale Veterans Administration studies involving a number of phenothiazines

in schizophrenic patients, and ultimately, one on antidepressants, as supplements to try helping what we now call negative symptoms, patients that don't show much motivation. The very first study was quite encouraging. We had four treatments; chlorpromazine, mepazine, not widely used but thought to be good because it didn't have many side effects, a positive placebo, phenobarbital, and an inert placebo. That study came out extraordinarily well. You couldn't have written the script any better; chlorpromazine was clearly effective, more so than any of the others. Mepazine had some effect, more than Phenobarbital, and inert placebo did nothing. We were able to differentiate between two effective drugs, one good and one not so good, and I thought that was a good level of sensitivity.

TB: The studies of the Veterans Administration with antipsychotics preceded the NIMH Collaborative Studies.

LH: These were the first major multi-clinic studies and we had done two or three of them before the Psychopharmacology Service Center decided to do theirs. There have also been a few States that have done studies. I think California had one, and I'm not sure that Fritz Freyhan didn't do one in Delaware. They were all modeled after the VA studies. In 1954, there were untreated patients all across the board, but by 1956 or 1957, when we began to do these studies, the drugs had already made inroads. But we were still getting a lot of new admissions. As you know, schizophrenia takes a while to develop. One of the thoughts that occurred to me early in the game was, all these guys are veterans and some of them are as crazy as can be. How in the world did they ever get into military service? I had done a great number of clinical examinations on people entering the military and I'd never let one of these guys through. At that time, it was not difficult to get their military records. So I would dig them out to see what their first contact with psychiatry was. The amazing thing was, that these youngsters, age eighteen or so, like most young soldiers were anxious, so the diagnosis of anxiety reaction was perfectly reasonable. But now, five or six years later, they were clearly schizophrenic. I never reported this, but I was at a cocktail party about that time and Roy Grinker was there. I mentioned this experience to him and he said, "I've had exactly the same experience in civilian life. These youngsters, the nervous kids, you think are just plain nervous but in a few years, they become psychotic." That reassured me; my observation was correct, but I don't think it's widely recognized. Grinker must have published it, because he's so well established.

TB: Prodromal schizophrenia.

LH: Yes, you've got the right word. There are some things in psychiatric nosology that are completely overlooked and some that become myths, like the fact that the conventional antipsychotics don't affect negative symptoms. That's one of the biggest myths ever perpetrated.

TB: Weren't you involved in some nosological research with John Overall?

LH: John Overall and I had some interest in this for years. When we were starting off, representatives of Smith, Kline & French said, "We'll give you all the chlorpromazine free. You can treat every patient in the hospital." They wanted to see what the impact was if we saturated the hospital with it. In those days, we didn't get six figure grants for doing fourteen patients. We got nothing. Everybody was clamoring for the drug, but there was no money involved. I thought that was a pretty good deal, because even at the market prices then, it would have been a fair amount of money for the hospital. I called up one of my best of buddies in the golfing world and one of the most cooperative and I said, "Roy, how would you like to have all the patients on the ward on chlorpromazine"? He replied, "Oh, my God, I've got so many patients now talking to me, who never said a word before, it's all I can do to keep up with them." If that isn't treating a negative symptom, I don't know what is. Some years later, when that idea became even more popular, the concept that conventional drugs didn't do much for negative symptoms, I looked over data from studies John Overall and I had done. We had BPS clusters, and one was particularly strong in negative symptoms and another was strong in positive symptoms; if you compared them, there was improvement in both, somewhat less in the cluster with the negative symptoms, but it wasn't nothing. At that time, I was in California and John was in Texas; I remember calling him up and saying, "John, our data clearly indicates what I mentioned." I said, "I think we ought to publish something on this before this idea gets more widespread." But, John wasn't very entranced about going over old data. He probably had the computer files tucked away, so to get the data would have required some work. He didn't have much enthusiasm and I wasn't motivated to press it. So, we never did that, but there's no question this is a myth and it's all the more developed now because of the atypicals, which are another myth, but that's beside the point. Let's see, where are we chronologically?

TB: We talked about the VA studies and started to talk about your collaboration with John Overall.

LH: I stayed with the VA collaborative system from 1957 to about 1961. In 1960, I happened to run into John Overall at one of the VA annual meetings, and John (all of my friends are good drinkers) and I were polishing off some booze and coming up with all kinds of wild, interesting

ideas. John was a very productive thinker and we decided to hook up and do a series of smaller, collaborative studies to keep up with the pace of drug development. We got grant support for that and it went on for many years. In the meantime, back in 1957, Nate had come up with the idea that combined drugs would be better, and I did a double-blind study with two drugs. You could do it just as easily with two as with one, using a combination of chlorpromazine and reserpine vs. placebo. Well, it turned out the combination wasn't better, it was worse, in terms of side effects. I must confess, I didn't give it a proper trial, because we used full doses of both drugs, so it's no wonder we got more side effects. That may have scotched the idea too early, because it died and whether we missed anything or not, I don't know. With the advent of antipsychotics with multiple actions on receptors, I keep thinking that maybe a pinch of reserpine plus some chlorpromazine might broaden the spectrum. But, I'm not convinced these other actions mean a damn thing, anyway. They're all still basically weak dopamine receptor antagonists and that's where the story lies. By 1957, I wrote one of the Medical Progress articles in the New England Journal, summarizing the concerns about side effects and complications of psychotherapeutic drugs, and I repeated that in 1960, and did another one in 1964, at about three or four year intervals. After that the number of new things didn't turn up that fast.

TB: Wasn't it about that time you did some work with thioridazine in depression?

LH: That idea came out of a very productive meeting. There were a lot of basic scientists there as well as clinicians. One of the things the basic scientists kept saying was that when they looked at antidepressant and antipsychotic drugs they don't find much difference in pharmacological activity. Of course, we didn't know the whole story at that time. Clinicians claimed, to the contrary, that some drugs were good for depression, and others, for schizophrenia. So I decided to do a study comparing both kinds of drugs in both indications. I figured no matter how it comes out, I'm going to win. So, I designed a triple-blind study in carefully selected depressed and schizophrenic patients. There were two separate studies, thioridazine, which we chose because it wouldn't take away the extrapyramidal reaction, versus imipramine. It turned out that in schizophrenic patients, thioridazine was clearly superior. Imipramine didn't make them worse, as was the myth at the time. On the other hand, in depressed patients, it was very difficult to see much difference. In Europe, there was an idea abroad that thioridazine was useful as an antidepressant. I think we might have been somewhat wrong about that, but nonetheless, it was an interesting design, because, it was triple-blind. The result was not as productive as the basic

scientists hoped, but by that time, they had discovered more meaningful differences between the two classes of drugs.

TB: Do you think that thioridazine has a place the treatment of depression?

LH: If you had a psychotic depression, it might be the antipsychotic of choice. However, the combination of perphenazine and amitriptyline seems to work so well, I don't think anybody proposes it. Plus thioridazine has an anticholinergic action, as well as imipramine, so if you use the combination, you may wind up with a lot of patients who have paralytic ileus or blurred vision. So perhaps, it's just as well that combination was never developed.

TB: I think you also did some work on the effect of thioridazine on the EKG?

