

An Oral History Of Neuropsychopharmacology

The First Fifty Years Peer Interviews

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American College of Neuropsychopharmacology

AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

THE FIRST FIFTY YEARS

Peer Interviews

Volume Six: Addiction

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

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AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY THE FIRST FIFTY YEARS

Peer Interviews

Edited by Thomas A. Ban

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VOLUME 6

ADDICTION

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VOLUME 6

Herbert D. Kleber

ADDICTION

Preface Thomas A. Ban

Dedicated to the Memory of Daniel X. Freedman, President ACNP, 1970

PREFACE Thomas A. Ban

Volume Six of this series is dedicated to addiction. The word itself refers to a group of disorders - alcohol, amphetamine, barbiturate, cannabis, cocaine and opioid abuse and dependence; phencyclidine and hallucinogen abuse; and tobacco dependence - that are classified in the DSM-III, and subsequent classifications, as Substance Use Disorders.¹

In the first five volumes of this series the focus is on different methodologies used in the study of psychotropic drugs; in Volume Six the focus shifts to the employment of these methodologies in the study of "addiction", a class of disease. Thus, while previous volumes deal with interviewees' contributions to the development of behavioral pharmacology, neurophysiology, neuropharmacology, psychopharmacology and neuropsychopharmacology, Volume Six deals with interviewees' contributions to the elucidation of the biological underpinning of addiction, and to the development of rational pharmacological treatments for addiction.^{2,3}

Addiction Psychiatry

Addiction psychiatry is a relatively new field. It was separated in the 1950s from "pharmacological psychiatry", which dealt with all "chemical intoxications" (accidental, industrial and medicinal). Such, intoxications included those caused by substances that may lead to addiction assumedly through their "pleasing psychological effects".⁴ The mental manifestations of chemical intoxications share the basic syndromes of "symptomatic psychoses", described in 1909 and 1910 by Karl Bonhoeffer^{5,6}.. The difference between the two is in the superimposed mental (psychological) effects of the different "addictive drugs".

By standardizing the language of "addiction" between 1950 and '57 in a series of Technical Reports, the World Health Organization (WHO)⁷ had a major impact on the development of "addiction psychiatry". Alcoholism was defined by WHO first, as any form of drinking which goes beyond the customary dietary use, or social drinking customs of the community.^{8,9,10} And, drug addiction was defined as a state of periodic or chronic intoxication produced by the repeated consumption of a natural or synthetic drug, that is detrimental to society and the individual. It was characterized by an overpowering desire or need (compulsion) to continue taking the drug and obtain it by any means,

a tendency to increase the dose (tolerance) and a psychic (psychological) and sometimes physical dependence on its effects.^{11,12}

Drug habituation was separated from drug addiction and characterized by a desire but not a compulsion to continue taking the drug. In drug habituation there is no tendency to increase the dose (tolerance) and even if there is some degree of psychic dependence on the effects of the substance, physical dependence with an abstinence syndrome is absent and the continuous taking of the drug has no detrimental effect on the individual.¹³

Tolerance was defined as an "adaptive state," and characterized by diminishing response to the same quantity of a given drug. It is demonstrable by increasing dose requirements to produce the same degree of pharmacological effects.¹⁴

Drugs with a potential to produce addiction were divided into three groups by the WHO. Substances of the first group produce compulsive craving, dependence and addiction in any individual if administered in a sufficiently high dose for a sufficiently long time. In the pathogenesis of addiction with these drugs, pharmacological action is paramount and psychological makeup is adjuvant. Substances of the second group differ from the first by not producing compulsive craving; they merely increase desire and encourage habituation. In the pathogenesis of habituation with these drugs psychological make-up is paramount and pharmacological action is adjuvant. Substances in the third group differ from both, the first and the second group; they produce compulsive craving, dependence and addiction, but in those individuals only who seek to find an escape in drugs. In the pathogenesis of addiction with these drugs pharmacological action plays a prominent role but psychological make-up is the determining factor.^{15,16}

In 1964 the World Health Organization replaced the term drug addiction with the term drug dependence¹⁷ and defined drug dependence as a state of psychic or physical dependence on a chemical which develops after periodic or continuous administration. Reviewing drug dependence, its significance and characteristics in the Bulletin of WHO in 1965, Eddy, Halbach, Isbell and Sievers emphasized that drug dependence and drug abuse might occur without the development of demonstrable tolerance.¹⁸ They also pointed out that the characteristics of drug dependence vary with the agent involved.¹⁹

Substances of Abuse

Among the different substances of abuse, the story of alcohol dates back to Paleolithic times. Its use in medicine and for religious purposes has been recorded over millennia. Subsequent to the discovery of distillation of alcohol in about 800 AD, its recreational use steadily grew; by the seventeenth century alcohol became a drug of abuse on a large scale.²⁰ The term "alcoholism" was coined by Magnus Huss²¹ in the mid-19th century and the disease concept of alcoholism -introduced by Benjamin Rush²² and Thomas Trotter²³ - got increasing acceptance in Europe and North America. In the United States the first special institution for inebriates (alcoholics) was opened in 1841 in Boston.²⁴ During the years of prohibition of alcohol - Russia 1914-25; Iceland: 1915-22; Norway: 1916-27; Finland 1919-32; US: 1920-33 - the disease concept of alcoholism lost its vogue. It was revitalized in the United States by the pioneering research carried out at the Yale center for Alcohol Studies during the 1940s and '50s.²⁵

Substances derived from the poppy plant (papaver somniferum), like opium, which produce euphoria and analgesia, have also been used since ancient times. Morphine, the active ingredient of opium was isolated in 1805 by Sertürner.²⁶ After Alexander Wood's introduction of the hypodermic needle in 1853,²⁷ the non-medicinal use of morphine spread so fast that by the turn of the 20th century a large number of people had become dependent on the drug. Heroin, diacetylmorphine, was synthesized by Alder Wright in 1874 and introduced for clinical use in 1898 by Bayer pharmaceuticals with the name of heroin initially as an oral cough medicine and later as a fast acting oral non-addictive substitute for morphine and opiates in general. It took about a decade to recognize that the substitute metabolizes into morphine.²⁸ Heroin addiction became a serious mental health problem in the 1960s in the United States. It involved mainly black ghetto populations. Meperidine (Demerol), another synthetic opioid, was synthesized in 1932 by Otto Eislib in the laboratories of IG Farben in Germany. Similar to heroin, the substance was introduced in the 1940s as a non-addictive substitute for morphine and other opioids.²⁹ It caused a mild epidemic of meperidine abuse among physicians.³⁰ A third synthetic opioid, methadone, was developed in 1937 in Germany and introduced ten years later in 1947 in the United States by Eli Lilly and company as a narcotic analgesic for the alleviation of pain. Isbell and Vogel were first, in 1949 to report on its addiction liability and its use for withdrawal from morphine.³¹

In the mid 19th century the use of hashish (marihuana), the most potent form of cannabis - endogenous in Central and South Asia - became widely used for recreational purposes in Europe, especially in France.^{32,33,34} Hashish was also tried in the treatment of psychiatric disorders.^{35,36} It took well over 100 years before the active ingredient of marihuana, Δ -tetrahydrocannabinol, was isolated by Mechoulam and Gaoni in the mid-1960s.³⁷ The first documented widespread marihuana abuse ("reefer madness") in the United States occurred in the 1930s. The second in the 1960s and '70s.^{38,39} Coca chewing has been endemic in the eastern Andes for thousands of years. Coca, the psychoactive ingredient of the coca plant was isolated by Frederick Gedecke in 1855, and its chemical structure was identified by Richard Willstatter in 1898.⁴⁰ The stimulating effect of coca on cognition was first reported by Paolo Montegazza in the late 1850s. He advocated the use of coca for "nervous nourishment".⁴¹ Sigmund Freud in the 1880s self-experimented with coca and found that it has local anesthetic effect. In his paper Über Coca (On Coca), he recommended its use for the treatment of depression and of addiction to alcohol and morphine.⁴² The first cocaine abuse epidemic in the United States occurred in the early 1900s, the 2nd about 80 years later, in the 1980s.

Many of the substances used in the control of anxiety, psychic tension, psychomotor restlessness and insomnia, traditionally referred to as sedatives and hypnotics, are potentially addictive. The oldest drugs of this category are henbane and other members of the Solanaceae family.⁴³ They were replaced by the bromides, first introduced into medicine by Magendie in 1821.44 In the second half of the 19th century bromides were extensively used for sedation and controlling seizures.⁴⁵ They were also occasionally employed in the treatment of addiction.⁴⁶ Then, in the mid-20th century it was conclusively demonstrated that bromides are toxic and addictive drugs.⁴⁷ In 1869, chloral hydrate,⁴⁸ the first synthetic sedative-hypnotic was introduced for psychiatric indications. In the late 19th century it led to addiction, especially in woman, on a large scale.⁴⁹ The first fifty years in the 20th century was dominated by barbiturates. The first, barbital (Veronal) was synthesized by Emil Fisher in 1902 and a year later, in 1903, Joseph von Mering demonstrated its hypnotic effect.⁵⁰ In the years that followed more than 2,500 different barbiturate preparations were synthesized, of which at least fifty found clinical use. There were numerous reports on physical and psychological dependence on barbiturates over decades. Yet, it was Harris Isbell first, in 1950, to conclusively demonstrate addiction to these drugs.⁵¹ In the second half of the 1950s the barbiturates were rapidly replaced in the treatment of anxiety by meprobamate, a propanediol preparation, linked to the name of Frank Berger at Wallace Laboratories of Carter Products. (See, Berger Volumes 3 & 9.) Meprobamate, was synthesized by B. J. Ludwig in 1950 and introduced for clinical use in the United States in 1956.52,53 Then, in the 1960s meprobamate was replaced by the benzodiazepines, chlordiazepoxide first in 1960 and diazepam in 1963, a group of drugs synthesized by Leo Sternbach, a pharmacist and chemist working at Hoffmann-La Roche's research facility in Nutley, New Jersey. The first benzodiazepine, chlordiazepoxide, was intrduced in 1860 and the second, diazepam in 1962.⁵⁴ The addiction-producing properties of

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meprobamate,⁵⁵ and chlordiazepoxide,⁵⁶ were first shown by Leo Hollister in 1960 and 1961, respectively.⁵⁷ (See, Hollister Volume 1 & 9.)

Many of the psychostimulants have abuse potential. The abuse of khat a substance derived from the shrub, Catha Adulis, native in East Africa and southern Arabia - had been a major concern in colonial Kenya.⁵⁸ The active ingredient of khat is cathinone, an amphetamine-like substance. The amphetamines are a group of psychostimulants. The parent substance, phenethylamine, was synthesized by Edeleano in 1887⁵⁹; its methylated analogue, methamphetamine (street name "speed") by Akira Ogata in 1919⁶⁰; and racemic amphetamine (Benzedrine) by Gordon Alles in 1927.⁶¹ In the mid-1940s, it was Nathenson first to report that Benzedrine in normal subjects produced a sense of well being, exhilaration and lessened fatigue.^{62,63} The first recorded major amphetamine abuse epidemic occurred in postwar Japan. It was so severe that it required the opening of special psychiatric facilities and stringent legal measures to control.^{64,65} In the United States amphetamines became a major abuse problem by the late 1950s.^{66,67}

In the 1950s psychomimetics emerged as a group of drugs with abuse potential. The story begins in 1943 with the accidental discovery of the psychomimetic (hallucinogenic) effect of lysergic acid diethylamide (LSD-25) by Albert Hofmann while trying to develop a new ergot analeptic⁶⁸ in the laboratories of Sandoz. In the late 1940s LSD was introduced for the facilitation of psychotherapy⁶⁹ and by the 1960s its efficacy was tested in the treatment of alcoholism and a variety of psychiatric disorders.⁷⁰ (See, Levine Volumes 4 & 9.) In the 1950s several other synthetic hallucinogens, e.g., psilocybin,⁷¹ dimethyltryptamine were introduced and more and more people, especially late adolescents and students on college campuses, were experimenting with them. (See, Szara Volume 1.)

Concepts and Treatments of Addiction

In the 1950s psychoanalysis was dominant in American psychiatry and addiction was conceptualized in various ways by the different psychodynamic schools. For Sandor Rado it was reactivation of the satisfaction of the "orgiastic experience" of infants after breast feeding by the dependency producing drugs.⁷² For Ernest Glover it served to control sadism, a protective device against paranoid psychosis.⁷³ For Thomas Szasz it served to deny any possible loss of primal love, a protective mechanism against phobia.⁷⁴

In Arthur Noyes and Lawrence Kolb's Modern *Clinical Psychiatry*, the most widely used textbook of psychiatry in the United States at the time, addiction was symptomatic of sociopathic personality disorder.⁷⁵

The US Government opened the Lexington Narcotic Farm (US Public Health Service Hospital) in 1935. It was to become one of the first Addiction Research Centers in the country.⁷⁶ Research at the center by the 1950s yielded two models of drug dependence, the "cellular model" and the "conditioning model". The "cellular model", pioneered by Harris Isbell, is based on the observation that to some drugs, as for example to opiates, tolerance develops, which then, is followed by physical dependence and later by psychic or emotional dependence. Isbell perceived the decreased response seen in tolerance as the result of "occupation of receptors on certain myelinated neurons", by the dependency producing drug. For Isbell, tolerance was the consequence of either a maximal cell-receptor saturation, or a change in the excitability of the cell body, or both.^{77,78,79} In the same frame of reference, it was suggested that physical dependence was the result of the increased excitability of the cell body in the period of abstinence by the "loss" of the protecting drug.^{80,81}

The "conditioning model", pioneered by Abraham Wikler, is based on the observation that "cured" opiate addicts experienced craving and repetition of some of the abstinence-syndrome manifestations when exposed to stimuli which were formerly strongly associated with their previous drug experiences. Wikler perceived drug dependence as a process of conditioning in which the actual drug experience serves as the unconditional stimulus and the associated environmental factors as conditional stimuli.^{82,83,84,85,86}

Conditioning was employed in the 1950s in the treatment of alcoholism.⁸⁷ In "aversion therapy," nausea and vomiting are elicited at the sight, smell or taste of alcohol (conditioned reflex) by associating it with the nausea and vomiting produced by the pharmacological effect of apomorphine (unconditional reflex).⁸⁸ The treatment was first described in 1915⁸⁹ and introduced in 1934 simultaneously by Markovnikov in the Soviet Union and Dent in England.^{90,91}

An alternative treatment of alcoholism was disulfiram (Antabuse). It is based on the findings of Hald, Jacobsen and Larsen in 1948 that disulfiram, by interfering with the metabolism of alcohol, produces a marked increase of blood acetaldehyde levels and sensitizes the organism to alcohol.⁹² The flushing of the face, sweating, dyspnea, headache and tachycardia experienced, even after a small amount of alcohol consumption, makes drinking difficult for patients on the drug.⁹³ In 1949 Jacobsen and Larsen were first to report on the use disulfiram in the treatment of alcoholism.⁹⁴

Conditioning and Addiction

Recognition by the 1950s that conditioning, classical or operant, plays a role in the pathogenesis of addiction, lead the identification of brain structures

and biochemical substrates involved in addiction. The signal difference between the two paradigms of conditioning is that in classical conditioning, the establishment and retention of conditioned reflex (CR) depends exclusively on the associated administration of the conditioned and unconditional stimuli, whereas in instrumental conditioning, a third factor, reward or punishment that follows the reflex also plays a role.⁹⁵ (See also in Preafce to Volume 2.)

The roots of the instrumental paradigm of conditioning are in Edward Thorndike's recognition in 1911 that some behavior is regulated by its consequences.⁹⁶ Miller and Konorski were first, in the late 1920s, to describe what was to become the instrumental paradigm of conditioning, in which the establishment and retention of a CR depended on reward or punishment that followed the reflex.⁹⁷ From the two modern learning theories, "contiguity theory" is based on the classical paradigm and "reinforcement theory" on the instrumental. For Edward Ray Guthrie^{98,99} and Edward C. Tolman,^{100,101} the basic condition necessary for learning is that of contiguity of experience. For Clark L, Hull drive reduction is crucial. If in the course of trial and error responses the organism performs the response that is associated with the reduction of motivation, the probability increases that the response will occur again under similar conditions. In Hull's "law of effect", drive reduction is the "principle of reinforcement".^{102,103,104}

In the mid-1930, H. Schlossberg demonstrated that autonomically-mediated, involuntary visceral reactions, follow the principle of association or "sheer contiguity", whereas voluntary "precise adaptive responses" of the skeletal muscles, follow the principle of success or reinforcement.^{105,106,107} .Schlossberg's "two-factor theory" was further elaborated by Burrhus Frederic Skinner, who introduced the term "operant behavior" and replaced the term "instrumental conditioning" with the term "operant conditioning". For Skinner, the difference between the two paradigms of conditioning is that in "operant conditioning" the animal only receives the reinforcing, rewarding stimulus, if it does something, e.g., operates a lever.¹⁰⁸ He argues that a stimulus is reinforcing if it strengthens the response that precedes it regardless whether it satisfies a drive.^{109,110,111}

In the early 1950s Delgado, Roberts and Miller at Yale University began work on learning and electrical brain stimulation. (See, Delgado Volume 2.) They found that stimulating a number of areas deep in the brain made the animals react if they were in pain. The animal could be taught to avoid an electrical stimulation in the area of its brain associated with pain as it could be conditioned to avoid a painful stimulus to the body.¹¹² In 1954, the same year Delgado and his associates published their findings, James Olds and Peter Milner at McGill University reported that they found areas in the brain where electrical stimulation was sought by the rat.¹¹³ With electrodes implanted in

the septal area, one of the "pleasure centers," some rats in Olds' experiments, stimulated themselves as often as 500 times per hour.¹¹⁴ Olds and his associates described the topographic organization of hypothalamic selfstimulation functions,¹¹⁵ employed self-stimulation of the brain as a screening method for tranquilizing drugs,¹¹⁶ and demonstrated "positive reinforcement" produced by stimulating certain areas in the hypothalamus with iproniazid and other drugs.¹¹⁷

An operant behavioral method for studying self-maintained morphine addiction with implanted electrodes in the "pleasure" centers was first developed in 1961 by Weeks.^{118,119} Martin demonstrated in the 1960's that a "protracted abstinence syndrome" (PAS) could be found six to nine months after stopping chronic opiate use in both humans and animals.¹²⁰

This was the state of art in the biology of addiction research at the time neuropsychopharmacology was born.