LH: The EKG work stemmed from the question of why some people died suddenly. We found that thioridazine was probably the worst in terms of increasing the time for ventricular repolarization, that is the duration of the QT interval, and this would increase the odds, which were remarkably small, of a re-entrant ventricular rhythm leading to ventricular fibrillation. We also found that was due to the thioridazine metabolite mesoridazine. It's surprising how much misunderstanding there is about sudden death. One of the most memorable medical papers I ever read was when I was an intern and it was by Allen Morris, the Chief Medical Examiner for Boston, who had his lab at the Boston City Hospital, where I was an intern. It had a fascinating title, Sudden Instantaneous Physiologic Death. He was describing deaths that occurred suddenly and unexpectedly, without obvious cause where you could find nothing post-mortem. You could only die suddenly one way, and that's to have your heart stop. And the heart stops mostly from ventricular fibrillation, although there are a few cases of sinoatrial electrical disturbance instead. That explained so many things, over the course of the years. I got interested in this problem when two lawyers talked about wanting to sue somebody because a patient was sleeping with her husband who noticed, about three o'clock in the morning that she made some movements and when he next awoke, about 4:30, she was dead. Was she poisoned by the drugs she was taking, because that's the only thing that medical examiners think of? They've got to find an answer for the death certificate. There are about four hundred thousand cases of sudden death in this country every year. About eighty-five percent of them are associated with obvious heart disease and there are some probably due to electrolyte disturbances. There are a few unexplainable cases and they're the ones that medical examiners go nuts over, trying to find what to put on the death certificate.

The big problem is being able to tease out the small numbers that are due to drugs like thioridazine and mesoridazine. Fortunately, it hasn't been a major issue.

TB: While doing this research with psychotropic drugs in the 1950s and 1960s what was your position at the VA?

LH: From the time I joined the Veterans Administration in the early 1950s, I was the Chief of Medicine, mainly at Menlo Park, California. It wasn't a very big position, because it was, primarily, a psychiatric hospital. But it was a rather odd title for somebody who, by the end of the 1950's, had become fairly well known in the field of psychopharmacology, to still be called Chief of Medicine. In 1960, a new hospital was built on the Stanford campus, called the Veterans Administration Hospital in Palo Alto a few miles away from Menlo Park. This was a Dean's Committee hospital taken over by the faculty and staff of the University and I was really nobody, as far as they were concerned. They didn't know what to make of me, because I wasn't part of the official family. I was just on the clinical faculty. They had somebody else in mind for Chief of Medicine, so they made me Associate Chief of Staff for Research, which meant I was responsible for meeting the needs of a lot of prima donnas for research space. As you know, most of these hospitals are built with no research space and you have to create it. Fortunately, I was an old hand in the VA, and I knew how to get things done. Over the course of the first three years, during the 1960's, we created a lot of new research laboratories for faculty members, and that was one of my main responsibilities. By 1960, I guess the CINP had formed, but I never attended the meetings because I had a young family and didn't want to be traipsing all over Europe with them.

TB: When did you become a member of the CINP?

LH: Around 1960. About the same time I remember getting a call from Ted Rothman, in Los Angeles. I knew him as a clinical psychopharmacologist and he was in the process of starting a new society to be called the American College of Neuropsychopharmacology. Would I like to join as a founding member? I said, "Ted, there are so many societies these days, and they've just formed a new international one. Why do we need another one"? I tried to talk him out of even starting it. Finally I said, "Well, if you want to start it, I'll be happy to join as one of the first members." There were two meetings in Washington, neither of which I attended. It turns out, according to the by-laws, after two meetings you miss that are unexcused, you should be booted out! Finally, I went to the third meeting which was also in Washington and punctuated by a blizzard that marooned us, but it was a good meeting. At the hotel, we were checking out, and Ted

and his wife were nearby, so I went over and said, "You were absolutely right to found this society. It's a great one, I'm glad you asked me and I'm proud to be a member." From that point on I don't think I ever missed a meeting.

TB: You became President of the College. When was that?

LH: I guess, in 1973. After that blizzard, we moved to warmer climates, most often to Puerto Rico, but also Phoenix, Las Vegas, and San Diego. We stayed away from snow.

TB: What about CINP meetings?

LH: I attended the first meeting, in 1964, in Birmingham, because my three oldest kids were old enough to travel and get something out of it. I got to know a lot of people in the CINP. One of the most impressive was Paul Janssen. I guess I was most impressed by Paul's facility with languages; like so many educated European scientists, he could switch from French to German to Belgian and English with no problem at all.

TB: So, you met Paul first in Birmingham?

LH: In Birmingham, and I considered him one of the few geniuses I have been privileged to know. He's a knowledgeable person.

TB: You, also, became the President of CINP.

LH: Well, later on, after a humble and reluctant beginning. I also met Phil Bradley, who was the host of the meeting, and later Phil came to do a sabbatical at Stanford, and I saw him periodically. I remember having lunch with Frank Ayd who I've known since day one in the field. He was one of the first people I knew, and I knew of his sojourn in the Vatican, where he was an advisor to a couple of Popes. On Christmas 1962 or 1963, my secretary was going through the mail and said, "It looks like you got a Christmas card from the Vatican." I said, "That's undoubtedly from Frank Ayd, if it's not a signed picture of the Pope, I'll be disappointed." Well, it was just an ordinary religious Christmas card. Having lunch with Frank, I mentioned this story and Frank just kept a straight face. But, next Christmas, I got another card from the Vatican. This one had a photograph of Frank with twelve of his fourteen kids and the Pope. So he got one up on me, it really floored me. My second son probably still has that photograph somewhere. It was a nice time to get acquainted on a larger scale; I guess I'm fundamentally an organization man. Every organization I've belonged to, I wind up being active and becoming some official. I became President of the ACNP. At that time, there had only been one U.S. President of the CINP, and that was Paul Hoch, who was the second or third President. Since I was an authority with the ACNP,

they figured I would be sort of a liaison as President of the CINP, and I was honored with that. I missed very few meetings of the CINP, one in Jerusalem and the one they had in Puerto Rico. Other than that, I've attended all the meetings. They, too, have been excellent.

TB: You were also involved with Jonathan Cole's Psychopharmacology Service Center.

LH: After the VA studies in 1957 or 1958, the Psychopharmacology Service Center decided to do a study, and Jon asked me to be one of the members of the committee to advise on that. That's where I first met Gerry Klerman, who was in the Public Health Service at the time. Gerry was a very impressive young man, had a lot of good ideas, and was a lot of fun to be around. Out of that came the nine hospitals Acute Schizophrenia Study, in which they recruited mainly from State hospitals. We also went to fancy places like Payne-Whitney Clinic. In those days, there was much less consciousness of mania than there is today and, undoubtedly, all these patients were not really schizophrenic, but were probably acute mania and that may have altered the results somewhat. The study first proved that the antipsychotic drugs worked, which was no surprise. I'd always said that any idiot could tell, after you saw two or three patients, without any controls, that something was working. But, at that time, the ranks of psychiatry were very much against drugs, especially academic psychiatry, which was dominated by analysts, or analytically oriented faculty. That's why, in the history of these drugs, it's largely been the non-academic centers that were involved, not the big academic centers. They thought this was all a fashionable thing. So, in order to persuade people there was really something to it, we had to do impeccable controlled studies to convince them this was not wishful thinking. We had to do what I call "massive scientific overkill." All these elegant controlled studies proved to the skeptics that there was something to it. Now this has become a routine affair. To get something through the FDA, you've got to do big controlled studies, similar to the early ones.

TB: Am I correct that you are saying these large multi-center studies were overkill?

LH: I think I can say this with no fear of having an axe to grind, because I was instrumental in getting that method going. Now we need to find new ways to prove these drugs that are simpler, cheaper and quicker, because to do these massive controlled studies, with a couple of hundred patients, costs tens of millions of dollars and takes about a couple of years to do. Furthermore, only people with big bucks can get into the field. If somebody has something that isn't patentable but works very well, you have overcome that. So, it's time to look for a different mode of operation.

TB: You got involved with Jon Cole's Early Clinical Drug Evaluation Units (ECDEU), as well?

LH: That's right. In fact, the government spent a lot of money establishing these ECDEUs, to do just that; to take flyers on drugs that might not have a big commercial backing and see whether they worked or not. That was a good idea, but it wasn't done in any systematic fashion. People did, more or less, what they wanted to.

TB: When did you get involved in the ECDEU network?

LH: When John Overall and I decided to split from the major VA studies and do these collaborative studies with maybe five clinics working together; we obtained one of the ECDEU grants to support that. And we went through a number of drugs and studies. We did a reprise on something I'd done earlier on chlordiazepoxide (Librium), studying possible withdrawal reactions. Around 1959, Roche was beginning to develop Librium. I had not studied it, but I was invited to a meeting in Princeton with the investigators, who had, and they were so uniform in their praise of the drug and all the patients swore by it. I said to myself, "If it's as good as they say, it's going to be abused." I previously mentioned I'd done a study with large doses of meprobamate in schizophrenics, so I thought I'd try similar large doses of Librium to not only study what it does in schizophrenia but, also, test the withdrawal reaction. I devised a study where we gave up to six hundred milligrams of Librium a day, after which most patients were ataxic, and then, very carefully withdrew them under controlled circumstances, measuring all kinds of typical criteria, including EEG's and plasma concentration. Unlike the other shorter acting drugs we had previously studied, the withdrawal reactions to Librium were delayed. The first couple of days, not much happened. By the third day, people began to get jittery, and by the fifth day, they had a withdrawal reaction, which was gone by the seventh or eighth day. From the plasma concentrations, we calculated the half-life to be about forty-eight hours. As a result, we described a new attenuated kind of withdrawal reaction, based on a longer half-life. Later on, that was done in our collaborative studies with diazepam, by one of the clinics without telling me, raising everybody to a hundred and twenty milligrams of Valium a day and suddenly withdrawing them to produce the same kind of reaction. The fundamental conclusion derived from this was that the onset and severity of the withdrawal reaction is a function of the half-life of the drug. We studied another, meprobamate-like drug with a half-life of two hours, but couldn't get anyone dependent on it.

TB: Was that drug, Tybamate?

LH: It was. With Phenobarbital, which had been used for many years in chronically epileptic patients, there had never been any withdrawal problems, because with a ninety-six hour half-life, it has its' own tapering off action. That principle, we derived from different half-life studies, has remained constant ever since and is still valid.

TB: Your idea of why there were no withdrawal effects with tybamate was rather novel.

LH: I think it was new. The whole idea of measuring blood levels, most of the drugs were new and the technology had improved. As the more complex drugs became available and more sophisticated methods were needed, this became a new area. In the 1960's, measuring plasma concentrations became fashionable.

TB: I think you were also involved in testing some of the biochemical hypotheses in psychiatry.

LH: Let's put it this way, I've always been a dilettante, and I've had the freedom to choose whatever I wanted to say. That's probably also been something of a disadvantage, because it hasn't kept me following a solid line of evidence, where I could develop a field entirely, but it has been interesting because I can go where I desire. Now, a number of things have come up from time to time that had theoretical implications in schizophrenia. For instance, one of the earliest was the pink spot. This was found only in schizophrenics, it was said, and chemically, it turned out to be 3,4 dimethoxyphenylethylamine, DMPEA. The dimethoxyphenyl group removed from mescaline. So, it was extremely interesting to think this might be the endogenous psychotogen that everybody was looking for, the chemical that caused schizophrenia. This had been postulated by Hoffer, Osborn, and Smithies about adrenochrome and various other substances. I heard that Arnold Friedhoff was playing around with it, so I decided to see what it did in man and took the first dose, which was rather small and nothing happened. We gradually increased the dose, until it was obvious the compound had no activity, or so little, that it didn't matter. In the meantime, Arnold had been working on it in the military and found it was very quickly metabolized with a half-life, measured in minutes. So, we published two papers, one on the metabolism, and one on the clinical aspects. That scotched that idea. Another notion was that, if the dopamine hypothesis was correct, too much dopaminergic activity might cause effect and, to this end, we studied a drug called acetyl methyl tyrosine, which has a specific effect on tyrosine hydroxylase, the main synthetic enzyme for dopamine. Sam Gershon and I were simultaneously beginning work on it but didn't get very far before they said we couldn't use it in man because in dogs it produced kidney stones. It turns out dogs have a very acidic urine and this material would normally be

precipitated. So it wasn't likely to cause any trouble in man, but we had to stop. We published our results showing it had no clinical effect at all. Those were a couple of approaches to theories on what might cause schizophrenia.

TB: By that time you were also interested in chemically induced psychosis, right?

LH: That happened around 1960. I looked over the field with LSD and wasn't keen about the work that had been done so far and thought I could do better. My first question with any drug is to find out what it does clinically. So, I took pains to elucidate the clinical syndrome that LSD produced. Up to that time, you could read a hundred papers on LSD and not know what it did in man. Other hallucinogenic drugs were coming, including psilocybin and mescaline, which was an old hand. It turned out all three were almost interchangeable, except for there was a difference in dose, with mescaline being the least potent and LSD the most. Otherwise, they were all qualitatively pretty much the same. One of the interesting questions was whether LSD produces a model psychosis similar to schizophrenia. The idea was to get some tapes from people on the drugs and compare the interviews with schizophrenics. Painstakingly, we edited the tapes for any references that might tip off which tapes were which. Then we asked about twenty psychiatrists to review them, and all of them could tell immediately which tape was from the subjects on LSD and which the schizophrenic patients were. Then we said, let's see if psychologists can tell. They could. Then, let's see if nurses can tell. They could. Then, let's see if social workers can do it. They could. So it was obvious there were major differences in what the subjects were experiencing and expressing. That killed the idea that LSD produced an honest to God model psychosis. I used to quibble about that with Danny Freedman, who was interested in LSD from way back and did similar work with LSD. We settled it by saying it might help in the very early stage of schizophrenia, but not with the later stage with the patients I studied. I still think I was right, but Danny was such a gentleman, you couldn't disagree with him with much enthusiasm. He was a fine, fine man. We did a lot of studies over the next 6 years from about 1960 to about 1966, where we looked at LSD in facilitating psychotherapy, which was one of the major claims. We used LSD, psilocybin, and mescaline in various doses, taking patients who were stabilized in psychotherapy, and doing one interview with no drug, one with placebo, and one with each of the three drugs. So we had five interviews and I had a blind rater evaluate the interview content for how much useful information, psychotherapeutically, might have been derived from it. It turned out they were the same, and I concluded that, if you wanted to loosen up a patient for psychotherapy, a couple of