Interviewees & Interviewers

Volume Six covers the first fifty years in the developments of the neuropsychopharmacology of addiction.

From the 22 interviewees included in this Volume, 3 (Noble, O'Brien and Schoolar), are MD, PhDs; 11 (Blaine, Charalampous, Jaffe, Jasinsky, Kleber, Klee, Kreek, Meyer, Primm, Schuckit and Volkov), are MDs; and eight (Adler, Barry, Kornetsky, Pickens, Schuster, Way, Wayner and Woods), are PhDs. From the 14 MDs, all, but one (Kreek) are psychiatrists. From the PhDs, including MD, PhDs, 6 (Barry, Kornetsky, Pickens, Schuster, Wayner and Woods), received their degree in Psychology; two (Adler and Schoolar), in pharmacology; and from the remaining three Noble received his degree in Biochemistry, O'Brien in Neurophysiology, and Way in Pharmaceutical Chemistry.

All but four interviewees (Blaine, Jasinsky, Pickens and Primm) are affiliated with ACNP. The 18 ACNP members include two founders (Klee and Kornetsky) and two past presidents (Meyer and O'Brien).

The interviews were conducted from 1995 to 2009 and with the exception of five (Blaine, Jasinsky, Klee, Pickens and Primm) were done at ACNP's annual meetings. Blaine, Jasinski and Pickens were interviewed in Washington, DC, Klee, in Baltimore, Maryland, and Primm, in Orlando, Florida.

The 22 interviewees were interviewed by 14 interviewers. Twelve of the interviewers are peers of the interviewees, knowledgeable in the same field, and 2 (Campbell and Tone), are medical historian. Ten of the interviewers (Campbell, Carpenter, De Lisi, Gold, Koob, Kosten, London, O'Brien, Sanberg and Stein) conducted one interview, and four conducted multiple interviews,

i.e., 2 (Healy and Tone), 4 (Ban), and 5 (Hollister). One of the interviewees (O'Brien) was interviewed by two interviewers (Hollister and Ban).

By the time the editing of Volume 6 began, one of the interviewers (Hollister) passed away.

Contributions of Interviewees

The 22 interviewees were involved in six broadly defined areas of research related to the neuropsychopharmacology of addiction. Many of them were also involved in the **social political arena of addiction**. In fact, the most important contribution of 1 of the interviewees, *Benny J. Primm* was the organization of clinical services, including methadone clinics for addicts in the black population of the United States in the 1970s and '80s.^{121,122}

Three of the interviewees (Adler, Meyer and Way) contributed to defining the **biological properties of addiction**. *E. Long Way*, in his life-time research - from the 1960s to the '90s - presented evidence that "tolerance" and "dependence" have a common biochemical basis. He demonstrated an increase of norepinephrine (NE) release in both.^{123,124}

In the late 1970s *Roger E. Meyer* reported that the subjective state associated with "craving" was rewarding and not aversive.¹²⁵ Meyer was among the first to demonstrate, in the 1980s, that psychopathology was a predictor of treatment outcome in alcoholism.¹²⁶

In the early 1960s *Martin W Adler* discovered that rats with chronic brain lesions have increased sensitivity to amphetamines.¹²⁷ He referred to the phenomenon as "denervation supersensitivity," adopting the term coined by Cannon in the late 1940s.¹²⁸ In the late 1990s, Adler was a member of the team that discovered chemokine receptors in a subset of neurons.¹²⁹ He suggested that chemokines represent a third transmitter system in the brain and was first to study chemokines in drug addiction.¹³⁰

Six of the interviewees (Barry, Kornetsky, O'Brien, Pickens, Schuster and Woods) were involved with **conditioning research in addiction**. *Charles O'Brien* was first in 1979 to demonstrate conditioned narcotic withdrawal in human.¹³¹ In the same year he had also shown conditioned limbic system activation in craving.¹³² In 1992, O'Brien was member of the team that reported on the effectiveness of naltrexone in alcoholism,¹³³ and in 2003 of the team that found that a functional polymorphism of the μ opioid receptor gene was associated with responsiveness to naltrexone in alcoholic patients.¹³⁴

Conan Kornetsky was among the first to show in the 1970s and '80s that both, morphine¹³⁵ and alcohol¹³⁶ increase sensitivity for rewarding brain stimulation. In 1994 he demonstrated that in the reinforcing effect and abuse of substances, the nucleus accumbens and olfactory tubercle play a role.¹³⁷

He also provided evidence that dopamine was a common substrate in the rewarding effect of brain stimulation for cocaine and morphine.¹³⁸ (See Kornetsky also in Volume 9.)

Charles R. Schuster was first in the mid 1960s to show that a stimulus associated with nalorphine administration could elicit signs of withdrawal in morphine dependent monkeys.¹³⁹ During the 1960s, Schuster developed animal models of self-administration¹⁴⁰ and demonstrated that drugs can be used as "reinforcers" in monkeys and man.^{141,142}. In the 1970s, in collaboration with Marian A Fishman and others, Schuster found a relationship between plasma concentration and the subjective and physiological (cardiovascular) effects of cocaine.^{143,144}

In the late 1960s, *James H. Woods*, in collaboration with Steven R. Goldberg and Schuster, was first to show conditioned increases of self-administration of morphine in monkeys.¹⁴⁵ In 1981, in collaboration with Young and Herling, Woods reported that history of drug exposure is a determinant of drug self-administration.¹⁴⁶ During the 1970s Woods demonstrated narcotic tolerance by a shift to the right in dose-effect relations in operant behaviour.¹⁴⁷

In the 1970s *Roy Pickens*' had shown that drugs of abuse in human are self-administered by animal.¹⁴⁸ In the 1980s Pickens showed that personality factors play a role in human drug "self-administration".¹⁴⁹

Herbert Barry III was first to employ drug-effects as discriminative stimuli in the differentiation of drugs of abuse. In 1972, in collaboration with R.K. Kubana he published on the stimulus characterization of marihuana components and demonstrated the discriminative effect of δ -9-tetrahydrocnnabinol.¹⁵⁰ Barry classified drugs according to their discriminative effects in rats¹⁵¹ and in collaboration with Krimmer he described the differential stimulus attributes of chlordiazepoxde and pentobarbital.¹⁵²

One of the interviewees, *Nora Volkow,* contributed to detection of structures involved in addiction with **functional brain imaging**. In the late 1990s Volkow reported on decreased striatal dopaminergic responsiveness in detoxified cocaine dependent subjects,¹⁵³ and in 2001 she had shown the involvement of the frontal cortex in addiction.¹⁵⁴

Six of the interviewees (Blaine, Jaffe, Jasinski, Kleber, Kreek and Wayner) were involved in the development of **treatment** for addiction. In 1966, *Mary Jeanne Kreek* co-authored one of the two papers of Dole and Nyswander on methadone in opioid dependence that launched substitution therapy with the substance.^{155,156} In the late 1960s she described the role of μ and K opioid receptors in normal physiology, responsiveness to stress and in specific addictive diseases. In the 1990s, the focus of Kreek's research shifted to genes associated with addiction.¹⁵⁷

Donald R. Jasinski was among the first to study the effects of naltrexone, a full antagonist, and of buprenorphine, a partial antagonist of μ and competitive antagonist of K opioid receptors, in the treatment of opioid dependence.^{158,159} A close collaborator of W.R Martin, one of the leaders of the Lexington group, Jasinski coauthored the paper with Martin in which the concept of "protracted abstinence" was introduced.¹⁶⁰

Jerome H Jaffe was one of the first in 1970 to report on the effects of levo-acetyl-methadol (LAAM), a long-acting orally available opioid, in the treatment of chronic heroin users and compare its effect with methadone.¹⁶¹,¹⁶² In the late 1970s Jaffe's interest turned to smoking as an addictive disorder.¹⁶³

Findings with LAAM in the treatment of addiction received further substantiation by *Jack D. Blaine* in the late 1970s.¹⁶⁴ Blaine was a member of David Janowsky's team (see, which studied the effects of marihuana on simulated flying ability.¹⁶⁵ (See, Janowsky Volumes 5 & 9.)

In the late 1970s, *Herbert D. Kleber*, in collaboration with Gold and Redmond, discovered that administration of clonidine, an α -adrenergic agonist, could ameliorate opiate withdrawal symptoms.¹⁶⁶ Ten years later, in the mid-1980s he demonstrated that co-administration of clonidine and naltrexone significantly shortens the opioid withdrawal syndrome without substantially increasing patient discomfort.¹⁶⁷ Kleber was one of the first to show that dronabinol, a synthetic levoisomer of tetrahydrocannabinol, could mitigate the symptoms of marihuana withdrawal.¹⁶⁸

In the mid-1990s *Matthew J. Wayner* demonstrated the effect of alcohol on lateral hypothalamic dentate granules and suggested a possible relationship between this effect, and alcohol-induced memory changes. Wayner had also shown that losartan, an angiotensin II inhibitor, improved performance in ethanol-intoxicated rats.^{169,170}

Three interviewees (Charalampous, Klee and Schoolar) were involved with **psychomimetics** in their research. In the late 1950s *Gerald D. Klee* studied the effects LSD-25 on mental performance and on time sense.¹⁷¹ In the early 1960s, he reported on the effect of the substance on ego functions.¹⁷² Klee was among the first in 1960 to explore the effects of 5-hydroxytryptophan on schizophrenia,¹⁷³ and to question the relationship between the action of LSD on serotonin and the mental effects of the substance.¹⁷⁴

The first autoradiogaphic study with LSD was carried out in the late 1960s, by *Joseph Schoolar* in collaboration with Idanpään Heikkilä. By tracking the substance in mice they found high concentrations in the brain, adrenals, hypophysis, kidney, liver and lung, and demonstrated that LSD passes the placental barrier.¹⁷⁵

Kanellos D. Charalampous was first, in the mid-1960s, to demonstrate the metabolic fate of mescaline in man.¹⁷⁶ He was also first, in the mid-1970s

to show the effects of acute ethanol administration on brain cyclic nucleotides¹⁷⁷ and of chronic morphine administration on cerebellar cAMP levels.¹⁷⁸

The remaining two interviewees (Noble and Schuckit) contributed to **genetic** research in addiction. In the 1990s Marc Schuckit demonstrated an increased risk for alcoholism among sons of alcoholics.^{179,180,181} He identified patterns of drinking in the offspring,¹⁸² and showed a different level of response to alcohol in the offspring of heavy drinkers.¹⁸³

In 1993 *Ernest P. Noble* and his team reported on an allelic association of the D2 dopamine receptor gene (DDR2) with cocaine dependence.¹⁸⁴ Subsequenly he found similar association between DDR2 and other substances, and hypothesized that DDR2 is a "reward gene".^{185,186}

Interviewees included in Volume 6 entered the field at different stages in the development of the neuropsychopharmacology of addiction. Hence the transcripts cover fifty years of history during which norepinephrine was replaced ny dopamine as the molecular substrate of reinforcement; opiate receptors were identified in the brain; the site of brain structures involved with addiction was extended from the limbic lobe to the frontal cortex; and behavioral methodologies in the study of addiction were supplemented with brain imaging and molecular genetic techniques.

Herbert D. Kleber, the editor of this volume, has been one of the leaders of addiction psychiatry in the past decades. In his Introduction and Dramatis Persnae he provides an overview of developments in the field and biographic information on the the interviewees with a précis of their contributions.

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ABBREVIATIONS

Prepared by Laura Bersacola Hill

variant of the µ-opioid receptor
American Academy of Addiction Psychiatry
art bachelor
Army Chemical Center
American College of Neuropsychopharmacology
Alcohol, Drug Abuse and Mental Health Administration
attention deficit hyperactivity disorder
atomic energy commission
acquired immunodeficiency disease
selective fire gas operated assault weapon
American Medical Association
Association for Medical Education and Research in
Substance Abuse
American Psychiatric Association
American Association of Psychiatry and Addiction
Addiction Prevention Treatment (Foundation)
Addiction Research Center
Addiction Research Treatment Corporation
American Society of Addiction Medicine
Addiction Severity Index
angiotensin
bachelor of art
Brookhaven National Laboratories
Biometric Research Institute
bachelor of science
Boston Unversity
National Center on Addiction and Substance Abuse
at Columbia
Centers for Disease Control
chief executive officer
cerebral blood flow
cognitive behavior therapy
T cell count
chief financial officer
Collegium Internationale Neuro-Psychopharmacologicum
Center for Mental Health Services
central nervous system

COMT	catechol-O-methyl-transferase
Columbia PS	Columbia University College of Physicians and Surgeons
	chronic obstructive pulmonary disease
	College on Problems of Drug Dependence
CPT	continuous performance test
CRE	continuous performance test
CSAP	Center for Substance Abuse Prevention
CSAT	Center for Substance Abuse Treatment
	donamine
	district attorney
	Drug Abuse Warning Network
	District of Columbia
	District of Columbia
	Department of Health, Education and Wolfere
	deprivilent of Health, Education and Weilare
	D2 depamine receptor conc
	Diagnostic and Statistical Manual of Mantal Diagradara
DSIVI	(American Develoption Accession)
	(American Esychiatric Association)
EEG	
	electroconvulsive therapy
	Enzyme multiplied assay technique
FASED	
	Experimental Biology
	Food and Drug Administration
	functional magnetic resonance imaging
	iree radical assay technique
GABA	γ-aminputyric acid
GURU	General Clinical Research Center
GED	General Educational Degree
GI	gastrointestinal
GI DIII	Serviceman Readjustment Act
GW	George wasnington (University)
GWAS	genome wide association study
HAARI	highly active anti-retroviral therapy
HDGC	hippocampal dentate granule cell
HEW	Health Education & Welfare
HGP	Human Genome Project
HHS	Health and Human Services
HIV	human immunodeficiency virus

HOC	Harlem Hospital Orientation Center
HRP	horseradish peroxidase
HRSA	Health Research and Services Administration
5-HT	5-hydroxytryptamin (serotonin)
5-HTP	5-hydroxytryptophan
FDA	Food and Drug Administration
ICPA	International Commission for the Prevention of Alcoholism
	and Drug Dependency
IBM	International Business Machine Corporation
IDAP	Illinois Drug Abuse Program
IND	Investigational New Drug
INRC	International Narcotic Research Conference
IRB	Institutional Review Board
IV	intravenous
JAMA	Journal of the American Medical Association
LA	Los Angeles
LAAM	levo-alpha-acetylmethadol
L-DOPA	levodopa (3, 4-dihydroxyphenylalanine)
LHA	lateral hyothalamic area
LR	level of response
LSD	lysergic acid diethylamide
LTP	long term potentiation
MATCH.	Matching Alcoholism Treatment to Client Heterogeneity
MD	medical doctor
MDA	methylene-dioxy-amphetamine
MDMA	methylene-dioxy-methamphetmanine
MGH	Massachusetts General Hospital
MHPG	3-methoxy-4-hydroxy-phenylglycol
MIT	Massachusetts Institute of Technology
MM	methadone maintenance
M&M	metacognition and motivation
MMHC	Massachusetts Mental Health Center
MMPI	Minnesota Multiphasic Personality Inventory
MPH	master of public health
MS	master of science
NCDEU	New Clinical Drug Evaluation Units
NDA	New Drug Application
NEGRO	National Economic Growth and Recreation Organization
NIAA	National Institute on Alcohol Abuse
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse

NIH	National Institute of Health
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartic acid
NRA	National Rifle Association
NY	New York
NYU	New York University
OB-GYN	obstetrics and gynecology
ONDCP	Office of National Drug Control Policy
OTI	Office for Treatment Improvement
PCA	para-chloroamphetamine
PCP	phencyclidine
PCPA	para-chlorophenylalanine
PET	positron emission tomography
PGY	post graduate year
PhD	doctor of philosophy
PHS	Public Health Service
PMF	Foundation of Clinical Pharmacology
PNAS	Proceedings of the National Academy of Sciences
PRC	People's Republic of China
PTA	Parents Teachers Association
QTL	quantitative trait loci
ROTC	Research Officers Training Corps
SAMHSA	Substance Abuse and Mental Health Service
	Administration
SAODAP	Special Action Office on Drug Abuse Prevention
SDPS	San Diego Prospective Study
SKF	Smith, Kline & French
SNP	single nucleotide polymorphism
SSPD	Society for the Stimulus Propensities of Drugs
STD	sexually transmitted disease
SUD	substance use disorders
TC	treatment corporation
THC	tetrahydrocannabinol
TRIMS	Texas Research Institute Mental Sciences
TST	Treatment Service Review
UCLA	University of California, Los Angeles
UConn	University of Connecticut
UCSD	University of California, San Diego
UCSF	University of California, San Francisco
UC Irvine	University of California at Irvine
UK	United Kingdom

UR	Urban Resource Institute
US	United States
USPHS	United States Public Health Service
UT	University of Tennessee
VA	Veterans Administration
VP	Vice President
WHD	Western Health District
WHO	World Health Organization
WRAIR	Walter Reed Army Institute for Research
WWII	World War II

INTRODUCTION & DRAMATIS PERSONAE Herbert D. Kleber

In terms of neuropsychopharmacology, the field of addiction is both one of the oldest and one of the newest. At the beginning of the 20th century, addiction was commonly viewed as synonymous with physical dependence and withdrawal. The prototypical drugs were the opiates with their dramatic withdrawal symptoms. Treating withdrawal symptoms was thus viewed as treating addiction and if the addict relapsed afterwards, it was clear evidence of moral failure for which society did not need to waste its compassion. Unfortunately, some of the withdrawal remedies were far worse than the withdrawal itself, not uncommonly causing toxic psychosis and even death. This ultimately led to opening clinics where heroin or morphine was given on a maintenance basis, the forerunners of our current use of methadone and buprenorphine. These were shut down in the early 1920s because of concern over diversion, not uncommon because the short acting nature of morphine meant either the addict had to return again to the clinic or be given take-out medication. The clinics were also deemed failures because they did not lead to abstinence. Following their closure, the government began a crack-down on physicians who prescribed maintenance narcotics to addicts. Over the next decades, approximately 25,000 physicians were indicted under the Harrison Act and as many as 10% were imprisoned. Treating addiction was seen as too risky for the medical profession and the addict became a stigmatized pariah. Treatment was scarce; prison common, and relapse likely. Successful pharmacologic treatment did not begin again until Dole and Nyswander began methadone maintenance in the early 1960's, approximately 40 years after the last maintenance clinic had closed.