martinis would probably give you much more reliable data, because LSD, psilocybin, and mescaline muck things up. So, that was one of our studies. Another study was derived from the fact that some engineer, who had become a quack in this field, was going around the country and giving alcoholics 600 microgram doses of LSD, which is a fairly good jolt, with the claim that after one dose you were cured. You got instant insight into everything that caused you to be an alcoholic. That seemed to be too good to be true, so we tried to do a control study; I thought the best control drug would be dextroamphetamine. I took the first dose of 60 milligrams, and if I hadn't known what I'd taken, I would have thought it was the world's best tranquilizer. Everything was working on all cylinders in perfect tune, and it was wonderful. I couldn't sleep, but who cared? So, we used that dose as the placebo and then gave them a substantial dose of LSD. We found there was no good alcohol rating scale. At that time, everything was, either you're a drinker or you're not. I thought that was a rather foolish criterion, especially when you're trying to do a quantitative comparison. So I got some psychological help to devise a drinking behavior inventory, which touched on the amount that people drank, the effect on their personal life, their job, and all areas likely to be affected by alcohol. It looked pretty valid and was able to make distinctions, but on further analysis, the major criterion for making these distinctions was how much you drank. Simply tabulating the number of drinks per day would probably have been as good. About ten years later, somebody rediscovered the scale, and I began to get inquiries about reprints but I never thought it was wonderful and I still don't think there are scales that quantitatively measure how much damage alcohol is doing. Not that I'm a convert to the idea of controlled drinking, which is very controversial, but since people are not generally going to be pro-abstinence, at least not most of them in treatment, getting them to reduce their drinking might be of value. We did every study we could with LSD, and by 1966, I decided to give up on it.

TB: Weren't you also involved with STP and THC?

LH: In the summer of 1967 in San Francisco, where all the hippies were born, there was a drug on the street called STP, which the Feds were quickly able to identify as 2,3 dimethoxyamphetamine. I was at a meeting in Washington on drug abuse reform and a chap who worked for them, named Milt Jaffe, told me about the problem in San Francisco with this drug and they didn't know what was going on with it. He had some in his desk drawer and gave me an armload of it. In no time at all, we found out it was identical, qualitatively, to the LSD, mescaline, psilocybin group. But, unlike them, tolerance developed fairly rapidly to repeated doses, and you

couldn't block the effects with chlorpromazine or antipsychotics; the notion being that if these drugs were truly models of schizophrenia, then antipsychotic drugs should help. But they don't, they tend to make things worse. We had that all wrapped up and I sent a report within about 3 or 4 weeks to the Committee on Problems of Drug Dependence. They had a meeting to consider this problem, and the person who chaired it, the dean of drugs of abuse, was Nathan Eddy. Nathan was very impressed by the report and there was nothing to do but to become a member of the committee, which began a long association with that group. At that time, it was under the auspices of NASNRC and we met in their building on Constitution Avenue. In a couple of years, I became the Chairman of the committee, and served for several years, until the NAS wanted to reduce the number of committees and decided to "off load" this one. So, it became my duty as Chairman to shepherd the committee from the NASNRC to an independent state. It took a lot of time and effort, but it was worth it, because the committee survives as a College on Problems of Drug Dependence, a membership organization and the most prominent, scientifically impeccable group, devoted to substance abuse. About 1966, Mechoulam in Israel finally determined the true structure of THC, which was not much different from the structure of the compound synhexyl discovered by Adams in England around 1940. When THC became available, I decided it would be interesting to study the clinical effects, and to know if synhexyl was like THC, because synhexyl had been used in a lot of clinical studies for possible therapeutic uses. At that time, there was a retired pharmacologist from Abbott, R. K. Richards, working in our area, who went back to Abbott and was able to get some twenty five year old synhexyl in a little glass vial that was in the freezer. It looked like a bunch of tar, but we reconstituted it in alcohol and water, and were able to make a hydro-alcohol solution, where we knew the dose and compared it with oral doses of THC. So the first study was a comparison between synhexyl and THC. To make a long story short, they were very similar, the major differences being synhexyl had longer latent periods and it was weaker. Otherwise, it was qualitatively quite similar, which gave validity to the previous work that had been done with synhexyl. We were also able to develop the clinical effect and time course of THC on neuron intoxication, and I plotted this on a time scale, graphically. Two or three years later, when labeled THC became available, Lemberger and Axelrod's laboratory did the same study using labeled material and it was the same one we drew from clinical observation.

TB: When did labeled THC become available?

LH: Around 1965 or 1966. Harris Isbell and his colleagues in Lexington had it first, and we were the second. A chap named Andy Weil got into the game at that time. He'd just graduated from Harvard Medical School, and he'd been a botany major as an undergraduate. So he was interested in drugs in plants and embarked on a study using marijuana. His paper was published in Science, but I wasn't bright enough to figure that this would be of interest to Science, so I published my results in the Clinical Pharmacology Journal. I must say, in all fairness and not being modest, our paper was more informative than his. Andy became propelled, all of a sudden, into the first ranks of substance abuse people, about which he knew nothing. When it came time for him to go into the military, he wanted to go to the Public Health Service and they offered to send him to Lexington. Anybody in their right mind, who wants to do things in substance abuse, goes to Lexington to learn the ropes, that's the Mecca. But, Andy turned them down. At one meeting, Andy was giving his paper and I was sitting next to Jerry Jaffe, who looked over at me and said, "Is this guy for real?" I replied, "You said it, Jerry, I didn't." So I'm not at all surprised he's currently the big guru of alternative medicine and probably making millions of dollars, but as a scientist, he was zilch. You do run into some strange people. Anyway, that got us started on studies with marijuana, which continued until recently. I don't think we've done anything for 3 or 4 years, but I've a couple of studies still not written up for publication and we covered, pretty much, all the aspects of marijuana.

TB: Could you review the most important steps in that research?

LH: I can't think of all of them. We did electrophysiological studies, things like contingent negative variation and continual EKG recording. We studied the biochemical effects vs. clinical effects, over and over, using the various isomers and found out that cannabidiol and cannabinol, the only other naturally occurring cannabinoids, were virtually clinically inactive and there was no interaction between them and THC. We studied a number of other interactions with THC. It was a sizeable body of clinical work and probably the largest on THC and marijuana that's around.

TB: What were your conclusions?

LH: If you got a big jolt of it, you get a very rapid heart rate and conjunctivitis, both of which we showed were accurate in determining how long the drug was effective. The tachycardia can be a problem in people with angina, but on the whole it was very safe.

TB: Do you think it should have a place in treatment?

LH: We came to the conclusion that there are very few contraindications to using it.

The evidence is shaky, but our clinical evidence suggests that if you have a history of schizophrenia or mental illness in the family, stay away from the drug. The Swedish experience suggested that there's a more direct relationship, but I'm not sure. We did notice when patients would go on week end passes at our hospital, they would often come back on Monday kind of loony, and if we did urine analyses, we'd find they had marijuana metabolites in their urine. This led to a routine practice of checking people when they came back from passes. Most of them, who had positive urines, also had some clinical deterioration. So, I don't think it's good for people with mental illnesses, or for people with coronary disease, to have it. Probably among social drugs, it's as safe as any, but maybe caffeine is a little safer. I don't know. It doesn't cause anywhere near the morbidity and mortality that nicotine, in the form of tobacco does, and certainly not as much as alcohol in its various forms. As far as therapeutic uses are concerned, the case is already made that oral THC can be effective to treat nausea and vomiting associated with cancer chemotherapy. It's on the market and rescheduled as Class 2 for that indication. The only trouble is, the company who makes this stuff and who got a totally free ride from NIDA in developing it, charges an arm and a leg. It's very, very expensive. If you do the same thing with marijuana cigarettes and buy them on the street corner, you could save a lot of money. There's no reason, pharmacologically, to believe that if the oral preparation works, the slow smoked preparation shouldn't work. It would be on a different time schedule, because the pharmacokinetics is different and we explored it extensively. The other possible indication is the relief of pain; nobody has any idea of how it does that, but there are enough reports that it has some analgesic effect. I rather expect that's going to await the development of the synthetic cannabinoid, which may not have the mental effects, and which could be patented in analgesia. There's also some reason to believe that it's effective against muscle spasticity, which is not very well relieved by any existing drug. That has hardly had any work and deserves much more. So, there are some valid medical indications that need more exploration and I don't see any reason to think that marijuana is any different from any other drug being developed.

TB: Have you published on that?

LH: The final draft is being typed up this week and will go off to Israel next week.

TB: To the CINP journal?

LH: Sure. It probably has 200 people submitting important papers, so it might help the new journal get off the ground, and secondly, they give a good review. I may not agree with all the referees, but I don't mind telling them when I don't, and when I do, I am very grateful.

TB: That's the last paper you wrote. Am I correct?

LH: I don't know whether I'm going to write any more or not.

TB: Well, let's just see.

LH: As you get older you do less original research and more review papers. I've got a paper coming out in the Canadian Journal of Psychiatry on Calcium Channel Blockers in Psychiatry. We did a study on that a few years back, which seemed to indicate that Verapamil was about equivalent to Lithium.

TB: You started to work with Calcium Channel Blockers years ago?

LH: I think our study was published about ten years ago and there were weaknesses in it. First of all, the sample size was small, and you had a very good chance of not being able to reject the null hypothesis. The second thing was, I don't know what was wrong with our patients, but none of them did very well and the results of the treatments were rather poor. But the American Psychiatric Journal accepted it and there were a few other reports that suggested it might be useful, including a number of papers on mania, going all the way back to the early 1980's. A fellow named Duboski in Denver has done most of the work. Curiously enough, there's a whole chapter on this in the new textbooks that the APA published. There have been two studies, one from Australia, which indicates it wasn't nearly as good as lithium, and the other one from John Davis' group, saying that it was ineffective compared with placebo. Now, if that doesn't kill it, I don't know what does.

TB: Let me just switch a little bit. When did you start to work with lithium?

LH: I never did much work with lithium.

TB: Why was that?

LH: Being an internist gave me a disadvantage, because I remember in the late 1940's, lithium chloride was introduced as a substitute for sodium chloride in patients with congestive heart failure. The idea was, you reduce the intake of sodium, but all of a sudden, a number of these people died and it was probably lithium toxicity, because due to the diuretics, they weren't getting rid of it. So, when I first heard of lithium in psychiatry, I said that's a poison. I couldn't imagine it could be useful. I think Sam Gershon did more than anybody, along with Cade's work in

Australia, to popularize it in this country. I regret I had very little to do with lithium, because it certainly was one of the major advances.

TB: Let's go back to the 1960's. Some of the theories about the mechanism of neuroleptics came about in 1963 by Carlsson and Lindquist, the dopamine theory. You worked with haloperidol, at first, in the early 1960's, and with some of the other buspirones. Is there anything you'd like to comment on in the treatment of schizophrenia?

LH: Recently, I had occasion to look at a paper I published in 1962, which I think was the first North American paper on haloperidol, and I was dumbfounded. The doses we used to produce an antipsychotic effect were two to four milligrams a day. I thought, oh my God, I forgot my own lesson, because I'd been using ten milligrams and had some people on massive doses, and we've all been using too damn much. It's interesting to think, in terms of the atypical antipsychotics, that if we compared them to four milligrams of haloperidol, instead of ten to fifteen, that the differences would not be so great in terms of extrapyramidal reactions or tardive dyskinesia, but we missed the boat. There were a couple of people in New York, one of them named Haase, who developed a dosage threshold, the onset of micrographia.

TB: That's right.

LH: They showed you could get detectable micrographia beginning at very low doses as a neuroleptic threshold, but I didn't believe it. They were right. We've been using, altogether, too much.

TB: Paul Janssen was very much for the handwriting test. In the late 1960's, he was so much in favor one should use it, that he published a book, Neuroleptic Drugs, written, a very small part by Janssen, the rest by Haase. So there was some kind of disagreement between the real clinical needs and marketing.

LH: I remember Paul telling me that the custom in Belgium was to have it in liquid form and let the nurses regulate the dose, drop by drop, literally. They were using low doses and very small increments, but we all missed that. If we did a new study comparing the atypicals with small doses of haloperidol, it might not look as different as people think.

TB: Did you work with the atypicals?

LH: No, I've not worked with any. By that time, I'd long since given up testing drugs. Back when John Overall and I were working, and nobody knew what the best ways were to give the drugs, what was the best way to use rating scales, or what were the best statistical procedures, it was

something you could contribute that was original and scientific. Now, it's all become so standardized, the drug companies have big groups of people designing protocols, rating scales and report forms, and analyzing statistics. They come to an investigator with a protocol about that thick, all written up, including the consent form, and if you say you'll do it they ask how much? I saw a protocol the other day for fourteen patients and it cost about \$140,000.00. It reduces the investigator to a mere peanut gallery, and most of the studies are done by the flunkies they hire, so there's no scientific input at all. Will they accept the investigator's article? No, they send it out to some flack firm that specializes in writing papers and it is written impeccably by people who know nothing about the study. The names on the paper go by how many patients you've contributed. Well, that's a helluva way to do things! I can't think of anything duller. So, I gave it up years back. The last study I contracted to do, I did only to get one of our new faculty started.

TB: So, you think we are missing the boat by having a bunch of people design something, then someone else generates the data and processes it.

LH: My feeling is that any time things get standardized, that's an excuse for not thinking. When things become routine and standard, that means you stop thinking. All the protocols now are impeccable and they sail right through the FDA. The FDA loves it, so all the companies want to do is get one or two of these multi-clinic studies.

TB: Do you think that any of these atypical neuroleptics might not be different if you look at some of the old drugs with receptor assays? Do any of these new drugs contribute anything major?