In the US, over 100,000 deaths annually are directly attributed to alcohol and drug use along with more than half a trillion dollars in related medical, behavioral and social costs. The 2008 National Survey on Drug Use and Health estimates that over 40 million people engage in binge drinking or heavy alcohol use. Within healthcare settings, a recent federal screening program found that 23% of patients in those settings screened positive for heavy alcohol and /or illicit drug use.

Despite the fact that substance use disorders (SUDs) represent major challenges to public health and health care costs, the vast majority of those who meet diagnostic criteria for substance abuse or dependence do not seek treatment, and remain unidentified. While about 2.5 million individuals with SUDs receive treatment each year in specialty treatment centers, over
20 million present elsewhere in our health care system, especially in primary care. Primary care physicians often fail to diagnose this medical condition and often provide inadequate care to those patients whom they do diagnose with substance use disorders. These statistics remind us that even almost a century after addicts were stigmatized as moral pariahs, we continue to inadequately treat them even in the presence of effective approaches.

In 1935, the US Public Health Service prison opened in Lexington, KY. It demonstrated the ambivalence our society felt about narcotic addiction. It was both a hospital where addicts could get treatment for their addiction and a federal prison. It held about 1000 individuals of whom approximately 2/3rd were prisoners doing 1 to 10 years and 1/3rd were "volunteers" who signed themselves in, often under pressure from licensure boards. In addition to the prison/hospital, there was the Addiction Research Center (ARC), the National Academy of Science's attempt to develop an addiction science out of which hopefully pharmacologic treatments would emerge. Prior to ARC, research was carried out primarily by individual practitioners and mainly focused on treatments for withdrawal. In the 40 years ARC was at Lexington, before it moved to Baltimore and became the intramural arm of NIDA, the groundwork for our current knowledge of addiction was laid with carefully controlled studies. Trying to find a "non-addicting narcotic" led to studies on numerous other drugs. Drugs such as methadone, naltrexone and cyclazocine were studied as well as THC and the hallucinogens. The theories about multiple brain receptors were developed. The early giants in this field were there at one time or another e.g. Harris Isbell, Abe Wikler, Bill Martin, Clifford Himmelsbach as well as sociologists such as Jack O'Donnell and John Ball.

A number of the scientists in this book spent time at Lexington, e.g., Jaffe, Jasinski, Kleber, Kornetsky, and others were in one way or another influenced by the work there. Adler describes how he received his 1st grant with the advice of Bill Martin and describes him as "an absolutely brilliant man, a remarkably strong influence on me and many other young scientists", especially in regards to receptor theory. Jaffe tells how he was interested in pharmacology, came across Wikler's book The Relationship between Psychiatry and Pharmacology and decided to go to Lexington to study with him. He ended up spending some years there with people such as Isbell, Martin, and O'Donnell and later, with Sid Sharpless, and developed a theory of receptor supersensitivity to explain withdrawal. Jasinski went to Lexington in 1965 after Wikler and Isbell had retired and gone to the University of Kentucky. Working with Bill Martin, he ran the Human Research Unit and was involved with the development of ideas of protracted abstinence, testing Wikler's ideas of conditioning and conditioned abstinence, and Martin's idea of multiple opioid receptors. He helped demonstrate that high doses of THC produced hallucinations with a mechanism of action different from LSD. He went on later to do classic studies on naltrexone and cyclazocine.

Kornetsky enrolled at the University of Kentucky in 1948 for his PhD and at the same time got a job at the ARC. He ended up spending four years there while working on his PhD and published a series of papers with Harris Hill and Abe Wikler. His dissertation demonstrated the importance of morphine's effect on anxiety and the contribution of this action to morphine's analgesic effect. His work with drugs and brain stimulation demonstrated the role of the reward system in drug dependence, and work on the long term effects of drugs of abuse laid the framework for brain plasticity associated with modern theories of tolerance and physical dependence.

Kleber spent two years at Lexington from 1964 to 1966, working not at ARC but on the clinical side of the facility and became concerned about the very high post-Lexington relapse rate. With the assistance of Bill Martin and the ARC, he developed a double blind research protocol using LSD, with dexedrine as the active placebo, in group therapy with volunteer addicts. The project was never completed as the LSD was recalled by Sandoz. LSD had become a "street drug" and although what was on the street did not come from the company, they wanted no connection with the agent. His experience at Lexington, however, led him when he returned to Yale in 1966 to continue working with addicts and ultimately to a long term career in the field pursuing research, treatment, and policy. He developed a model multimodality treatment and research program in 1968 at Yale. He was involved in the dissemination and improvement of methadone maintenance (MM), the research on naltrexone, and attempts to develop medications for cocaine and marijuana dependence. One of his earliest findings with Mark Gold was the use of clonidine, an α -adrenergic agonist, to treat opiate withdrawal, the 1st non-opiate to ameliorate many of the opiate withdrawal symptoms. Clonidine, still being used for this purpose, helped make possible rapid opiate detoxification using narcotic antagonists. Decades later he played an important role in the approval and dissemination of buprenorphine. Perhaps most important, he developed a cadre of researchers, 1st at Yale and then at Columbia where he started the Division on Substance Abuse in 1992 along with Marian Fischman, that continue to be the leaders in the country in substance abuse research.

One of the earliest treatment pay offs for the ground breaking work at Lexington was the development of MM at the Rockefeller Institute in the mid-1960s. Methadone was developed by the Germans during World War II in their search for a synthetic analgesic, their normal supply of narcotics from the east being disrupted by the Allied submarine efforts. The ARC research led to it being used 1st as an opiate withdrawal agent. The pioneering work of Dole and Nyswander, with the collaboration of Kreek, is described in her interview in this volume. Based on their work MM is now used in countries around the world to treat narcotic addiction. There are over 250,000 individuals maintained on MM. in the U.S. and it is credited with saving thousands of lives but, still remains controversial. Ironically this is often due to the same concerns that led to the closing of the morphine maintenance clinics in the 1920s – especially, that it usually does not lead to abstinence and is essentially just trading one narcotic for another. These concerns miss the essential advantage of MM, that it's long duration of action permits once daily dosing and that addicts stabilized on it often go on to lead stable productive lives free of illicit drug use, points emphasized by Kleber in the White Paper on Treatment he authored while in the White House.

Following the initial development of MM, its wide dissemination in the US is described in the interview with Jaffe who had moved from the University of Chicago to serve as the head of the Special Action Office on Drug Abuse Prevention (SAODAP) in the Nixon White House. In that role, as the 1st "Drug Czar", Jaffe used the concern over the returning Vietnam veterans and their possible involvement in street crime secondary to their narcotic habit picked up in Vietnam, to get Nixon committed to expanding MM in the United States. Earlier, at the University of Chicago, he had carried out the 1st studies of LAAM.

Following MM. came the translational research on narcotic antagonists such as naltrexone and on partial agonists such as cyclozocine, both of which had been studied earlier by the Lexington based ARC. Cyclazocine, because of its side-effects, never caught on but its relative, pentazocine, became a popular analgesic, and drug of abuse in the 1980's. Naltrexone, however, became approved by the FDA for treatment of opioid dependence in 1984 and for alcohol dependence in 1994. The latter is especially due to the work on it by O'Brien. Its use for treating opioid addiction has never been a large one because of poor acceptance by addicts and a high drop out rate. Clearly agonists are preferred by most of them for treatment, perhaps because of issues related to receptor changes and secondary to the protracted withdrawal syndrome, shown by early studies at the Lexington ARC. Major work on na-Itrexone for opiate dependence was done by Jasinski both at ARC and later at Johns Hopkins. He also did early studies on buprenorphine long before it became available for treatment of opioid dependence. In the 7 years since it has become available for that purpose, it has pulled ahead of methadone as a maintenance agent with over 270,000 currently maintained on it.

Kreek, in addition to her long term research on methadone, went on to document the role of the endogenous opioid system in cocaine, alcohol and heroin addiction. For example, the μ opioid receptor endorphin peptides

actions in rewarding effects, and K opioid receptor dynorphins in countermodulatory actions with suppression of dopamine and resultant dysphoria and depression-like effects.

Adler, early in his career, advanced the Lexington work on opiates by demonstrating that lesioning different sites in the brain could abolish various signs of withdrawal. While at that time opiate receptors had not yet been discovered, although postulated earlier by Martin, Adler focused on central sites of action of the opioids and the role of substance P and somatostatin in the spinal cord. Adler made a number of findings on the importance of endogenous and exogenous opioids on analgesia, thermoregulation, and brain excitability. Most recently he has focused on neuroimmunopharmacology, especially the interaction of chemokines and drugs of abuse which could improve treatment of chronic pain.

Eddie Way went from studying the biologic activity of arsenic compounds in the mid 1940's to studying the biodisposition of opiate drugs such as morphine, heroin, meperidine, and methadone for about 20 years. His main research accomplishment was proving that the two biological properties of opiates after chronic administration, tolerance and physical dependence, had a common underlying biochemical basis, norepinephrine release. It took 20 years and shifting from in vivo to in vitro techniques to obtain the conclusive evidence necessary. The 1st paper on this was published in 1968 by Way and his colleagues and the final one in 1990. The final proof ended up using the vas deferens of the mouse: this tissue has a "twitch" response to electric stimulation that is inhibited by opiates. As tolerance developed, more morphine was needed to inhibit the norepinephrine release; after producing withdrawal by washing out the morphine, there was substantial increase in norephinephrine release. Way retired from UCSF soon after this finding and went on to a successful 2nd career in his 70s and 80s.

O'Brien developed his interest in addiction during a tour of duty as a US Navy medical officer from 1969 to 1971 treating marines and navy personnel returning from Vietnam with heroin and other drug addictions. He then founded the University of Pennsylvania VA Addiction Treatment Center. He became very interested in Abe Wikler's behavioral research and applied it to human heroin addicts. He demonstrated in human lab studies in 1977 that craving and withdrawal are conditioned responses with physiological concommatants. This was one of the earliest demonstrations that addiction was a learned response, a memory that continued long after the drugs were gone from the body. Twenty years later his group, especially Childress, showed via brain imaging that drug-related cues produced conditioned limbic system activation along with strong drug craving. In the late 1970's he and McLellan developed the Addiction Severity Index (ASI), now translated into over 20 languages. As noted earlier, he and Volpicelli conducted the 1st studies of naltrexone for alcohol dependence and later found that individuals with a gene variant of the μ opioid receptor had enhanced naltrexone efficacy. If confirmed, this finding would lead to the 1st genomic indication in psychiatry.

Schuster's early work was related to conditioned opiate withdrawal. He developed a method of getting monkeys to self-administer morphine via indwelling jugular catheters and found that stimuli associated with morphine injections could temporarily reverse the signs of opiate withdrawal. Working with Jim Woods he found that stimuli associated with giving a narcotic antagonist to morphine - dependent monkeys could by themselves elicit some of the signs of withdrawal. After moving from the University of Michigan to the University of Chicago he studied the neurotoxicity of methamphetamine, MDA and MDMA and worked with Marian Fischman to study the pharmacodynamics of cocaine. Working with Balster and Johanson, they developed data indicating that animals would self-administer the same drugs that humans abuse and avoid those that human find aversive, validating these procedures as an animal model of drug abuse / dependence. From 1986 to 1992 he was the Director of NIDA where he established the Medication Development Division which has played a very important role in trying to develop new medications.

The interest in opiates, especially the role of opiate withdrawal in relapse was a consistent theme both at the Lexington ARC and among scientists in academia, competing at times with the importance of conditioning factors that Wikler had stressed. Key players in this book in the behavioral pharmacology research included Schuster, Woods, and Barry. O'Brien, perhaps Wikler's best known heir, applied the role of conditioned factors to his work with heroin addicts.

Behavioral pharmacology research can trace its lineage to the Lexington ARC. Seavers, the Chair of Pharmacology at the University of Michigan had a long-standing interest in the abuse liability of narcotics, using rhesus monkeys as his model. He hired Bob Schuster who in turn hired Jim Woods and when Schuster left for the University of Chicago, Woods took over the behavioral pharmacology lab. Woods whole career has been spent at the University of Michigan carrying out pioneering animal work on opioids, central stimulants and sedatives. Currently he is trying to develop new pharmacotherapies for cocaine. He has been a creative scientist and a successful mentor for many graduate students and postdoctoral fellows. He received the Mentorship Award in 2001 from CPDD for this, and in 2004 the Eddy Award, the highest research award CPDD gives. A number of other scientists in this book have also received the Eddy Award including: Adler, Jaffe, Kleber, Kornetsky, Kreek, O'Brien, Schuster and Way. Barry in the late 1960's was one of the earliest participants in research on drug effects as discriminative stimuli. This technique enables the laboratory animal to inform the experimenter whether the animal believes it is drugged or normal. It enables tests of dose effects and other drugs and is used by many pharmaceutical companies to determine whether a new drug resembles a prototype such as an opiate or stimulant. The Lexington ARC had as one of its goals developing a non-addictive pain reliever, and studies like these developed out of their work. Barry spent most of his career, from 1963 to 1995 doing pre-clinical psychopharmacology research at the University of Pittsburgh. He and Kubena were the 1st to demonstrate a discriminative stimulus effect of δ -9-tetrahydrocannabinol (THC), the principal active ingredient of marijuana.

Jack Blaine spent almost all his professional career at NIMH and NIDA where he played an important role in helping to shepherd the development of medications including levo- α -acetylmethadol (LAAM) and buprenorphine / naloxone for opioid addiction and medications for cocaine abuse. In addition he worked on studies to improve various psychosocial approaches. He was chief of the Treatment Research Branch at NIDA from 1986 till his retirement in 2003. His achievements were recognized by a number of Public Health Service Awards as well as the CPDD Morrison Award for outstanding contributions in scientific administration.

Jaffe after leaving the SAODAP went to Columbia and then to the University of Conn. where he worked with Roger Meyers' group in studies on nicotine and on alcohol. He left academia in 1984 to head for 5 years the ARC which had moved to Baltimore in the late 1970's. The ARC was unable to continue in Lexington because Congress, reacting to the Tuskegee scandal on syphilis, forbade research on prisoners.

Most of the scientists profiled in the volume primarily focused on issues related to illicit drug use. Some of them, however, were more involved with studying alcoholism. Marc Schuckit is best known for his work on genetic factors in alcohol disorders. Most important was a 25 year follow-up study with a 94% follow-up rate about every 5 years for 1600 subjects. The results showed that a low level of response to alcohol characterizes children of alcoholics and other high risk groups for alcoholism and can be a useful predictor of future heavy drinking and alcohol problems. In later work, after recognizing that genes associated with alcoholism only explain approximately half the risk, he also focused on the role of comorbid psychiatric disorders, especially depression, anxiety and psychotic syndromes and the importance of distinguishing temporary substance induced conditions from psychiatric syndromes that develop outside of heavy substance abuse.

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Noble is best known for his genetic studies of alcoholism and other drug dependence. He was one of the 1st directors of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) from 1976 to 1978 and spent much of his career as Director of the UCLA Alcohol Research Center. His major discovery was the gene D2 Dopamine Receptor (DRD2) and its association with alcoholism. He later found this same gene was associated with cocaine, nicotine, heroin and food addiction as well. He went on to investigate the various phenotypic expressions of the DRD2 gene and its possible utility in the prevention and treatment of substance use disorders.

Meyer had a career that encompassed both heroin addiction and alcoholism studies. He began his addiction career at NIMH in 1966 at the new Center for Studies on Narcotics and Drug Abuse. This later became the newly created National Institute on Drug Abuse (NIDA). Meyer was named Acting Director of the Center in July, 1967 and among his accomplishments was the funding of six community based treatment programs, the two most successful ones being Kleber's at Yale and Jaffe's at the University of Chicago. He left NIMH in July 1968 and eventually established a NIDA-funded research program on opiate addiction in Boston using biobehavioral chemical and parallel animal model research pioneered by Jack Mendelson and Nancy Mello in alcohol studies. His book on these studies, The Heroin Stimulus reported on findings including that reports of craving were validated by drug self-administration behavior and that the craving was rewarding and not aversive. The research established a novel method for screening medications to treat addictive disorders as well as techniques to improve medication adherence. In 1978 he became Chair of Psychiatry at the University of Connecticut where he established an NIAAA funded alcohol research center - which carried out biological and behavioral studies of craving, medication development and heritability - and developed a major research team which still exists there.