LH: That's a big issue right now. I was recently at a meeting convened by a group of mental health and mental retardation administrators and they're getting terrible pressure to purchase these new second generation atypical antipsychotics for all of their schizophrenic patients, which would break their budgets. They wouldn't have anything left for anything else, because these things cost up a hundred times as much as haloperidol. I don't think anybody realizes how terribly expensive they are and how cheap haloperidol is. Ten milligram tablets of generic drugs probably cost less than ten cents. You're talking pennies versus dollars. So, there's a big drive to petition the State legislature to appropriate fifty million dollars or whatever to buy atypicals for more patients and citizens' groups are demonstrating at the Capitol. Some of the people from NAMI and other advocacy organizations are claiming this is a magnificent new era of psychotherapeutic drugs, we are doing patients an injustice, and it would be unethical not to treat them with these drugs. Now, you know where that orchestration is coming from. It's very well organized by the drug

companies, because they would like nothing more than to have these drugs declared first line treatments. I don't agree with that and I tried to point out the difference, so people don't get misled. If you had unlimited amounts of money, then sure, treat everybody with a drug that costs several dollars a day. What difference does it make if somebody else is paying for it? But if I had to pay for it, out of my own pocket, I might have a little perspective.

TB: You are still of the same mind as when you wrote a book with Ole Rafaelsen, Mini Psychopharmacology. When was it?

LH: Sometime during the 1970's. It was Ole's idea and became enormously popular. He thought of it as guide for developing countries and I forget how many languages it was in.

TB: At least ten or twelve.

LH: I didn't think it was going to be so popular, but it was essential information, which even the barefoot doctors in China could use and it was probably translated into Chinese.

TB: I think it was. If my recollection is correct, you said in that book, chlorpromazine and haloperidol are the two drugs you can do everything with. So you would still say that, right? LH: I don't work in the field of basic receptors; but the only difference between the atypicals and the older conventional drugs, if you look at the receptor profiles, is that common to every atypical is a weak blocking action on D<sub>2</sub> receptors, while serotonin blockade is variable. Besides, there's no way of proving that serotonin blockade has a damn thing to do with extrapyramidal reactions or schizophrenia. Tensin, which is probably the best available 5HT<sub>C2</sub> receptor blocker, has no effect, or Janssen would be selling it. Nobody knows what D<sub>1</sub> blockade does while D<sub>3</sub> and D<sub>4</sub> are the same story. I was talking to somebody recently, who said there's a current study going on with a D<sub>2A</sub> receptor blocker, showing an antipsychotic effect. If that is the case, there might give some truth to the idea, but, so far, I don't think there's any evidence. The new drugs work exactly the same as the old ones, only less.

TB: What makes olanzapine and risperidone so successful then?

LH: Joe Siegleman claims that is due to the fact they do not bind as tightly to a receptor as the conventional drugs and are easily disassociated, so they're in and out. But if this occurs, why should they not also produce extrapyramidal reactions as well as antipsychotic effects? Well, he thinks it has to do with the rate of firing, with the extrapyramidal dopamine receptors firing more rapidly than the others. That may be the explanation. Of course, if you look at the evidence that's accumulating, all of them will produce extrapyramidal reactions. It's simply a matter of dose. I

don't see what is so monumentally different from what we had before. Now, what could be the effect of a weak D<sub>2</sub> receptor antagonist? It could reduce extrapyramidal reactions, especially when you're comparing it with fifteen milligrams of haloperidol. It could in turn, allow these extrapyramidal reactions to be mistaken for negative symptoms, apathy and so on. That may explain the atypicals so called superiority in treating negative symptoms, which may be more apparent than real. It could also be because some of them don't seem to have a whole lot of sedative effects; although clozapine and olanzapine have plenty. It could account for the improved cognition, which I think is minimal anyway. So, if patients are less impaired by extrapyramidal reactions or sedation, it may contribute to social rehabilitation. But, these speculations are not proven. They're just possibilities and I think we're buying a lot of expense we don't need.

TB: You are more or less saying that not only are we buying a lot, but, even with the old drugs, we are overdosing. Forget about the new drugs, because there is not sufficient evidence they are different, but are you saying that with drugs like haloperidol, we should get back to the old handwriting test or something like that, and use lower doses?

LH: I would be tempted to start every day on a very small dose of haloperidol and use the classic tests to determine the neuroleptic threshold. If, at that time, the psychosis hadn't responded, using diazepam to control the behavior, then, perhaps, add a very small dose of one of the newer drugs to increase the blockade, but not crossing the neuroleptic threshold. That would save us an enormous amount and reduce use of the new drugs and pair them with older drugs where they might have some effect. Let's just say it's theoretical. I don't know of anybody who's doing this.

TB: What you are saying is understandable and I agree with you. Let's stick with that topic, because you and John Overall were not psychiatrists, but were among the first who tried to tease out which patients were responding. Am I correct?

LH: To find the right drug for the right patient has been a very frustrating experience. John and I tried it. Jim Clavin and some others in the VA tried it, and we all seemed to come to no conclusion.

TB: Would it not be possible that responders remain hidden because of the measurement instruments you employed?

LH: It may be that the questions you ask determine the answers you get, and when you use these instruments all you are doing is codifying the mental status examination, and the questions determine what areas of psychopathology you learn about. It may be that kind of clinical approach is past and we ought to think in terms of biological outcomes.

TB: Are you sure we might not benefit if we would get better clinical feedback compared to this receptor kind of thing?

LH: I wouldn't want to knock anything clinical. I'm a hundred percent for that.

TB: I'd be surprised if you weren't.

LH: You can learn a lot by talking to patients, looking at them, and observing. I've never been impressed by these elegant studies of behavioral pharmacologists on drugs of abuse, where they show that a drug abused on the street is self-administered by monkeys. You'd have to be an idiot to think it wasn't. So I keep wondering are we doing things the hard way, rather than taking a simpler and more direct approach. Of course, the simple things don't look so scientific. If you get self-administration diagrams that's science, compared to if you can show that people, given a chance, self-administer the drug.

TB: Let's push that in a slightly different direction. With atypical antipsychotics, the very first papers were not in schizophrenia. The effect moved to schizophrenia when something had to be verified in a more homogeneous population, other than all psychotic patients combined. Everything is now depending on the assumption that we have a homogeneous category, a disease entity which was artificially constructed and a measuring instrument designed to show change in it. But if the disorder is biologically heterogeneous and our measures insensitive to these differences, how would we be able to demonstrate that drug responsiveness differs? It would be very difficult to tease out. Is that what you're saying?

LH: Yes. Of course, you have to look at it from an historical point of view. In 1955, the New York Academy of Scientists had their second meeting on reserpine, which was all on schizophrenia. They had everybody who was using the drugs, or almost everybody, including Nate and me. Not a paper in that whole bunch told what kind of psychiatric patients they were treating. Mine was the only one that tried to use the DSM II, I think it was.

TB: It was DSM II.