Wayner's career was focused on alcohol research primarily using a rat model. He was interested in the lateral hypothalamic area (LHA) especially in regards to the anterograde amnesia for short-term memory ("blackouts") caused by alcohol. He and his colleagues found that this phenomenon was related to alcohol acting on hippocampal dentate granule cells (HDGC). Stimulation of the LHA inhibits granule cell long term potentiation (LTP). In 1977 they concluded, therefore, that certain cells in the LHA that are extremely sensitive to alcohol project to the HDGC and produce the anterograde amnesia for short term memory. In addition to his laboratory work, he was also Editor in Chief of four significant journals that he founded.

Charalampous in the mid 1960's, following on the ARC's work on mescaline, studied its effects and its metabolism in humans. Later at Baylor Medical College he set up a neurochemistry lab to study the effects of morphine, naloxone and alcohol on cyclic nucleotide in animals. He was also involved with studying the effects of alcohol on driving.

No discussion of addiction is complete without mentioning the scourge of HIV that was spread both by unprotected sex and by needle sharing by injecting addicts. Primm and Pickens both played key governmental roles in the late 1980s and early 1990s, in helping combat the epidemic which has now become in this country because of new medications, more of a chronic disease than the death sentence of the earlier years.

Primm, the only African – American in this volume, was originally trained in Anesthesiology but noted early in his career, in 1963 at Harlem Hospital, that 90% of emergency surgeries involved substance abuse directly or indirectly. He developed a unit to encourage substance abusers to enter treatment and in 1969 set up his own MM program, the Addiction Research and Treatment Corporation (ARTC). He modeled it after the multimodality program set up by Jaffe in Chicago. In 1971 he joined Jaffe at SAODAP and went with him to Vietnam to set up the 1st in – country testing and treatment program. Under the program set up, United States soldiers if they were addicted to opiates were not permitted to return to the U.S. until they had undergone withdrawal. He became the 1st director of the Office of Treatment Improvement (OTI) under the 1st President Bush and then served as the 1st director of the agency that it morphed into, the Center for Substance Abuse Treatment (CSAT). He has been a major advocate for integrating HIV treatment into substance abuse centers.

Pickens studied with Travis Thompson at the University of Minnesota and spent his early career working with animals on behavioral dependence on non-narcotic drugs such as cocaine, amphetamines and barbiturates. He switched over to human research and became interested in genetics, carrying out twin studies in relation to alcoholism. Most of the rest of his career was at NIDA where he became Director of the Division of Clinical Research and in 1986 in charge of NIDA's AIDS research program as well. He oversaw an expansion of the program over the next 3 years from \$3 million to \$142 million in 1986, due to Schuster's pushing Congress for the extra funds. The program focused on education of addicts as to how HIV was spread and evaluating the effectiveness of various approaches, including handing out small bottles of bleach. He moved to the ARC in 1989, returning to his earlier interest in gene-environment interaction.

Volkow began her pioneering imaging work in substance use disorders at the University of Texas in 1984 and soon after in 1987 moved to Brookhaven National Laboratory (BNL) on Long Island. She remained there until 2003 when she became the Director of NIDA, a position she still holds. Her research has been instrumental in changing the view of addiction from a

behavioral choice to a brain disease and has shed light on the neurobiology underlying motivation and self-control. Viewing it as a chronic and relapsing disorder of the brain, she has argued for it to be treated as a medical disorder rather than as criminal behavior. Her research has focused on the role of the dopaminergic system in substance use disorders. For example, she has shown that in normals, the reinforcing effects of these drugs of abuse are associated with sharp increases in dopamine but in addicted individuals such drug-induced dopamine increases are markedly attenuated. Instead there is a heightened response to conditioned cues that drives the increased motivation to take the drug. She has shown that the decreased D-2 receptors in striatum are found not just in substance related disorders but in a wide variety of addictive behaviors such as compulsive food intake in obesity. She has stressed the importance of the frontal cortical systems such as in the orbitofrontal region when the focus had been on the limbic system. As NIDA director, she has emphasized the need for better medications and involvement of the healthcare system in the screening and treatment of substance use disorders. In addition to numerous awards, she was nominated by Time Magazine as one of the "100 people that have affected our world the most" and by US News and World Reports as "Innovator of the year".

As noted earlier, one of the interests of the ARC was studying drugs such as LSD. Klee developed an early interest in these after his chair at the University of Maryland, Jacob Finesinger, received a grant from the Army Chemical Center to support research on this class of drugs, starting with LSD. Klee volunteered as an LSD subject himself to learn what the reaction was like for the subject and wrote a detailed account of the experience. Among the many functions he and his colleagues studied were immediate memory, abstracting ability, time sense and perceived changes in body image. Other areas he pursued were the mechanisms of action of LSD and its interactions with endogenous substances such as serotonin. In 1966 he was invited to testify as an expert witness before a US senate subcommittee cochaired by senators Robert F. Kennedy and Abraham Ribicoff. LSD and other drugs of the class were becoming popular on college campuses, enough so that Kleber during his Yale residency saw a number of students with bad reactions to them and published in 1967 Prolonged Adverse Reactions from Unsupervised Use of Hallucinogenic Drugs. In 1961, Klee was invited to become a founding member of ACNP. The remainder of his career was devoted to integrating public health and epidemiology with patients and their families. Other scientists in this book were also studying LSD at that time. Kornetsky, for example, around 1953 was interested in the psychological effects of LSD, especially its effects on perceptual distortion or "perceptual constancies" as he termed it. Schooler at Baylor was studying LSD effects on the rat brain via brain autoradiography.

No discussion of LSD research would be complete without mentioning the early research on LSD of the man to whom this volume is dedicated – Daniel X. Freedman. Danny X. as he was affectionately called was a mentor to a number of the scientists in this volume, including myself for whom he was a mentor from my residency days through my government service and beyond. The psychedelic drugs, also called hallucinogens or psychomimetics or entheogens, over the past 50 years went from intensive research interest for therapeutic potential or knowledge of the brain, to illicit street drugs and most recently back to being agents of interest for conditions for which pharmacotherapy is lacking.

Schoolar's career was a combination of research, education and clinical practice with the latter two predominating. He spent his career primarily at Baylor College of Medicine, becoming Director of the Texas Research Institute of Mental Sciences (TRIMS) and Chief of the Division of Psychopharmacology at Baylor. His earlier research focused on autoradiography of the brain in rats, chiefly on cocaine and LSD. In the 1960's, while influenced by Bill Martin of the Lexington ARC. he disagreed with Martin's position that addicts were "psychopathic" to begin with, having observed clinically that many went on to do quite well once they gave up drugs.

In the past decade more emphasis has been put on genetics and imaging. A number of the scientists reviewed in this book had a special emphasis on the role of genetics, the best known being Schuckit and Noble. Finally, the ground breaking work of Volkow has played an important role in changing the view of addiction from just a behavioral choice to a brain disease with individual and environmental concomitants.

Despite numerous drug trials and large expenditure of money, no approved medication is yet available for the treatmnet of cocaine or methamphetamine, nor for marijuana which has gained markedly in popularity.

The major advances over these decades have been greater understanding of the role of conditioning in perpetuating addiction and increasing relapse; the role of genetics as a major risk factor for addiction with as much as 50% of addiction having a genetic base; the increasing importance of epigenetic factors; the role of brain imaging in shedding light on what is happening in the brain; the role of various receptors in addiction; the development of effective medications especially for opioid and alcohol dependence; and overall a much better understanding of the brain chemistry in bringing about both addiction and relapse. Although it would be premature to say that addiction is no longer a stigmatized disorder, there is increased understanding that addiction is a brain disease rather than just a behavioral choice. Further, like a number of medical disorders, it is a chronic relapsing disease, a view especially popularized by the past 2 NIDA directors, Drs. Leshner and Volkow. As Volkow put it, "studying the neurobiology underlying addiction is helping understand us the neurobiology that enables us to exert free will".

Dramatis Personae

Martin W. Adler received his BA from New York University in 1949. Following three years at the Brooklyn College of Pharmacy, he received his BS in Pharmacy and was drafted shortly thereafter. He spent two years in the Army, including a year in Korea. He enrolled as a graduate student at Columbia and received his MS in Pharmacology in 1957. He then left Columbia and went to the Albert Einstein College of Medicine in the Department of Pharmacology as a graduate student under Dr. Alfred Gilman. Dr. Adler was the first student at Einstein to be awarded a PhD, in 1960. As part of his graduate training, he took the first two years of medical courses. Upon completing his graduate studies at Einstein, Dr. Adler accepted an appointment as Instructor in the faculty of the Department of Pharmacology at Temple University School of Medicine. He remains at Temple and is completing his 50th year on the faculty. He rose to the rank of Professor, became the Laura H. Carnell Professor of Pharmacology, and received the Honored Professor Award from the Alumni Association in 2004. In 1998, he founded the Center for Substance Abuse Research at Temple. He has received numerous awards from Temple and from scientific societies.

While a graduate student at Einstein, Dr. Adler worked with Dr. Murray Jarvik investigating the effects of a variety of centrally acting drugs on visual discrimination and delayed response tests in monkeys. When one of the monkeys died from a moderate dose of amphetamine, Dr. Adler was curious as to the reason. He found that the monkey had a prefrontal lobotomy performed at NIH a couple of years earlier and wondered if the ablation was causally related to the death. He decided to switch the thesis research he had begun with Dr. Jarvik in monkeys to a study of brain damage and sensitivity to drugs in rats. Dr. Seth Sharpless became a co-mentor for the research. Dr. Adler found that lesions of the prefrontal cortex and the occipital cortex resulted in an increased sensitivity to drugs such as amphetamine, but the effect varied with the site and duration of the lesion, as well as with the particular drug. He called the phenomenon "denervation supersensitivity," the term that had been applied before only to the peripheral nervous system by Cannon and Rosenbluth. After a battle with the editors of JPET, who did not want the term "denervation supersensitivity" used, the paper, with the term, was accepted and published. That term became generally accepted for the

central nervous system and subsequent studies by others determined the mechanisms involved.

Dr. Adler continued his research with behavior and with brain lesions when he went to Temple. The research was supported by grants from NIMH. Some of the studies dealt with the acute and chronic effects of drugs such as amphetamine and tetrabenazine on locomotor activity. However, most of the research involved the effects of brain lesions in rats on sensitivity to antiepileptic drugs. Dr. Adler's interest in morphine and other opioids began when Joe Cochin, whom he had just met at a FASEB meeting, suggested that he use morphine in his studies of seizures and brain excitability. That casual suggestion started Dr. Adler on his research path with opioids for the next 40 years. It became increasingly apparent to him that the response to brain damage was dependent not only on the drug being tested and the duration of the lesion, but on the particular site of the lesion. A neurosurgeon with whom he did some work at Temple noted that a couple of his patients that had surgery for intractable pain showed no signs of withdrawal from the high doses of morphine taken over many months. These particular patients had received lesions of the centre median nucleus of the thalamus. Dr. Adler produced lesions in the same area in rat brains, even though rats do not really have this nucleus. At that time, little was known about different brain sites involved in addiction and withdrawal. He demonstrated that no one site, among the 10 or 15 sites lesioned, could abolish all the signs of withdrawal, but that different sites were responsible for specific signs of abstinence.

When it was decided in the early 1970s that NIDA would become a separate institute, Dr. Adler received a call from NIH asking if he would object to having his NIMH grant on brain lesions and drugs shifted to the new Institute with the new number of DA00049. He agreed and, shortly thereafter, received a call from NIDA asking if he would be interested in submitting a grant for any work he deemed appropriate for NIDA. He put together a group of six faculty members at Temple and submitted a proposal called "Narcotic Receptors in Addicted and Non-Addicted States," which continued for 30 years, including as a MERIT award in the last 10 years of the grant. Opiate receptors hadn't been discovered yet, but being a pharmacologist, Dr. Adler had to think in terms of receptors. His studies on analgesia focused on central sites of action of the opioids, on interactions with other drugs, and the role of Substance P and somatostatin in the spinal cord; in terms of thermoregulation, he demonstrated that the EP3 receptor in the preoptic anterior hypothalamus was responsible for the actions of opioids on body temperature, that effects of cytokines on body temperature were via that receptor, and that opioids produced temperature changes primarily via changes in heat production; with the pupil, he showed that the mydriasis produced by morphine in

the rat consisted of rapid fluctuations in the size of the pupil; in terms of brain excitability, he demonstrated that the increased in EEG seizure-like activity of morphine and similar drugs was accompanied by an increase in seizure threshold in rats. The person Dr. Adler credits most in terms of the opiate work is William (Bill) R. Martin, whose seminal work with opioids in dogs, and seizures in rabbits, as well as his advice when he and Saul Schanburg sitevisited him, really set the stage for Dr. Adler's research. He credits his findings of the importance of endogenous and exogenous opioids on analgesia, thermoregulation, the pupil, and brain excitability, in large measure, to Dr. Martin's initial guidance and insights.

For the past 20 years, much of the focus of Dr. Adler's research has shifted to the field of neuroimmunopharmacology. This was a direct result of a small dinner meeting called by Monigue Braude of NIDA in 1986 to determine if NIDA should become involved in studying the relationship between drugs of abuse and AIDS. Dr. Adler was the lone pharmacologist among immunologists that included Drs. Herman Friedman, Arthur Falek, Robert Donahoe, and Joseph Wybran. With Dr. Francis Havas, Professor of Microbiology/ Immunology at Temple and Ellen Geller, his research collaborator, he decided to see if cocaine would alter antibody formation in the mouse, but the findings were negative. After Dr. Havas retired, Dr. Adler approached Dr. Toby Eisenstein, also a Professor of Microbiology and Immunology, and they began a collaboration that is still ongoing and is supported by numerous grants from NIDA. They found that morphine had a profound effect on antibody formation in the mouse. Several other faculty members at Temple joined them and research in neuroimmunopharmacology became a vibrant field at Temple and has become increasingly important in biomedical research. Dr. Adler considers his newest research in the area, involving chemokines and drugs of abuse, to be his most important contribution to research. Indeed, he has proposed that chemokines are a third transmitter system in the brain, joining neurotransmitters and neuropeptides. New evidence from his and other groups, lend strong support for the theory. Extensions of the interactions of opioids, chemokines, and other drugs have led him to propose new methods of treating various forms of chronic pain.

In addition to major research findings listed above, Dr. Adler has made decisive contributions to science in administration and support functions. He served on NIDA and NIH review committees for almost 35 years and chaired many of those committees, including the Drug Abuse Biomedical Research Review Committee of NIDA, and was the first Chairman of the NIDA Review Committee on Center Grants. He also chaired the VA Merit Review Board in Clinical Pharmacology and the Integrative and Functional Cognitive Neuroscience of NIH. He also served on the NIDA Long-Range Planning Committee on Neurosciences and was a member of Search Committee for Director of NIDA for Alan Leshner.

Finally, it should be noted that Dr. Adler serves as Executive Officer of the College on Problems of Drug Dependence (CPDD), a position that he has held since 1986, shortly after Joe Cochin died. Conan Kornetsky and Mary Jeanne Kreek took over Joe's position until Dr. Adler was elected. For those who do not know, CPDD is the oldest organization devoted to research on drug abuse and addiction. A committee of the National Academy of Sciences until 1976, it became an independent society and was sponsored by 12 major scientific organizations, including ACNP; a number of scientists, including Drs. Kornetsky, Kreek, Way, Cook, Keith and Eva Killam, Harris, O'Brien, Schuster, Kleber. Brady and Hollister have held important leadership positions in both CPDD and ACNP.

Herbert Barry III began his preclinical psychopharmacology research in 1957, as a post-doctoral research fellow funded by the NIMH Psychopharmacology Service Center. His sponsor, Yale Psychology Professor Neal E. Miller, had been the principal advisor of Barry's dissertation for the PhD degree, received in the same year. Barry's initial research on the postdoctoral fellowship was published in 1958 as an article by Philip G. Zimbardo and Barry, with the title *Effects of caffeine and chlorpromazine on the sexual behavior of male rats* in *Science*. Zimbardo is not a psychopharmacologist but subsequently has been President of the American Psychological Association. More than 20 years earlier, in 1935 and 1936, Miller had published with Walter R. Miles two articles, on effects of caffeine and alcohol on behavior of rats, in the *Journal of Comparative Psychology*.

Several years of research and several publications by Barry and Miller were funded by a research grant to Miller from the NIMH. Barry's research fellowship was followed by appointment as Instructor, then Assistant Professor, at Yale. Barry was one of the earliest psychologists to choose a career in a pharmacology department. He did preclinical psychopharmacology research at the School of Pharmacy in the University of Pittsburgh from 1963 to 1995.

Barry was one of the earliest participants in research on drug effects as discriminative stimuli. This technique enables the laboratory animal to inform the experimenter whether the animal believes that it is drugged or normal. It enables the testing of the effects of doses, time intervals, other procedures, and other drugs. The technique is used by many pharmaceutical companies to determine whether a new drug resembles a prototype, such as an opiate or anti-anxiety medication or stimulant

The technique was begun by Donald A. Overton, using a T-maze in which the animal chose to turn right or left. Barry and Kubena, in two articles published in 1969, introduced the technique of recording the choice

between different responses in an operant conditioning chamber. Barry and Kubena were the first to demonstrate a discriminative stimulus effect of Δ -9-tetrahydrocannabinol, the principal active ingredient of marijuana. Barry and Krimmer were the first to demonstrate differential discriminative effects of two sedative drugs, chlordiazepoxide and pentobarbital.

A major contribution by Barry to preclinical psychopharmacology was his function as editor of the journal, *Psychopharmacology* for manuscripts from North America on drug effects in laboratory animals from 1974 to 1991. He received more than 2,000 manuscripts and accepted for publication more than 1,000. He required revisions of almost all of the accepted manuscripts. His predecessor was Conan Kornetsky. His successor is Klaus A. Miczek. Subsequent to the interview by Thomas A. Ban, Barry contributed to the same Journal an article *Censorship by a tobacco company* that was published in 2006; a review article by Barry and James B. Appel with the title, *Early preclinical studies of discriminable sedative and hallucinogenic drug effects* that was published in 2009.