LH: My studies were blind and controlled, and that captured the attention of the press. We tried to grade the improvements clinically, but no instruments were used. The attraction to my paper caused them to feature it on the news wire, and in a day or two, every newspaper in the country had an article about the new drug for schizophrenia with me as the principal investigator. A couple of days later, the mail started in from all over the country. I've got a son; I've got a daughter; I've got a husband; I've got a wife who is schizophrenic. Nothing is helping; can I bring them to get

this new treatment? It took a lot of time to answer every one of them personally, but it was impressive to see the power of the press, and the anguish of people who had a relative with a catastrophic illness. Nate fully expected to go to that meeting and be the star, but I upstaged him! The Lasker award, at that time, was brand new. Mary Lasker had decided to honor her husband with the award and she was very interested to make the award for advances in the treatment of mental illness. When the award came out Heinz Lehman and DeLay got it.

TB: As well as Deniker and Laborit.

LH: And, Bob Noce. Nobody had heard of Noce before and nobody's heard of him since. He was just a State Hospital psychiatrist that Dick Roberson said would try our job. I was talking to David Healy and he said, "Why didn't you get the Lasker Award?" Then I realized I probably screwed myself out of it by upstaging Nate, because Mary Lasker listened to him. That does seem to be the only rational explanation of how Bob Noce, who was a nice simple minded guy, could wind up with a Lasker Award. I'm not even sure that Noce had any major publications.

TB: Let's discuss the antidepressants. Theorizing about the antidepressants starts in 1962 with Axelrod and norepinephrine reuptake, and simultaneously, with the Brodie group. If my recollection is correct, you had a paper on desipramine.

LH: Desipramine, but we never saw a whole lot of results from it, because we used too small a dose.

TB: What was the dose?

LH: Between 75 and 150 mgs, and 100mgs is probably too small. I remember Brodie, who could be somewhat sarcastic; although we got along well, said if you want a drug to work, you've got to give it in the proper dose, and he was right. So, I never felt keen about that study; we don't hit homeruns every time we go to the plate. Sometimes we strike out.

TB: But independent of whether the dose was adequate or not, it triggered a development which moved things from the non-selective view of tricyclics all being similar. Was that warranted?

LH: At that time, I don't think there was much interest in trying to separate the norepinephrine depressions from the serotonin depressions. Desipramine is a selective norepinephrine blocker, but we had nothing that was selective for serotonin in those days. So, you couldn't test the hypothesis in a clean way; although, I'm sure many people, as well as myself, thought of it. Wouldn't it be nice to do the study? The closest I came to it was when I suggested that to some group, and Sandy Glassman said he took a crack at treating depressed patients initially, with desipramine, a

norepinephrine blocker, and then the failures, with amitriptyline, which was the most serotonergic of the mixed drugs, to see if we could tease them out. But after they treated eight or ten patients, they all responded to desipramine, so they had no way to make the comparison, and they stopped the study. I don't even know whether they published it. There was no way until the selective serotonin uptake inhibitors came along to test the hypothesis and I don't know anybody who did that. Do you know anybody that tested selective serotonin inhibitors vs. desipramine?

TB: There are isolated studies, which were in both directions, but you have to have a 60 percent response rate before the whole thing is meaningful. So it's very difficult. Do you have an opinion about whether there is anything to separating out the two groups? Do you think any major contribution has been made since imipramine in the antidepressant category? LH: In my opinion, the most interesting and original antidepressant is not a serotonin uptake inhibitor, but bupropion, (Wellbutrin).

TB: So, dopamine?

LH: Which, as far as we can tell, works on dopamine, but it's not clearly defined as to how. If you look at the molecule, it's the basic phenylethylamine structure, but they modified the side chain and this attenuated some of the amphetamine like effects. So when I see a patient and I think the depression would be ideally treated with something like amphetamine, I prescribe Wellbutrin, and it works.

TB: Would that be a particular kind of depression? In the 1964 paper with John Overall, you had four different types of depression. Would one or another be more suitable for Wellbutrin?

LH: I don't use the subtypes characterized by that rating scale. I guess I could. One thing that came out of that was the tricyclics were effective for endogenous or what we called retarded depression.

TB: Are there any other useful sub-types of depression in terms of treatment?

LH: Deniker's group has classified a mixed anxiety depression syndrome. We called it anxious depression. We brought attention to that, which is beginning to become a very popular idea. People are beginning to think there is some sort of comorbidity, or maybe, anxiety is part of depression. I remember raising this question with a psychiatrist and he said, "I can imagine somebody being anxious and not being depressed, but I have trouble imagining somebody being depressed and not being anxious." I thought that was not a bad summary statement. So, more and more, you're getting overlaps, where panic disorder, for instance, is being treated with antidepressants, and

sociophobia and some of the other anxiety syndromes have more overlap with clinical depression. Trying to separate these isn't valid and may be due to our desire to oversimplify.

TB: Is there any study to compare bupropion with a norepinephrine uptake inhibitor?

LH: I think it would be interesting to compare bupropion and reboxetine.

TB: But is there any?

LH: No.

TB: Do you think it should be done?

LH: From a theoretical point of view it would be very nice.

TB: And with dopamine agonists we are actually pushing more of the receptor activity approach?

LH: Bupropion also emphasized that it doesn't interfere with sexual function. That's a good selling point with Viagra being so successful. Another drug that would have been very interesting, if it had lasted, was nomifensin.

TB: It died because of side effects.

LH: All the evidence accumulated before they stopped it was very clean. It must have broken their hearts to take that off the market.

TB: That was the first drug effective on the dopamine system. Now bupropion is sidetracked with another indication.

LH: I don't have any idea why it works in making people give up nicotine, but it apparently does.

TB: It looks like it. But you weren't as much interested in this norepinephrine and serotonin comparison?

LH: Many people use the response of imipramine to formulate the idea of serotonin in obsessive compulsive disorder, but they forget the metabolite is mainly acting on norepinephrine, so I didn't think that was a very clean example. But there are others now that link serotonin and obsessive compulsive disorder, like Zimelidine.

TB: Arvid Carlson claims it was the first one. He keeps on telling people about tryptophan passing the blood brain barrier.

LH: I've never been very convinced that the precursors loading strategy is good evidence. First of all, tryptophan goes into the brain, but it doesn't know where to go, so it goes everywhere. You flood the brain with tryptophan and presumably increase serotonin everywhere, but that doesn't answer many questions and it could be there are places you don't want it to remain. We did try a

precursor loading strategy with choline, trying to treat Huntington's chorea, tardive dyskinesia, and ultimately, Alzheimer's.

TB: The argument you used for neuroleptics, wouldn't that apply to antidepressants; you wouldn't feel there is a justification to buy the new expensive ones?

LH: One of the earliest meta-analyses was a comparison between serotonin uptake inhibitors, as a group, and the tricyclics taking all the published papers where there was some direct comparison. It was published in the British Journal of Psychiatry about 1994, and concluded, in terms of efficacy, there was no difference. In terms of side effects, it was a trade off with a marginal value for the selective serotonin uptake inhibitors, but in terms of people completing treatment, there was no difference.

TB: There is another meta-analysis, a very recent one, and they claim that there is no difference in side effects, as well.

LH: I've taken tricyclics and they're not pleasant. I also took fluoxetine, (Prozac), twenty milligrams a day for about ten days and I wouldn't have been sure I was taking anything. I was impressed by the fact there were hardly any discernable side effects, which was much different from the tricyclic. If I had to have an antidepressant and was given a choice between a tricyclic and fluoxetine, I'd probably choose the newer one.

TB: In an advisory capacity to the State of Texas, would you suggest: if there is a major price difference, to use the newer drugs or would you say to stick with the cheapest?

LH: I'm in favor of the treatment where you get the most bang for your buck, and when the price differential is great as with the antipsychotics, I prefer the generic haloperidol which is dirt cheap. With antidepressants, the differential is not so big. One of the things that seem to stand out is that the more disturbed you are, the more tolerant you are of side effects. Most normal people find antipsychotics to be intolerable and the same is true of antidepressants. When you're truly depressed, the side effects are more tolerable. It may be you could be justified using conventional drugs first, and if the patient becomes intolerant or non-responsive, switch to the newer ones. I figure you're going to get your money's worth if they are better tolerated and more effective. In everything in life, you have to make a judgment between cost and benefit. Since there seems to be a finite amount of money for treating psychiatric patients, I'm going to think a long time before I spend that money. When the patient says, "I feel a little better on one drug than I do on the other, well, that's tough." You're getting well. That's what counts. In the case of a local situation, if

schizophrenic patients are admitted to the mental health authority and treated with the new drugs, there wouldn't be any budget left. Nothing for lodging, nothing for social rehabilitation, nothing for vocational assistance, all of the other services that patients need in order to function in life and stay out of the hospital, so if you're buying expensive drugs and have to give up all the rest of the treatment, that's a bad bargain. We have to view the situation broadly. Nobody thinks that drugs, alone, are going answer the problem. The best we can do is make it possible to use other avenues to try to improve the lot of the patients, and if you can do that by allowing them to live or function in the community and do some sort of productive job, those are the outcomes by which we measure success. We don't have a lot of people who have been schizophrenic go back to being concert pianists. They may try, but it seldom works. So, you have to set your sights as you would for any handicapped person, because if they have a physical handicap, you try to teach the patient how to work around it and do the best they can with the handicap. You don't think you're going to get rid of it, but you're going to try to work around it, and I think we have to do that with our impaired psychiatric patients.

TB: You became interested again in choline, so, could elaborate on how you have contributed?

LH: We didn't have anything to do with the development of it. That came from Peter Whitehouse and his colleagues where they traced these cholinergic tracks in the brain and showed there was some relationship between them and Alzheimer's. There was indirect evidence suggesting a cholinergic hypothesis, and I and Kenneth Davis, got very interested in this. I had run across an abstract in Federation Proceedings by the guy at MIT who worked with Axelrod, in which they indicated you could use choline as a precursor for acetylcholine in the brain. Again, we flooded the whole brain. It turned out not to be very practical, because when we started using it on patients, the ward smelled like an old fish market; the choline changed to trimethylamine and that is what makes dead fish smell. We tried a number of cosmetic devices to try to deal with that but had the impression we were losing the nursing staff, so we stopped it. Lecithin has to be metabolized in the body to free choline and it made much more sense. We also tried physostigmine and replicated studies Dave Janowsky had done with it in mental patients, and that too, caused a rather dramatic change. One of our manic patients, as we were doing the physostigmine infusion, suddenly became very depressed, starting crying, felt awful, and we had to stop. That was a rather dramatic change of mood which suggested acetylcholine might play a role in the switch process, which has never been fully elucidated. Most people think it's due to dopamine. In tardive

dyskinesia, with the physostigmine infusion, we could show by videotaping them and blind ratings, there were substantial changes in abnormal movements, but they are extremely difficult to show because they're so variable anyway.

TB: Anything else in Alzheimer's? You worked with Hydergine at the very beginning and did you work with any of the nootropics?

LH: No, but I was first with Metrazol and Hydergine. We did one study where we used six milligrams a day versus three milligrams of Hydergine and got a little result. There was a question of the basis of response, but we couldn't take the dose higher because it was rather expensive.

TB: You have contributed to many, many areas in psychopharmacology. What would you think was your most important contribution?

LH: I feel somewhat disappointed I can't point to a single real discovery in the sense of something vastly new or revolutionary. I attribute it partly to my free will, to the freedom I've been given to follow wherever I want to go, which tends to make you more diffuse compared to somebody who says I'm going to focus on one thing and find the answer. If I had it to do over again, I'd be more focused.

TB: But you kept things close to real, to Mother Earth, all through, because you kept on reevaluating and trying to establish where we really are. You contributed an awful lot just reviewing the whole field. You did that with great regularity. Am I correct?

LH: Yes, I think one of the contributions you can make is to try to reduce data into something understandable and coherent. I had a good ability to do that. As far as the experimental contributions are concerned, I would say the most important, probably, was the introduction of controlled clinical trials in psychiatry, which is still a major influence. It would have happened without me, but I think I gave it a little push.

TB: A start. You were the first.

LH: The first. The second thing might have been the ability to look at drugs beyond the psychiatric, to their general medical effects, including the complications of the use, which I don't think a whole lot of people in the field were able to do.

TB: You wrote several books and some of them had several editions. I think one of them is just getting into the fourth edition, right?

LH: Just three editions; "Clinical Pharmacology and Psychotherapeutics." The co-author was one of my brightest protégés, John Samanski, who's now one of the Washington University faculty,

but I don't think he's very anxious to do a fourth edition. I suggested we try to do a 3rd edition, focusing on what might be called Evidence-Based Therapy, but, although it's a catchy approach, I don't think it's all that good.

TB: Was the book translated into any other languages.

LH: No, the publishing house doesn't seem to have much zip.

TB: So the book which is in all kinds of languages is with Ole, right —*The Little Book*?

LH: Yes, Ole and I never made a penny off that book, but that wasn't the goal and it served the purpose Ole had in mind. Ole was a truly remarkable person. I remember the first time I went in, someone had referred him to me, and I said, "Come on over to the hospital" and he replied, "I'd like to see what's going on in the research area." So, at that time, I was Associate Chief of Staff for Research and knew all the research going on, so I took him everywhere, neurology, cardiology, psychiatry and surgery. Within one minute, he could be talking intelligently to the person describing their research. I never ran into anyone who had such a broad based knowledge of medicine as Ole. He knew what was going on.

TB: He was involved in research in diabetes, right?

LH: Yes, I visited his outfit in Copenhagen and he had several things going, but some of them were not psychiatric. He, also, had been trained in medicine first; although he did have some formal training in psychiatry, which I never bothered to get. But, I had the utmost respect for him and he was a delightful person. One of his unknown accomplishments was a book of erotic limericks of his own composition. He was just a wonderful person.

TB: We have a few more minutes to talk about a couple of people you collaborated with, or who you would like to mention.

LH: The former president of the CINP is always supposed to have some say in who follows him, but you were kind enough to ask me several times after my term ended. The first person I wanted, was Arvid Carlsson, and we got him. The next person I wanted was my other idol, Paul Janssen, and we also got him. Finally I got Ole, after Pual Kielhotz and Biff Bunney. When Ole took over, it was only two or three years later he had the tragic accident that killed him. If he had lived, he would have been a big figure.

TB: Leo, thank you very much. I think we used up our time. I really appreciate your contribution. It was very enjoyable.

LH: Well, you've been enjoyable, too.

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