Concurrent with Barry's contributions to preclinical psychopharmacology have been unusually diverse other research interests. As a senior at Harvard College, in 1952 he carried out cross-cultural comparison, using ethnographic accounts of the customs of more than 100 societies, distributed throughout the habitable world. Most recently, in 2009, he served as guest editor of a special issue of a *Journal Social Evolution & History*. The Journal is published in Russia but entirely in the English language. The interview by Thomas A. Ban mentioned also research on empathy.

Jack D. Blaine received a BA degree in biological sciences from Rutgers College in 1964 and a MD degree in 1968 from the Albert Einstein College of Medicine of Yeshiva University. During his fourth year of medical school, he was awarded a Manealoff FoundationTraveling Fellowship to study the British system of narcotics control in London, England. He completed an internship at University of California at Los Angeles Affiliated hospitals in Los Angele in 1969 and then entered the United States Public Health Service where he served as the Special Consultant for Medical Sciences at the Center for Studies of Narcotics and Drug Abuse in the Division of Narcotic Addiction and Drug Abuse, National Institute of Mental Healthin Chevy Chase, Maryland. His primary focus was the effect of marijuana on humans. In July 1971 he was appointed the Assistant Director of the National Commission on Marijuana and Drug Abuse in Washington, DC. During his residency in psychiatry from 1972 to 1975 at the University of California at San Diego School of Medicine, he worked with David Janowsky, MD to conduct a study to determine the effects of marijuana on airplane pilots' performance of a simulated flying task. Following his residency, he returned to the US. Public Health Service where he worked with Pierre Renault, MD in the Clinical-Behavioral Research Branch in the Division of Research at the National Institute on Drug Abuse where he was the coordinator of the pharmaceutical development of levo- α - acetylmethadol for the treatment of opiate dependence and also established a research program on diagnosis and treatment of psychiatric co-morbidity and opiate addiction. He was also the NIDA representative for the World Health Organization in the Alcohol, Drug Abuse and Mental Health AdministrationInternational Program on Diagnosis and Classification of Mental Disorders, Alcohol and Drug Related Problems. From 1980 to 1986 he worked with Robert Prien, PhD in the Affective Disorders Section of the Pharmacologic and Somatic Treatment Research Branch at NIMH where he coordinated the Electroconvulsive Therapy clinical research program. After his return to NIDA in 1986 he became the Chief of the Treatment Research Branch in the Division of Clinical and Services Research, where he remained until his retirement from the US Public Health service in 2003 finally serving as the Deputy Director of the Center for the Clinical Trials Network. During this time at NIDA, collaborating with Lisa Onken, PhD, the Behavioral Therapy Development Program was established. He initiated the research program for buprenorphine/naloxone for the treatment of opioid addiction and also for medications for the treatment of cocaine abuse and dependence. He served as a collaborating investigator for the WHO/ ADAMHA Joint Project on Diagnosis and Classification of Mental Disorders, Alcohol and Drug-Related Problems; for the NIDA Cooperative Collaborative Multi-site Trials on the Efficacy of Psychotherapy and Drug Counseling in the Outpatient Treatment of Cocaine Dependence; and, on Motivational Incentives for Enhanced Drug Abuse Recovery: Drug Free and Methadone Clinics; and on Buprenorphine/Naloxone; and for Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults. His achievements have been recognized by a number of US Public Health Service Awards as well as the J. Michael Morrison Award for Outstanding Contributions in the Area of Scientific Administration from The College on Problems of Drug Dependence.

Kanellos D.Charalampous received his MD from Baylor Medical College, Houston, Texas in 1958. After graduation he stayed on the faculty of the Department of Psychiatry and in the 1960s he became involved in clinical investigations with numerous psychoactive drugs in collaboration with John Kinross-Wright.

In the mid-1960s Dr. Charalampous studied the effects of mescaline and reported on the metabolic fate of the substance in man. He also spent time in Turkey, Greece and Morocco interviewing users of hashish and health care professionals about hashish users. In the early 1970s Charalampous set up a neurochemical laboratory at Baylor Medical College to study the effects of morphine, naloxone and alcohol on cyclic nucleotide in animals. At the same time, in a project supported by the US Department of Transportation he was involved in studying the effects of alcohol on driving. He was also among the first in Texas to set up a clinical inpatient program for the rehabilitation of alcoholics in a large general hospital.

From1978 to 1980 Dr. Charalampous served as Chairman of the Department of Psychiatry at the University Medical School in West Texas where he established specialized out-patient clinics for patients with different diagnoses. Subsequently, until his retirement he dedicated his time to clinical work, mental health service organization and teaching.

Jerome H. Jaffe received his AB and MA.in Experimental Psychology, and MD degrees in 1954, 1956, and 1958 from Temple University As a psychiatry resident and medical officer at the Public Health Service Hospital at Lexington, Kentucky he developed a close relationship with Abraham Wikler, whose work had a lasting influence on his career. He left the PHS to take a postdoctoral fellowship at Albert Einstein College of Medicine in Alfred Gilman's department of pharmacology. While at Einstein, he worked with Seth Sharpless on pharmacological denervation supersensitivity as a model for the development of tolerance and physical dependence. After completing his residency in psychiatry, he held faculty appointments in pharmacology and psychiatry. He also became progressively more involved in clinical treatment of heroin addicts, utilizing opioid agonists as well as a newly developed opioid antagonist, cyclazocine, to test Wikler's ideas of conditioning. In 1963, Al Gilman invited him to contribute a chapter on drug addiction and abuse to the third edition of The Pharmacological Basis of Therapeutics, published in 1965. This chapter, covering all aspects of what was known at the time about addiction, was updated every five years for each subsequent edition until the ninth, in 1995, when it was taken over by other authors. In 1966, he joined the Department of Psychiatry at the University of Chicago and at the same time was selected to develop and head what became the Illinois Drug Abuse Programs. The multimodality treatment system that he established was one of the first of its kind in the United States. In Chicago, his clinical research included further studies with methadone and cyclazocine, and the first studies of LAAM. By 1970, IDAP and Jaffe had attracted the attention of the White House. His academic understanding of drug abuse, experience with treatment programs, and his proposal for a public health intervention that became successful in controlling a heroin epidemic among US servicemen in Viet Nam led to his appointment, in 1971, as Special Consultant to the President for Narcotics and Dangerous Drugs and as the first Director

of the White House Special Action Office for Drug Abuse Prevention, the first "Drug Czar". Many of the basic and epidemiological research programs that formed the groundwork for current efforts in drug abuse research and treatment were initiated during his tenure in that office, including expansion of methadone treatment and the establishment of NIDA. He returned to research and teaching in 1973, at Columbia University College of Physicians & Surgeons, and later moved to the University of Connecticut. His work at Columbia and Connecticut included studies on nicotine and alcohol dependence. In 1984, he left academia again to head the NIDA Addiction Research Center in Baltimore, a position he held until 1989. Pivotal studies of buprenorphine were conducted during his time there. He also served briefly as Acting Director of NIDA, and subsequently held various policy positions in other government agencies, including the Center for Substance Abuse Treatment. He retired from government service in 1997 and returned to teaching, research, and consulting. He is currently Clinical Professor of Psychiatry at the University of Maryland, School of Medicine. His publications include peer reviewed journal articles, invited chapters in widely used textbooks of psychiatry, pharmacology, and drug abuse, and books for the general public. He has served on numerous national and international committees and editorial boards. He is a fellow of the ACNP, CPDD, American Psychiatric Association, AAAP, Royal College of Psychiatrists (Hon. UK), and the Society for the Study of Addictions (Hon. UK), and has been the grateful recipient of honors and awards from his colleagues in recognition of his contributions to the field of addiction.

Donald Jasinski obtained his pre-med education at Loyola University of Chicago. In the fall of 1959, he enrolled as medical student at the University Of Illinois College Of Medicine, receiving his MD in the spring of 1963. During his medical school training, he took graduate courses in the Pharmacology Department and conducted pre-clinical neuropharmacological research studies. In July of 1963, he began a one year rotating medical internship at the University of Illinois Research and Educational Hospital. The next year was spent as a fellow in neuropharmacological research in the Department of Pharmacology at the University of Illinois under the mentorship of Klaus Unna. His research activity during this year was on the early electrophysiological changes after denervation of skeletal muscle and was conducted under the direction of Buzz Salafsky.

In July 1965, Dr Jasinski enlisted as a Commissioned Officer in the United States Public Health Service and was assigned for a two year period as a staff physician at the NIMH Addiction Research Center in Lexington Kentucky. He converted to permanent staff and remained at the Addiction Research Center for twenty years as a scientist and administrator. His major scientific

interest was the human pharmacology of substances of abuse. Under the mentorship and in collaboration with William R. Martin, he conducted studies to understand the causes, treatment and prevention of addiction. Studies included protracted abstinence from morphine and methadone and demonstration of the human pharmacology of multiple opioid receptors. Studies of narcotic antagonists led to the recognition and introduction of naloxone as an antidote for morphine poisoning. Subsequently, initial human studies were conducted with naltrexone that recognized its potential as a treatment agent for opiate addiction. In collaboration with Harris Isbell studies demonstrated that THC was the active ingredient in marijuana and that in large doses THC was hallucinogenic. Methods were developed and a number of opioids, sedative hypnotics and amphetamines were assessed for abuse potential. During this period, the human pharmacology and abuse potential of buprenorphine was studied with the recognition that buprenorphine had the potential as a treatment drug for opiate addiction. In 1976, Dr Jasinski succeeded William R. Martin as Director of the Addiction Research Center. Upon the closure of the human research program in 1976, Dr Jasinski identified and facilitated the relocation of the Addiction Center to its current location in Baltimore Maryland where it currently is the intramural research program of the National Institute on Drug Abuse. The human research program was re-established. Significant studies included the demonstration that nicotine was the agent responsible for the reinforcing properties of tobacco, further studies of buprenorphine, clinical pharmacological evaluation of clonidine to treat opiate abstinence, and the introduction of methods to assess the abuse potential of benzodiazepines.

In 1985, Dr Jasinski retired from the USPHS and joined the Department of Medicine of Johns Hopkins University School of Medicine where he is Professor of Medicine. He developed the Center for Chemical Dependence that function as a division within the Department of Medicine at the Johns Hopkins Bayview Medical Center. The division provides services to medically ill addicts and alcoholics including those with HIV/AIDS. Within the division, Dr Jasinski developed a clinical research unit that conducted studies with substances of abuse. A major research activity was directed toward assessment of the abuse potential of a number of substances that such as transnasal butorphanol, tramadol, diazepam, sumatriptin, odansetron, modafinil, testosterone, atomoxetine, methlphenidate patches, and lisdexfetamine. He also evaluated a number of agents as treatment drugs for cocaine, alcohol, nicotine and opiate dependence including studies in pregnant opiate abusers. Treatment evaluation studies were conducted in patients on buprenorphine maintenance, and in patients with HIV/AIDS. He counts among his major achievements the development of a medical faculty focusing on addiction medicine.

Herbert D. Kleber received his BA from Dartmouth College in 1956, his MD from Thomas Jefferson Medical College in 1960, and completed his psychiatric residency at Yale University Medical Center in 1964. He spent the next two years as a commissioned officer in the Public Health Service at the US PHS facility in Lexington, KY, one of only two facilities that treated narcotic addicts, as well as the home of the Addiction Research Center with Bill Martin, Abe Wikler, and Harris Isbell. Being at Lexington launched his life-long career in carrying out research, treatment, and policy in the field of addiction.

Dr. Kleber returned to Yale in 1966 and spent the next 23 years there, carrying out his pioneering addiction work. He became Professor there in 1975. In 1968, he received his first grant from NIMH, NIDA not yet in existence, which established the Drug Dependence Unit as one of the first true multimodality treatment and research endeavors, the major other one being Jerry Jaffe's at the University of Chicago. The controversy at the time was between methadone maintenance programs and drug-free programs, especially therapeutic communities. His program included both, and helped legitimatize maintenance outside of the New York area. The program was also one of the first to research new agents such as narcotic antagonists, developed new psychosocial approaches as well, and demonstrated the prevalence and importance of other psychiatric disorders among narcotic addicts. In 1978, he and his colleagues were the first to show that α -adrenergic agonists, e.g., clonidine, could ameliorate opiate withdrawal and in the early 1980's combined clonidine with naltrexone to produce rapid opiate withdrawal. His studies on naltrexone were the 1st to demonstrate that tolerance to its narcotic antagonist effects did not develop even after years of maintenance on it.

Around 1980, when many were still portraying cocaine as a benign recreational drug, he and his Yale colleagues recognized its dangers and were among the first to try various medications to treat this addiction. Unfortunately, after trying dozens of agents, no generally effective agents to treat cocaine addiction, has been shown, although a vaccine looks promising.

In 1989 he was invited to Washington by Bill Bennett, the new Drug Czar, and President George H. W. Bush and confirmed by the Senate to be the first Deputy Director for Demand Reduction at the newly established Office of National Drug Control Policy. He held the position for approximately two and a half years during which his office carried out a number of initiatives, including doubling the federal funds for treatment and prevention; improving the national data bases e.g. expanding the Monitoring the Future High School Survey to include 8th and 10th grade, and requiring the Household Survey to

be carried out yearly rather than every 3 years; forcing the VA to markedly expand its substance abuse treatment; issuing a Treatment White Paper defending methadone maintenance as a vital part of opioid addiction treatment after the Reagan White House had condemned it; setting up Community Prevention Programs; and overseeing the transfer of NIDA to NIH.

When he left Washington in November 1991, Kleber and his new wife, Marian Fischman, a renowned cocaine expert and Professor at Johns Hopkins, went to Columbia Medical School where they set up a treatment research program similar to his program at Yale and human behavioral laboratories similar to hers at Johns Hopkins. The cocaine laboratory was especially productive, including what many regarded as the most significant cocaine research since Freud's "Über Coca" in 1885. She was the first scientist since Freud to use controlled scientific experiments with humans to examine cocaine's effects. The Columbia Division on Substance Abuse headed by Dr. Kleber been ranked among the top three in the country for the past decade by US News & World Report, as has his former unit at Yale. His Center Grant for Medication Development from NIDA has been continiously funded since 1994 and the Addiction Psychiatry Fellowship Grant since 1993 from NIDA.

In 1992, he and Joe Califano formed CASA, the Center for Addiction and Substance Abuse at Columbia, which became a leading substance abuse policy center. From 1992 until Marian's death in 2001, Kleber was half time at CASA and half time at the Medical School and since then full time at the Medical School, carrying out research on cocaine, opioids, and marijuana and opening one of the first community buprenorphine programs. The marijuana research, for example, was the first to demonstrate that there was a physiologic marijuana withdrawal and that dronabinol could successfully treat it. A multicenter trial he headed with Margolin at Yale demonstrated the lack of efficacy of acupuncture for treatment of cocaine dependence.

Dr. Kleber is the co-Editor of the American Psychiatric Press Textbook of Substance Abuse Treatment, now in its 4th edition and probably the leading textbook in its field. He has received numerous awards, including: the CPDD Nathan B. Eddy Award for excellence in drug abuse research; the AMERSA McGovern Award, the ASAM Smithers Distinguished Scientific Award, and the APA Foundations Fund Gold Research Awards among others. He also has received two honorary degrees, is listed as one of the "Best Doctors in America" and "Best Doctors in New York"; served on numerous Boards and Councils, including the National Advisory Council to NIDA (twice), the councils of CPDD and ACNP, and the Boards of the Partnership for a Drug Free America, Phoenix House and the Betty Ford Institute. He has also served on the APA Council on Addiction for over a decade. He was elected in 1996 to be a member of The Institute of Medicine of the National Academy of

Science. He is most proud of the superb researchers he has mentored at Yale and Columbia, including many of the most prominent in the field.

The country was in World War Two when *Gerald D. Klee* completed high school in 1944. He enlisted in the Army and was sent to Princeton to study engineering. He and his unit were later transferred into the infantry. After the war Klee was in pre-med at McGill University. Then, he was admitted to Harvard Medical School, graduating in 1952. He then enlisted in the US Public Health Service, serving 2 years. His first year was spent in an internship in the Marine PHS Hospital in New York; the next year he was at the US Medical Center for Federal Prisoners in Springfield, Missouri where he did general medicine.

In 1954 Dr. Klee began a Johns Hopkins Dean's Committee psychiatry residency at the Perry Point VA Hospital in Maryland. Thorazine (chlorpromazine) was introduced in 1954. At the time Klee was working with severely regressed schizophrenic veterans who had been there for years. In most cases they improved dramatically on Thorazine; many could eventually be discharged.

In 1950 Jacob Finesinger came from Harvard Medical School to Maryland to found the University of Maryland, Department of Psychiatry and recruited Klee in 1956.

Finesinger got a grant from the Army Chemical Center in Edgewood, Maryland to support research with psychoactive chemicals starting with LSD. Over the next three years the group conducted biological, behavioral and cognitive studies with LSD and other psychoactive substances. Klee volunteered as an LSD subject himself to learn what an LSD reaction was like for the subject and wrote a detailed account of his experience. This served as a basis for studies of how a wide variety of cognitive and perceptual functions are affected by LSD. Among the many functions studied were immediate memory, abstracting ability, time sense and perceived changes in body image. Other studies were devoted to examining the mechanisms of action of LSD, as well as its interactions with endogenous substances such as serotonin.

In May 1966 Klee was invited to testify before the United States Senate Subcommittee on Executive Reorganization, Co-Chaired by Senators Robert F. Kennedy and Abraham Ribicoff. As an "expert" witness Klee was asked about his views on the drug abuse epidemic on college campuses, about scientific research with LSD and similar substances, and whether Klee favored restrictions on the availability of such chemicals in order to limit recreational use. Klee stated that such drugs should be restricted to scientific research and expressed the hope that Congress would support measures to provide treatment for them.

In 1970 Klee sent a letter to President Nixon about Nixon's proposal to ban the military use of chemical weapons, fearing that if ban included "psychochemicals" it would discourage scientists from studying them. Klee told Nixon that between 1956 and 1959 he had studied LSD and that LSD had no military value. Klee received a disappointing reply - it wasn't possible to discontinue work with psychochemicals.

Klee's entrance into the international Nneuropsychopharmacology community took place in 1958 in Rome at the first meeting of the Collegium Internationale Neuropsychopharmacologicum, where he presented a paper about LSD. In 1961 Klee was invited to become a founding member of the ACNP.

Before Finesinger died in 1959, he arranged for Klee to be the Director of the Outpatient Psychiatric Service at Maryland. Klee fulfilled a dream of getting into public health and epidemiology and integrating them with working with patients and families in the field. Across from the UM Psychiatric Institute was the Western Health District of Baltimore City Health Department. In 1959 Klee made a liaison with the health officer and staff, who knew the families in the district. Next, Klee became a consultant to the NIMH Office of Biometry and worked with them in developing the Maryland Psychiatric Case Register which provided statistics used for planning and research. They also collaborated closely with the Maryland Department of Mental Hygiene staff. With their data they made important correlations. Klee saw public health, psychiatry, neuropsychopharmacology, general medicine, and epidemiology linked in complex ways. The epidemiology study Klee is most proud of is one in which they studied mental illness broken down by census tract in Baltimore with data for many issues. This information served to guide coordination of services.

Outside of psychopharmacology, epidemiology and public health, Klee's professional interests have been in clinical work and teaching. He continued seeing patients in private practice until his retirement. He continued supervising psychiatric residents and helping them learn how to do psychotherapy and to combine it effectively with the use of medications. He taught at the University of Maryland, then at Temple University in Philadelphia.

Conan Kornetsky received his BA in Psychology from the University of Maine in 1948. His undergraduate work was interrupted for almost two years, from March 1944 to November 1955, by service in the US Army Air Corps. In the fall of 1948, he enrolled at the University of Kentucky for his PhD and at the same time got a job at the Addiction Research Center in Lexington,

Kentucky. After receiving his PhD in Clinical Psychology at the University of Kentucky in June 1952, he took a position at NIMH and carried out from July 1952 to August 1953, a field study of juvenile addiction in New York City and was then assigned to study from September 1953 to August 1954, the effects of LSD with Murray Jarvik at Mount Sinai Hospital in New York City. He spent the next five years, from September 1954 to June 1959, at NIMH at their Laboratory of Clinical Science in Bethesda, Maryland. Dr. Kornetsky then went to the Boston University School of Medicine, Departments of Psychiatry and Pharmacology, where he remains currently.

The work of Dr. Kornetsky has led to four major and enduring seminal contributions. First, his early work in schizophrenia identified an important, perhaps critically important, attentional deficit. Second, his creative work with animal research has been a prototype for the modern physiological psychologist and neuropsychopharmacologist. More importantly, he displayed innovativeness in his research directions and techniques that have opened whole new avenues of research. Third, the long term effects of drugs of abuse characterized by Dr. Kornetsky has laid the framework for the study of plasticity of the brain associated with modern theories of tolerance and physical dependence. Fourth, Dr. Kornetsky's work with drugs and brain stimulation reward clearly demonstrated the role of the reward system in drug dependence.

During his tenure at Lexington from 1948 to '52 he published a series of papers with Harris Hill and Abraham Wikler plus a dissertation that demonstrated the importance of morphine's effect on anxiety and the contribution of this action to morphine's analgesic effect in humans.

In 1954 at NIMH he began a comprehensive series of experiments in collaboration with AF Mirsky on the behavioral effects of centrally acting drugs on human behavior. In 1959 he moved to Boston University School of Medicine where these studies continued and were instrumental in the development of an attentional model of schizophrenia. This model postulated that the functional deficit in schizophrenia was due to a centrally over-aroused state that resulted in the schizophrenic patient filtering incoming stimuli. Using the Continuous Performance Test (CPT) he found that approximately 40 percent of the unmedicated schizophrenic patients showed a deficit in attention. This poor performance, as Orczak and Kornetsky presented in 1971, correlated with mental illness in the family. These patients upon receiving neuroleptic medication showed some improvement on the CPT. However, as presented by Wholber and Kornetsky in 1973, schizophrenic patients even in good remission, holding jobs and functioning socially, and not medicated showed a deficit in CPT performance under conditions of sensory overload. Kornetsky found, and reported in 1976, that contrary to current belief at the time, schizophrenic patients were hyporesponsive to amphetamine. Also, he devised an animal model of the impaired attention of schizophrenic patients. In this experiment he designed an attention task in rats in which low level stimulation of the mesencephalic reticular formation resulted in a deficit in the animal version of the CPT and this deficit could be reversed by chlorpromazine as shown by Kornetsky and Eliason in 1969.

In the 1970's he developed a rate independent psychophysical method for determining the threshold for rewarding intracranial self stimulation. By the judicious use of opiate, dopamine and noradrenergic agonists and antagonists he provided extensive evidence that the dopamine system is important for all abused substances. Although as early as 1957, it was shown that the psychomotor stimulants facilitated brain stimulation reward, it was not until a 1974 paper by Marcus and Kornetsky, making use of classic psychophysics, clearly demonstrated that morphine increased the sensitivity of animals to rewarding brain stimulation.

By making use of the 2 [¹⁴C] deoxyglucose autoradiographic method, in collaboration with Linda Porrino they found that in addition to the nucleus accumbens, the olfactory tubercle may play an important role in the reinforcing effects of brain-stimulation reward, and abuse of substances. These findings were publiashed in papers by Porrino, Huston-Lyons, Bain and Kornetsky in 1990 and Kornetsky, Huston-Lyons, and Porrino in 1991. Also, using the 2DG technique they found that morphine in the presence of pain does not simply reduce metabolic activity in the brain but it actually increases metabolic activity in the midbrain, suggesting that morphine's analgesic actions are an active process.

Mary Jeanne Kreek, MD, is a graduate of Wellesley College and the Columbia University College of Physicians & Surgeons, where she received the MD degree. Dr. Kreek joined "The Rockefeller Institute for Medical Research" in 1964, and, with the late Dr. Vincent P. Dole, and the late Dr. Marie Nyswander, performed the initial studies of the use of a long-acting opioid agonist, methadone, in chronic management of heroin addiction.

Dr. Kreek is the Patrick E. and Beatrice M. Haggerty Professor and Head of the Laboratory of the Biology of Addictive Diseases at The Rockefeller University, and Senior Physician of The Rockefeller University Hospital. Until March, 2008 Dr. Kreek had held a Senior Scientist Award from NIH-NIDA for many years (K05-00049). She is Principal Investigator and Research Director of an NIH-NIDA P60 Center grant (DA-05130) – "Treatment of Addictions: Biological Correlates." She also has several grants from NIH-NIDA and NIH-NIMH. She is author or co-author of over 450 scientific research papers.

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By molecular, cell biological, neurochemical, behavioral, basic clinical research, and human molecular genetics studies, she has documented the role of the endogenous opioid system in cocaine, alcohol and heroin addiction: the pleasurable or "rewarding" effect of μ -opioid receptor-endorphin peptides, and the countermodulatory actions of K-opioid receptor-dynorphins, with suppression of dopamine, and resultant dysphoria and depression-like effects.

Her group has also identified novel polymorphisms in the coding and noncoding regions of human mu and kappa opioid receptor genes and shown associations of these two opioid receptor genes, as well as other identified variants of two opioid peptide genes, dynorphin and enkephalin, and two more opioid receptor genes, the Δ and nociceptin/orphanin FQ receptors, with three different specific addictive diseases, opiate addiction, cocaine addiction and alcoholism.

Her laboratory elucidated the very different cellular-molecular functional properties of a major variant of the µµopioid receptor (A118G), and predicted, then showed, along with other investigators, that specific components of the hypothalamic-pituitary-adrenal axis, and functions thereof, is altered in healthy people with one or two copies of this gene variant. Further, she predicted that this variant, which alters stress responsivity, would be associated with two addictive diseases characterized by altered stress responsivity; her group went on to demonstrate strong associations of this functional variant with both heroin addiction and alcoholism by studying a modestly admixed population in central Sweden. Her laboratory is currently studying selected epigenetics questions, in humans and also in rodent models and has identified epigenetic changes in the promoter region of the human μ opioid receptor.

In collaboration with the CDC in 1983 and '84, she was the first to identify parenteral drug users as the second risk group for acquiring HIV-1/AIDS infection. She has conducted many studies on hepatitis B, hepatitis and hepatitis C, alone, and in combination with AIDS, in the addictive disease populations.

She has received several awards for her scientific research, including the Betty Ford Award from AMERSA in 1996, the R. Brinkley Smithers Distinguished Scientist Award and Lecture of ASAM in 1999, the Nathan B. Eddy Memorial Award for Lifetime Excellence in Drug Abuse Research in 1999 and the Marian Fischman Award in 2005; the latter two both presented by the College on Problems of Drug Dependence. In 2000, she was conferred the Doctor Honoris Causa by the University of Uppsala, Sweden, and was made a Fellow of the New York Academy of Sciences.

Dr. Kreek has been a very loyal and active member of ACNP since 1985. She began attending the meetings on an annual basis from the time she went on the Executive Committee of the Board of Directors of the College of Drug Dependence, which then had all of its interim meetings during the ACNP meeting. While President of CPDD in 1985, she was elected to membership in ACNP and became a Fellow in 1993. She has served actively on many committees, including the Committee on Relationships with Advocacy Groups; the Credentials Committee for two different terms; and the Human Research Committee. She was selected by Dr. Joseph Coyle to serve a special one-year year term on Council to fill a vacancy and later, was elected to a full term from 2004 to 2007 on Council. She also was selected to chair an important ad hoc task force for ACNP in 1998 which addressed what was correctly perceived by ACNP as inappropriate suggestions by a Presidential Commission; their recommendations which would have led to legislation to prevent anyone with any DSM-IIIR diagnosis, including any affective or other mental disorder, including drug abuse or addictions, from signing any informed consent to participate in research. The Task Force was able to convince members of Congress, through their staffers, that legislation to put into effect these suggestions, i.e., to disallow those with any mental health disorders from signing consents, would be inappropriate, since many members of Congress themselves, as well as their staff, had suffered, at some time in their life, anxiety, depression, or other disorders in the mental disease categories.

In 2004, Dr. Kreek was awarded the Columbia University College of Physicians & Surgeons Alumni Association's Gold Medal for Lifetime Distinguished Achievements in Academic Medicine. In 2005, she received the International Narcotics Research Conference Founder's Award. An Honorary Fellowship in the American College of Psychiatrists was conferred on Dr. Kreek in 2006. In 2007, Dr. Kreek was awarded a Doctor Philosophiae Honoris Causa from Tel Aviv University, Israel. In 2010, Dr. Kreek was awarded a Laurea Doctor Honoris Causa by the University of Bologna, Italy.

She considers her and her colleagues most important contributions to be: developing a hypothesis that addictions are diseases of the brain with behavioral manifestations, which led immediately to the logical conclusion of the need for pharmacotherapies; the development of methadone maintenance treatment; and that studies of functional human molecular genetics are critical for the understanding of addictive diseases, with their early finding of the μ opioid receptor variant which is functional both in molecular cellular constructs, as well as in healthy humans.

Roger E. Meyer received his MD from Harvard Medical School in 1962. Following a medical internship with Dr. Robert Petersdorf at the University

of Washington, he went on to complete his residency in psychiatry at the Massachusetts Mental Health Center. In July 1966, he came to the National Institute of Mental Health to work with Dr. Jonathan Cole in a new program focused on addictions within the Psychopharmacology Research Branch at NIMH. Within six months, a new reorganization at the Institute separated the addictions program into a new Center for Studies on Narcotics and Drug Abuse. The Center, which would eventually morph into the National Institute on Drug Abuse, had responsibilities for identifying and funding the first federally funded community-based drug addiction treatment programs, research on the biological and psychosocial causes and consequences of addiction, the development and evaluation of new treatments, and the assessment of emerging public health issues in relationship to a burgeoning epidemic of illicit drug use among the young across the country and in the military. Dr. Meyer was named Acting Director of the Center in July 1967. Under his leadership, an interdisciplinary scientific review committee was launched, six community-based treatment programs were funded, including those directed by Drs. Herbert Kleber at Yale and Jerome Jaffe at the University of Chicago, mechanisms were established to oversee the distribution of psychedelic drugs and cannabis for research purposes, and other initiatives were developed to address urgent public-health concerns. In July 1968, determined to learn about and contribute to more at the local level, Dr. Meyer left NIMH for Boston where, with Drs. Joseph Cochin and Conan Kornetsky, and Drs. Jack Mendelson and Joseph Schildkraut at Harvard, as well as his first mentee, Dr. Steven Mirin, he eventually established a NIDA-funded interdisciplinary research program in studies on opiate addiction, using biobehavioral clinical and parallel animal model research methods pioneered by Drs, Jack Mendelson and Nancy Mello in studies with alcohol. The clinical laboratory studies, which were summarized in the book The Heroin Stimulus, found among other things that subjective reports of "craving" were validated by actual drug self administration behavior, and that the anticipatory subjective state, "craving," was rewarding and not aversive. The results from studies in rodents were consistent with the findings in human subjects; and, the overall research established a novel method for screening medications to treat addictive disorders, as well as techniques that might improve medication adherence. In 1977, Dr. Meyer moved on to become Professor and Chairman of the Department of Psychiatry at the University of Connecticut where, in 1978, he was able to establish an NIAAA-funded alcohol-related research center. At UConn, he continued his work on biological and behavioral studies of craving, medications development, and heritability. The Center itself played a major role in a number of NIAAA-related initiatives including the Collaborative Study on the Genetics of Alcoholism, and Project MATCH,

the largest comparative psychotherapy project ever conducted by the federal government. Dr. Meyer is proudest of the team that he recruited and/ or trained at the University of Connecticut, which has continued to serve as a major NIH-funded resource for clinical research in the alcohol field for 33 years. At Connecticut, in addition to serving as Chair of the Department and Director of the Alcohol Center, he also served as Executive Dean before moving on in 1993 to George Washington University Medical Center as Executive Dean, Vice President for Health Affairs, and CEO of the Medical Center.

Over the course of his career, he has served as consultant to a number of federal agencies, to the White House drug abuse office during two administrations, and, during the past 13 years, as a consultant to a number of pharmaceutical companies, and as CEO of Best Practice Project Management, a company that he established with Dr. Frederick Goodwin and some other colleagues. Most importantly, he is a past president of the American College of Neuropsychopharmacology.

Ernest P. Noble received his PhD in biochemistry from Oregon State University in 1955 and his MD from Case Western University in 1962. He completed residency training in the Department of Psychiatry at Stanford and was Assistant Professor in that department from 1965 to 1969. Noble was a Visiting Scientist in 1966 with Julius Axelrod at the NIMH. He became an Associate Professor in the Department of Psychiatry at UC Irvine in 1971 and was promoted to Professor in 1971. He became the Director of the National Institute on Alcohol Abuse and Alcoholism in Washington, DC from 1976 to 1978, and Associate Administrator for Science, ADAMHA/ DHEW from 1978 to 1979. He came to UCLA in 1981 and was appointed Pike Professor of Alcohol Studies and Director of the UCLA Alcohol Research Center. In 1990, Noble and colleagues were the first to discover a D2 dopamine receptor gene, or DRD2, associated with alcoholism. He later found this same gene to associate also with cocaine, nicotine, heroin, and food addiction. He is currently investigating the various phenotypic expressions of the DRD2 gene and its possible utility in the prevention and treatment of substance use disorders. Noble has performed research as a Fulbright Scholar at the Sorbonne in Paris, France; as a Guggenheim Fellow at the Centre de Neurochimie in Strasbourg, France. He was also a Senior Fulbright Scholar at the Max-Planck Institute in Munich, Germany and a NIMH Career Development Awardee. His achievements have been recognized by different honors and awards. He was President of the International Commission for the Prevention of Alcoholism and Drug Dependency with headquarters in Washington, DC. He served as a Trustee of the National Citizens Commission on Alcoholism. He received the Sidney Cohen Award in Drug Abuse Medicine and the R. Brinkley Smithers Award for Excellence in the Genetic Studies of Alcoholism and other Drug Dependencies. He was given the Recognition of Inventors Award, by the UCLA Academic Senate.

Charles P. O'Brien received his MD degree in 1964 and his PhD in 1966 in Neurophysiology from Tulane University. His residency training was in both psychiatry and neurology at Harvard's Mass. General Hospital, Tulane, University of London, and University of Pennsylvania. His interest in addiction began during a tour of duty as US medical officer from 1969 to 1971, responsible for marines and navy personnel returning from Viet Nam with heroin addiction or other drug problems. He founded the Penn/VA Addiction Treatment Program in 1971 and was Chief of Psychiatry, at the Philadelphia Veterans Medical Center from 1980 to 2001.

His key research accomplishments included translating Abraham Wikler's research in animals to human heroin addicts. He demonstrated in human lab studies that craving and withdrawal are conditioned responses with physiological conditioned responses. This was the first demonstration, published in 1977 in Science, that addiction was a learned response or memory that continued long after drugs were no longer present in the body. Subsequently, in 1999, his group, Childress et al, published evidence from brain imaging that drug related cues produce conditioned limbic system activation and strong drug craving. He proposed an Addiction Severity Index at a NIDA meeting in 1975 and worked with Tom McLellan to develop the ASI, published in 1980, now used world wide and translated into over 20 languages. With George Woody and colleagues he conducted in 1983 the first controlled studies of psychotherapy for addictive disorders.and the first studies of na-Itrexone for the treatment of alcoholism. Despite widespread skepticism among alcohol researchers he demonstrated with Volpicelli et al in 1992 the efficacy of naltrexone in decreasing alcohol use that eventually led to FDA approval. Subsequently he led the team that discovered enhanced efficacy of naltrexone in alcoholics possessing a gene variant of the µ opioid receptor, published with in 2003. His current prospective randomized studies, based on genotype, are underway. If successful, these studies will lead to the first genomic indication in psychiatry.

With Anna Rose Childress and colleagues he has conducted PET and fMRI studies that demonstrate conditioned limbic activation in response to drug cues in cocaine addicts, nicotine addicts and heroin addicts. The group has also reported in 2008 rapid activation of the amygdala to very brief cues, 33 msec, that do not reach conscious detection. His team has reported numerous clinical trials of medications for the treatment of cocaine addiction, including efficacy for modafinil that has already had replications, but also failures so the current status is uncertain.

He has won many research awards including election to the Institute of Medicine, National Academy of Science; Wikler Research Award; NIDA; APA Research Award; Eddy Award, College on Problems of Drug Dependence; Gold Medal Award, Society of Biological Psychiatry; John P. McGovern Award for Excellence in Research and Medical Education in Substance Abuse from AMERSA; Fischman Award, Columbia University. Other honors include being President of the Association for Research in Nervous and Mental Disease, President of the American College of Neuropsychopharmacology; Doctorate Honoris Causa, University of Bordeaux, France; member work group on substance disorders, DSM-III-R. He also has many educational accomplishments. He has founded in 1989 a full 25 hours required course on addiction for all medical students at Univ. of Pennsylvania, the 1st of its kind in the country. He also founded in 1977 a research post doctoral MD & PhD training program on addiction at Penn and in 1995 a clinical program approved for Addiction Psychiatry.

Roy Pickens received his BA degree and his PhD in Psychology from the University of Mississippi in 1965. He then went to the University of Minnesota for a postdoctoral training program under Travis Thompson. He became interested in addiction after reading an article by Weeks and Collins in 1962 on *Self Administration of Morphine by Rats*. While at Mississippi, he went to Michigan for a one day visit with Weeks and learned how to canulate rats. His 1st grant from NIMH was on Behavioral Dependence on Non-Narcotic Drugs. He studied drugs such as cocaine, amphetamines and barbiturates and found that the same drugs humans abused were the drugs that animals would self-administer. He then switched over to human research and became interested in genetics, receiving a grant from NIAAA to do twin studies in relation to alcoholism.

In 1985 he put his research on hold and went to NIDA to become Director of the Division of Clinical Research. Soon he also became in charge of NIDA's AIDS program since a key vector for the spread of AIDS was IV.drug use and the sharing of needles. Their AIDS budget went from \$3 million to \$142 million between 1986 and 1989. The program involved educating IV drug addicts as to how HIV was spread; evaluating the effectiveness of various approaches; and handing out small bottles of bleach to sterilize the needles and syringes. In 1989 he moved to the Addiction Research Center, by that time NIDA's intramural research program. In 1994 he retired from that and went back to the lab. In addition to his major contributions in his administrative positions, his major accomplishments have been in the gene-environment interaction. His later work was in identifying subtypes of addiction that has clinical relevance. *Beny J. Primm* was born in Williamson, West Virginia, in 1928. He moved with his family to New York City in 1940 and returned to West Virginia State College, now University, from which he received his BS in 1950, majoring in Biological Sciences and German. While in college Prim was a member of ROTC. As the first black officer integrated to command white troops in the US Army, he was a paratrooper in the 82nd Airborne Division stationed in Fort Bragg, California, from which he obtained a medical discharge in 1953. Primm applied to medical school in an era when strict quotas still governed the number of African-Americans accepted, so he applied to European medical schools. He received his Certificat de Fin d'Etudes Medicaux, the equivalent of an MD Degree from the University of Geneva, and his Doctorat aux Medicin after writing a thesis on pharmacology in 1959. He interned at Meadowbrook Hospital on Long Island, now Nassau County General Hospital, where he was the first chief resident in anesthesia.

In 1963 Primm began working at Harlem Hospital, where he found that 90% of emergency surgeries involved substance abuse directly or indirectly. He was known for therapeutic innovations such as the first crash cart for a Code Blue and the creation of the Harlem Hospital Orientation Center (HOC), a unit designed to encourage substance abusers to enter treatment. Through his work with neurosurgeon Thomas Matthew, MD, Primm became Director of Professional Services for Interfaith Hospital, part of the National Economic Growth and Reconstruction Organization from 1965 to 1968.

During the earliest years of Primm's medical career, New York State and City politicians faced a growing substance abuse problem. A strong proponent of multi-modality substance abuse treatment and critical of the racial dimensions of methadone maintenance, Primm advanced the concept of "neoclassical" methadone maintenance and pioneered ways to move from methadone to abstinence. He set up his own program, the Addiction Research and Treatment Corporation in 1969 with assistance from the Vera Institute of Justice and the federal Model Cities Program. He modeled the program on the Illinois Drug Abuse Program directed by Jerome H. Jaffe in Chicago, using what he had learned from a visit to the Addiction Research Center in Lexington, Kentucky.

In 1971 Primm began working for the White House Special Action Office for Drug Abuse Prevention, accompanying Jaffe to Vietnam to set up the first in-country testing and treatment program. Primm trained Army and Veterans' Administration personnel to assess soldiers returning from Vietnam. During the 1970s, Primm advised the National Institute on Drug Abuse; the Alcohol, Drug Abuse, and Mental Health Administration; and the Food and Drug Administration committee on drug abuse liability. In 1988 he was appointed to Reagan's Presidential Commission on the Human Immunodeficiency Virus Epidemic. Under the first Bush administration, Primm was appointed first director of the ADAMHA Office of Treatment Improvement. When the Substance Abuse and Mental Health Services Administration was formed under President Clinton, Primm served briefly as the first director of the Center for Substance Abuse Treatment..

A national spokesperson for comprehensive care, Primm advocated for integrating HIV treatment into substance abuse treatment in the 1990s. As an adviser to the Centers for Disease Control in 1998, he joined activists in drawing attention to the critical dimensions of HIV/AIDS in African-American and Latino communities. After sponsoring a Linkage Initiative with Republican Senator Orrin Hatch, of Utah and Frederick Goodwin, ADAMHA Administrator, Primm was appointed to the Joint Advisory Commission to the CDC and the Health Resources and Services Administration. He served for five years on President George W. Bush's Advisory Commission on HIV and AIDs, where he called for universal testing and treatment. Primm prides himself on his ability to influence focus on the inadequacy of attention to HIV/ AIDs in Puerto Rico and in the US prison system. While serving five presidential administrations, he has been the ARTC Executive Director for more than 40 years.

Joseph Schoolar is Professor Emeritus, Pharmacology and Psychiatry, Baylor College of Medicine. He was born and grew up in the Mississippi Delta. At 17 he joined the US Army and was assigned to Clemson College as an engineering student. He was then transferred to the Japanese Language School at the University of Minnesota and, after language school, served in General MacArthur's headquarters.

After discharge from the Army he entered the University of Tennessee, receiving his BA in 1950 and MS, in cell physiology, in 1952. The research for his Master's degree had to do with the effects of x-radiation on living tissue, particularly the central nervous system. He then joined the UT-AEC laboratory of Dr. John Rust in Oak Ridge, Tennessee, working on the effects of ionizing radiation on living systems, again emphasizing the CNS.

In 1953, Schoolar moved to Chicago as a graduate student under Dr. Lloyd Roth. His dissertation focus was the blood-brain barrier and, with Dr. Charles Barlow, developed an autoradiographic technique for use in a variety of studies on the brain, chiefly drug distribution and cerebral blood flow. He was awarded the Doctor of Philosophy degree in Pharmacology in 1957 and the Doctor of Medicine in1960.

After general rotating internship at the University of Chicago, Dr. Schoolar moved to Baylor College of Medicine for residency training in psychiatry. He then joined the staff of the Texas Research Institute of Mental Sciences as well as the Baylor faculty, in the latter with joint appointment in the Departments of Pharmacology and Psychiatry.

Since then Dr. Schoolar's work has been in research, education and clinical practice in psychopharmacology and psychiatry. He became Chief of the Drug Abuse Research Section at TRIMS in 1966, Assistant Director and then Director of TRIMS in 1968 and 1972, respectively, and in 1973 Chief of the Division of Psychopharmacology in the Pharmacology Department at Baylor. From that combined vantage point he was able to be active politically at the national, state, and local level; to direct the research of other staff and of graduate students in basic pharmacological and in clinical research; to play a leadership role in determining the state needs for and composition of training programs and treatment facilities addressing the multiple levels of concern with respect to substance abuse, from basic science to spirituality. He was an early and strong advocate of the use of methadone in the treatment of opiate addiction, and established the first methadone maintenance clinic in Texas.

Since TRIMS closed in 1985, Dr. Schoolar has confined his work largely to clinical psychiatry and to psychiatric and psychopharmacologic education. He stresses the unique, focused individuation that is an absolute requirement of effective treatment. In evaluating his career thus far, he states that every aspect has been a source of tremendous satisfaction: the educational, scientific, political and administrative opportunities. He cites the brain autoradiographic techniques as having been "useful"; and appointments, recruitments, accolades and the like as truly gratifying. In a special category are those occasions when a fellow scientist/clinician says, "I was your student in 1965", or "You taught me in 1975 or '85". But the absolute pinnacle of success is marked by the statement of a well-integrated individual who says, "I was your patient". Those, one doesn't have to try to remember: they have never been forgotten. His honors include the annual Schoolar Lectureship in Psychopharmacology; Distinguished Alumnus Award, University of Chicago; Membership in many leadership and scientific organizations, including the Danforth Foundation.

Marc Alan Schuckit received his MD from Washington University, St. Louis, in 1968, completed a rotating internship at Cedars-Sinai Hospital in Los Angeles in 1969, and subsequently completed two years of psychiatry residency at Washington University, St. Louis, with the third year as a senior resident at the University of California, San Diego, Department of Psychiatry. Subsequently, he served on active duty as the Special Assistant to the Commanding Officer of the Naval Health Research Center from 1972 to 1974, and became the Director of the Alcohol and Drug Abuse Institute of

the University of Washington in Seattle from 1975 to 1978. Then he returned to UCSD where he has remained.

Dr. Schuckit's work has included four areas of research. First, he proposed that a low level of response, or low sensitivity, to alcohol might be a risk factor for later heavy drinking and alcohol problems. To test this hypothesis, over the years he has gathered prospective data from a UK sample of 12 to 14 year olds, blue-collar adolescents and young adults from the Collaborative Study of the Genetics of Alcoholism, and from adults and children from 453 families in the San Diego Prospective Study. The latter investigation produced a 94% follow-up rate about every five years over 25 years for 1600 subjects, including the original male probands, their spouses, and their offspring. The results revealed that a low level of response (LR) to alcohol is one of several alcohol reaction-related phenomena that characterize children of alcoholics and other groups at high risk for alcoholism. The prospective work documented the importance of a low LR in predicting future heavy drinking and alcohol problems. This series of studies, along with data gathered from approximately 350, 18-25-year-old pairs of siblings, have identified polymorphisms likely to relate to the low LR to alcohol as an alcoholism risk factor.

The second emphasis in his work grew out of the recognition that genes for characteristics associated with complex genetically-influenced conditions such as alcoholism only explain approximately half of the risk. Therefore, he has gathered data from both the SDPS and COGA samples to prospectively evaluate additional characteristics that might help mediate between a low LR to alcohol earlier in life and future alcohol problems. Subsequently, structural equation models, latent trajectory analyses, and survival analyses have indicated the potentially important mediational roles for heavy drinking peers, more positive expectations of the effects of alcohol and intoxication, and suboptimal coping mechanisms as contributors to how a low LR influences adverse alcohol outcomes. He is currently beginning to test potential prevention approaches focusing on these additional characteristics in hopes of identifying and diminishing the risk for adolescents with a low LR to alcohol as a risk factor for later problems.

The third area of research relates to Dr. Schuckit's longstanding interest in the role of comorbid psychiatric syndromes in the course of substance use disorders, especially for depressive, anxiety, and psychotic syndromes. His data, along with those of several other groups, support the prognostic and treatment implications of distinguishing between temporary substanceinduced conditions observed during intoxication or withdrawal and independent psychiatric syndromes that developed outside of the context of heavy substance use. A fourth area of work has focused on the development of clinically-useful diagnostic criteria for substance use disorders. Here, he served as the Chairperson of the DSM-IV Substance Use Disorders Workgroup, and is currently a member of the DSM-V Substance Use Disorders Committee, serving as Chair of the Criteria Development Subcommittee.

In addition, Dr. Schuckit has twice served on the Advisory Council for NIAAA, and three times as a regular member of an Initial Review Group at NIH, and has been editor of the *Journal of Studies on Alcohol and Drugs* for more than a decade. His work has been recognized by the Hoffheimer, i.e., the President's, Award of the American Psychiatric Association for Outstanding Research in the United States and Canada, the Middleton Award for Outstanding Research Across Hospitals in the United States, the Distinguished Research Award from the Research Society on Alcoholism, the Gold Medal Award from the Society of Biological Psychiatry, and international awards that include the James B. Isaacson Award for genetics research, and the international Jellinek Memorial Award.

Charles R. Schuster received his Bachelors Degree from Gettysburg College, a Masters Degree from the University of New Mexico, and his doctorate in Psychology from the University of Maryland. After completing his Masters Degree in 1953, Dr. Schuster spent several years at Temple University School of Medicine working in the Department of Endocrinology. While there he worked as an assistant to Dr. Bernhard Zondek, a visiting Professor from Israel and one of the pioneers in endocrine research.

Subsequently Dr. Schuster was hired by Smith, Kline and French Pharmaceutical Company to work as an assistant to Dr. Donald Bullock, a psychologist charged with developing behavioral methods for screening new chemical entities for their possible use as medications for the treatment of psychiatric disorders. After six months, when Dr.Bullock left Smith, Kline and French Laboratories, Dr. Schuster took over the laboratory. In 1958 Dr. Schuster met Dr. Joseph Brady who was both a Major in the army stationed at Walter Reed Army Institute for Research (WRAIR) and a Professor at the nearby University of Maryland. Dr. Brady had recently received an NIH grant to set up a behavioral pharmacology laboratory at the University of Maryland. Dr. Schuster was recruited as a graduate student to use his knowledge of pharmacology to help set up this new laboratory and obtain his doctorate degree. While there Dr. Schuster became aware of a surgical procedure developed at WRAIR to allow obtaining venous blood samples from chronic indwelling jugular catheters. Observing this he realized that such a catheter could be used to administer drugs. Based upon his early life experiences as a jazz trumpeter, Dr. Schuster wondered whether it might be possible to get monkeys to respond in order to get an injection of a drug that is abused by humans. After
many false starts Dr. Schuster in conjunction with Dr. Travis Thompson succeeded in getting monkeys to self-administer morphine. In this same study it was found that stimuli associated with morphine injections could temporarily reverse the signs of opiate withdrawal. Dr. Schuster continued his research after joining the Department of Pharmacology at the University of Michigan in 1962. There in conjunction with Steven Goldberg and James H. Woods, Dr. Schuster investigated the phenomenon of conditioned withdrawal. They demonstrated that stimuli associated with the administration of a narcotic antagonist to monkeys physically dependent upon morphine could elicit some of the signs of withdrawal. In addition he and his students continued to explore what other drugs of abuse would be self-administered by monkeys. In 1968 Dr. Schuster joined the Department of Psychiatry at the University of Chicago as an Associate Professor and Associate Administrator of the State of Illinois Drug Abuse Treatment Program. In addition to these clinical activities, Dr. Schuster brought his animal research grants to the University of Chicago and continued those activities as well. In the clinic working with Dr. Jerome Jaffe he was part of the team that established the efficacy of Iacetyl methadol for the treatment of opioid dependence. After three years Dr. Schuster left IDAP to found the Drug Abuse Research Center in which both animal laboratory and human laboratory studies of drugs of abuse could be conducted. With Dr. Louis Seiden and many graduate students Dr. Schuster investigated the neurotoxicity of methamphetamine and other amphetamines as well as MDA and MDMA. In addition with Dr. Marian Fischman he conducted the first human investigations of the pharmacodynamics of cocaine since the work of Sigmund Freud. In the animal laboratory working with Drs. Chris-Ellyn Johanson, Dr. Robert Balster as well as many graduate students, Dr. Schuster gathered data indicating that animals would self-administer the same drugs that humans abuse and avoid those drugs humans find aversive, thus validating these procedures as an animal model of drug abuse/ dependence.

In 1986 Dr. Schuster was recruited by the federal government to assume the position of Director of the National Institute on Drug Abuse, a post he held until 1992. While there he established the Medication Development Division and oversaw NIDA's growth in funding from \$85,000,000 to over \$400,000,000 per year. This increased funding allowed a marked increase in the scope of the NIDA's research portfolio into areas of etiology, prevention and treatment of drug abuse/dependence as well as the associated disease of HIV. Dr. Schuster has been the recipient of many awards including the Nathan B. Eddy Award and the Mentors Award from the College on Problems of Drug Dependence; the Distinguished Scientific Award for the Applications of Psychology of the American Psychological Association and the Peter B. Dews Award from the American Society of Pharmacology and Experimental Therapeutics. Dr. Schuster is a member of the Institute of Medicine of the NAS.

Nora Volkow received her MD degree from the National University of Mexico in 1980. Once she completed her MD degree she left Mexico to do a residency in Psychiatry at New York University during which time she started doing imaging research on schizophrenia. After finishing her training in Psychiatry in 1984 she took a position as Assistant Professor in the Department of Psychiatry and Behavioral Science, University of Texas Medical School where she started her imaging work on substance use disorders. In 1987 she moved to Brookhaven National Laboratory, where she would remain for fifteen years carrying out imaging research on the effects of drugs, aging, obesity and ADHD while also holding several leadership positions: Director of Nuclear Medicine in 1994, Chairman of the Medical Department in 1997, and Associate Laboratory Director of Life Sciences, in 1999. During this period she was also Professor in the Department of Psychiatry and Associate Dean of the School of Medicine at SUNY-Stony Brook at BNL. In 2003 she left BNL to become the Director of the National Institute on Drug Abuse; a position she still holds.

Dr. Volkow's scientific trajectory has triggered numerous fundamental advances in the field of biological psychiatry. To start with, her research has been instrumental in transforming the perspective of addiction from that of a behavioral choice to a brain disease and in the process has shed light on the neurobiology underlying motivation and self-control. Her work has given the basis for the notion of addiction as a chronic and relapsing disorder of the brain that should be managed as a medical disorder rather than a criminal behavior.

A major focus of her research has been on studying the relevance of the dopaminergic system in substance use disorders in humans. Among some of her contributions include her work showing that the reinforcing effects of drugs of abuse in the human brain are associated with abrupt increases in dopamine but that in addicted subjects the drug-induced dopamine increases are markedly attenuated and instead there is a sensitized response to conditioned cues that appears to drive the enhanced motivation to take the drug. Her imaging work also brought attention to the reduction of dopamine D₂ receptors in striatum as a common abnormality in a wide variety of addictions, which others have shown to be associated with impulsivity, and of the importance of the dysfunction of frontal cortical regions, orbitofrontal, cingulate, in drug addiction at a time when the focus had been on limbic regions. Her imaging work led her to propose as model of addiction, a "conflict between circuits" that results from the impaired interaction between several func-

tional brain circuits, i.e., reward/saliency, motivation/drive, inhibitory-control/ executive-function and learning/conditioning. The model supports a multiprong treatment for addiction to ameliorate these deficits. She uncovered similar processes underlying compulsive food consumption in obesity. She has also made major contributions in Attention Deficit Hyperactivity Disorder and its treatment; for example her studies on drug pharmacokinetics documented in humans that both rate of stimulant drug uptake and clearance in brain modulate their reinforcing effects, a finding relevant for distinguishing reinforcing versus therapeutic effects of stimulant drugs when used for ADHD; and that the dopaminergic effects of stimulant medications enhance the saliency of tasks as a mechanism underlying their therapeutic actions in ADHD. She also showed evidence of an association between dopamine reward pathway deficits and motivation and attention deficits in ADHD.

As a director of NIDA she has focused her leadership on the use of science to tailor more effective prevention and treatments for substance use disorders with a special emphasis on the need for better medications and for the importance of the involvement of the healthcare system in the screening and treatment of substance use disorders.

Dr Volkow has written over 480 peer reviewed articles and over 60 book chapters or white papers and edited three books on brain imaging. Dr Volkow has received many awards including election as member of the Institute of Medicine in the National Academy of Sciences. She was nominated one of the "100 people that have affected our world the most" by *Time Magazine,* mentioned as one of the "20 people to watch" by *Newsweek* magazine, and named "innovator of the year" by *US News & World Report*.

E. Leong Way was born in California and started college at University of California Berkely in 1934. He majored in chemistry and spent two years there before deciding that he was more interested in drugs than in "dancing atoms and electrons". Then, he transferred to the San Francisco campus where he received a BS in pharmacy in 1936. He went on to graduate school there receiving an MS in 1940 and a PhD in 1942 in Pharmaceutical Chemistry. After a brief stint there studying arseno – sulfa combinations as antibiotics, he became an instructor in pharmacology at George Washington University Medical School in Washington, DC where he remained for 5 years. His interest shifted from the arsenic compounds to narcotic drugs and his research got focused on drug metabolism, specifically the biodisposition of opiate drugs including morphine, heroin, methadone and LAAM. He received an NIH grant for this work, a grant that he held for 20 years.

His main research accomplishment was proving that the two biological properties of opiates after chronic administration, tolerance and physical dependence, had a common underlying biochemical basis. This common basis related to neurotransmitter release. It took 20 years to obtain the conclusive evidence necessary. The 1st paper on this was published in 1968 by Way and his colleagues and the final one in 1990. The final proof ended up using the vas deferens of the mouse: this tissue has a "twitch" response to electric stimulation that is inhibited by opiates. As tolerance developed, more morphine was needed to inhibit the norepinephrine release; after producing withdrawal by washing out the morphine, there was substantial increase in norephinephrine release. Way retired from UCSF soon after this finding and went on to a successful 2nd career in his 70's and 80's.

After retiring in 1990, he spent a year in Japan helping to establish a neuropharmacology department at Grenma University and after returning spent a year at NIDA. He then followed his earlier love of herbal pharmacology and became an international expert on it, especially on Chinese herbal pharmacology.

Way was a founding member of the International Narcotic Research Conference (INRC). He joined ACNP in 1969 and is a Life Fellow Emeritus. His vision for the future is that knowledge and experience applied with common sense can result in wisdom.

Mathew J. Wayner, received his BA from Dartmouth College in 1949, followed by an MS degree from Tufts University and a PhD from the University of Illinois. While at Dartmouth his research career and interest in psychoactive compounds began with his work with Prof. Karwoski in the experimental psychology teaching lab. His interest was in the effects of mescaline on inducing blue and green visual hallucinations during the ritual dances, exploring whether this was due to enhancing the blue Purkinje after image during the visual stimulation associated with the dancing. This ultimately resulted in a publication a few years after Dartmouth graduation. He began his academic career as assistant professor at Syracuse University.

Wayner's career was focused on alcohol research primarily using a rat model. He was interested in the lateral hypothalamic area especially in regards to the anterograde amnesia for short term memory "blackouts" caused by alcohol. He and his colleagues found that this phenomenon was related to alcohol acting on hippocampal dentate granule cells. Stimulation of the LHA inhibits granule cell long term potentiation. They concluded, therefore, in 1997 that certain cells in the LHA that are extremely sensitive to alcohol project to the HDGC and produce the anterograde amnesia for short term memory. In addition to his laboratory work, he was also Editor in Chief of four significant journals that he founded.

James H. Woods received a bachelor's degree from Ohio University, and completed graduate studies in Psychology at the University of Virginia. He took a position in Pharmacology at the University of Michigan before receiving

his PhD Degree, and he has been there throughout his career. He has held teaching position in both Pharmacology and Psychology at the University; he is also affiliated with the neuroscience program and the Substance Abuse Research Center. During the years, he has trained a number of successful graduate students and postdoctoral fellows. Woods received the Mentorship Award from the College on Problems of Drug Dependence in 2001. Subsequently, he also received the Nathan B. Eddy Award from the College in 2004.

He has carried out a variety of research in different areas of central nervous system pharmacology e.g., opioids, central stimulants and sedatives. He is currently interested in pharmacotherapies for cocaine abuse and smoking cessation.

INTERVIEWEES & INTERVIEWERS

MARTIN W. ADLER

Interviewed by Larry Stein San Juan, Puerto Rico, December 12, 1996

- LS: I am Larry Stein and it's my very great pleasure to have this conversation with a most distinguished pharmacologist, Dr. Martin Adler.* I think we want to call each other Marty and Larry because we've known each other so long. I should say, for the sake of the record, that many of the years in my early career I spent in Philadelphia, where Marty has spent a lot of his career. We know each other well, personally. Both of us have done a lot of work in the field of drug abuse, so we are also familiar with each other's activity in science. But, nevertheless, Marty, I would be interested in how you got started in science and in pharmacology.
- MA: I needed a job. Actually, I always wanted to be a physician and my interest was really very strong in the history of medicine. In high school, I did a lot of reading on ancient Egyptian medicine, and it was something I really enjoyed. When I started college at New York University (NYU) in 1946 virtually everyone was a bit older. I was not vet seventeen at the time. Most of the other students had been in the army. When I graduated from NYU and applied to medical school, I was an alternate at some schools, but was not accepted. In fact, only one or two out of three hundred of the non-veterans got into medical school that year. So, I was looking for something else and somebody had suggested pharmacy school to me, so I applied to pharmacy school. I remember going on my interview and they asked me, "What do you want to do"? And, I said, "I want to do medical research". And, they said, "Well, first of all this isn't a medical school". And, I said, "I know that". And, they said. "Well, we don't do too much in research". I said, "Well, I figure it's a pretty good background for me to go into research". Anyway, I got admitted. I was going to finish at NYU, as I said, with a Bachelor of Arts and I started pharmacy school.
- LS: This was which school?
- MA: Brooklyn College of Pharmacy. As it turned out, someone who had been my lab instructor in biology at NYU was now a faculty member at Brooklyn College of Pharmacy, teaching pharmacology, but, frankly, I didn't know what pharmacology was. His name was Jim Ingalls. He started a group of five students, who wanted to do research, all of whom had a Bachelor's degree before coming to pharmacy school. We were doing research in Pharmacology and we all had teaching fellowships and I was teaching organic chemistry, and, so on. When finished

^{*} Martin W. Adler was born in Philadelphia, Pennsylvania in 1929.

there I did not want to practice pharmacy, but Uncle Sam reared his ugly head and I got drafted and ended up in Korea. I used to try to call my wife every month if I could and I'd hitch a ride down to Seoul to try to get through. One October I remember, I got through and she said, "How would you like to go back to school"? I said, "What are you talking about"? She said, "I talked to Jim Ingalls. He called me and asked if you'd like to go back to school to Columbia". I said, "Gee, I don't know; I haven't thought about it". I said, "To study what?" She said, "Pharmacology, of course". I said I would think about it. The following month, when I called her, I said I would go and Jim Ingalls and Toby, my wife, set up everything for me. I was accepted with a full fellowship and that's sort of how I got into pharmacology.

- LS: There were some great pharmacologists at Columbia at the time.
- MA: Yes, I was at the pharmacy school where I was teaching and doing research. My course work was all up at the medical school at Columbia. There were some wonderful people there at the time.
- LS: Who was the Chair at Columbia at that time?
- MA: I can't even remember, but one of the people I interacted with was Wong, who was a neurophysiologist. He did a lot work on the vomiting center with Herb Borison and I had thought about staying on with him for doing my PhD. This might not be the most political thing to say, but I was turned off by Columbia. The PhDs were looked down upon. I took a course in biochemistry and there was one of these huge laboratories, you know 150 students or so and in the last row were the graduate students. The instructors would walk down to that last rows but never get to the last row. They'd turn around and walk back. I decided that this was not the attitude I wanted.
- LS: So, the curriculum was really designed for the medical students. The PhDs became much more prominent and important to the faculty in later years as research got more significant and the role of the graduate students in research became decisive, I would assume.
- MA: Absolutely, but it...
- LS: I think, what I'm hearing, Marty, is that you got your first peek into CNS pharmacology with in work in the pons and medulla and you have ended up in higher regions of the brain in terms of drug addiction, learning and memory and these kinds of things, but, at least, there was a pharmacology of the brain that you saw.
- MA: Absolutely. But we'll backtrack for a second. The research I did for my Master's degree at Columbia was on stress. I was very interested in it and I thought I'd continue in that field for the PhD. When I decided I

wanted to leave Columbia. I went to Einstein where I was interviewed by Al Gilman. I was accepted by him and started with him. However, they had nobody doing work on stress. So, he said, "You can choose any other area you want, but not stress". That's when I started working with Murray Jarvik and got into the learning and memory field, the effects of drugs on delayed response and visual discrimination in monkeys. And, as you know, Larry, what got me out of that area, was that I had discovered the monkeys were much smarter than I was. When Murray and I would set up these programs we would design and build the circuits for the visual discrimination and delayed response tests in old refrigerators. I would set one up for Murray and he would set one up for me and we'd each sit in the refrigerator and see how long it would take us to solve the task. If we could do it in a reasonably short period of time, we'd figure the monkey could too. One time he designed something and I sat in that blasted box for an hour and couldn't solve it. When we put a monkey in there and inside of two minutes, the monkey had it solved, I said to Murray, "I'm finished"!

- LS: Back to the stress research.
- MA: That's right, but we, also, were working with some monkeys that had brain damage. Mort Mishkin had done the lesions in the animals.
- LS: Was Mishkin at Albert Einstein?
- MA: No he was at NIH and he had done some of these for Murray. I don't even know why they were done and we started using them. I saw some changes in those animals compared to the normals and that's what got me interested. I decided to get out of the learning and memory field and got interested in the brain lesion work. I started with rats. Seth Sharpless was doing some work with rats. I decided that I wanted to see what would happen with brain damage, what sort of recovery of function we could see after brain damage.
- LS: You got your PhD in Pharmacology from Einstein?
- MA: PhD in Pharmacology from Einstein.
- LS: And, your mentor was Jarvik?
- MA: Yes, Jarvik and Sharpless.
- LS: Jarvik and Sharpless were both your mentors?
- MA: Right and, actually, I was the first PhD student from Einstein in anything, as it turns out.
- LS: You were the first PhD to graduate from Albert Einstein? Now, that's very interesting
- MA: The difference between Einstein and what turned me on to research as compared to the situation at Columbia, was the fact that the graduate students were treated well. Let me give you an example. I took

Pathology at Einstein. Laboratory classes were in small groups of 12. Three of us were graduate students and the rest were medical students. The first day of the class the Head of Pathology, Angrist, walked in and said, "I understand there are some graduate students in here". And, I said, "Oh, blankety-blank, here we go again", you know. And, he turns around to the medical students and he says, "I want you to take a look at these people. That's the future of knowledge and the future of science". And he gave us a job where we helped set things up and the attitude was one towards the advancement of knowledge.

- LS: So, the student was treated a little bit more as a junior colleague?
- MA: Absolutely, and we were fully integrated into the medical class. We took courses that were mostly medical school courses, with a few exceptions, and included some of the clinical courses, as well.
- LS: You had already done your army service, so now that you had your PhD, you were free to take your first job and what was that?
- MA: At Temple, where I still am.
- LS: Ah, so your first and current job, forty years later?
- MA: Almost. It is thirty-six years.
- LS: Almost forty years. So, we will trace your research and your Temple career, simultaneously. I take it you were recruited as a young faculty member at Temple in the Department of Pharmacology. Off you went to Philadelphia, where you had grown up?
- MA: I really grew up in New York. I was born in Philadelphia, but my family moved to New York when I was six.
- LS: What was Temple like when you joined the faculty?
- MA: Well, I was the fourth member of the Department of Pharmacology. I was, only, the third person in the school who did any neuroresearch of any sort. The Head of Physiology did some neurophysiological research. Ernst Spiegel was at Temple, and for those who don't know, Ernst designed the first instrument for using stereotactic surgery, which is in the Smithsonian. He was a great man, really. But, nobody else was there in the neuro-field, I mean, there were some clinical neurologists, but nobody in terms of people doing research. The Psychiatry Department was doing traditional psychoanalytic type of research. There was no interest in biological psychiatry, let alone research going on
- LS: For a resourceful and dynamic self-starter that you are this represented a little bit of an opportunity to form a group without the distraction of others. So, what was the first project that interested you as a faculty member and at what point do we enter the world of grants? We might be interested in learning how that early research was funded and what

were the circumstances of your first grant? By the way I am asking that because one of Marty's important contributions to pharmacology is that he has been Chair of the Pharmacology Study Section for many, many years and he has made important contributions to the funding of research in pharmacology. But I am interested to hear how that activity originally started and, perhaps, the story of the first grant, which may have shaped your attitudes as a study section chairman.

- MA: It did. In fact, it's one of my favorite stories. I won't mention the name of the person who site visited me. I put in for a grant right away. It wasn't a huge grant. I asked for eighty-two hundred dollars a year, which covered the full cost of a full time technician, as well as all of my research costs. I applied for the grant, and, as you well know at that time, essentially everybody was site visited. A site-visitor came up, we sat and we talked about baseball and we talked about football and he met the chairman of the department and we had a cup of coffee. I had tea; he had coffee. And, he said, "Well, I have to leave. I have an appointment". And, I said, "Don't you want to talk about the research"? And, he said, "Why should I, you got your degree with Murray Jarvik, Seth Sharpless and Al Gilman. What am I going to ask you"? And, I got the grant.
- LS: Times have changed.
- MA: But, it's very important in my thinking, because what I would like to see is some way of getting young people, who have good educational pedigree and are thought well of by the people that they train, get started. That's what we can't do now.
- LS: You found that in terms of funding, it was relatively easy to get started.
- MA: Yes, no problem.
- LS: And, so you have made efforts, throughout your career, to try to get young investigators started and that's been one of your important contributions. Your first grant was on what subject matter?
- MA: Brain lesions. Recovery of function in brain damage, primarily involved with seizure mechanisms. That was the area that I was involved in most of my work and in my thesis. I also did some work with amphetamine and locomotor activity. But, I focused mostly on brain damage. I got into my present work strictly by fluke.
- LS: Are you referring to your drug abuse research area? It will be interesting to hear the transition from brain lesions to drug abuse.
- MA: That was an interesting experience, although, very traumatic at the time. I was up for my second renewal of the grant in 1966 and I was site visited, as was common at the time. One of the visitors felt that the work had no basis in fact, because the test that I was using was empirical.

I was using chemically induced seizures and electrically induced seizures and he asked about the mechanisms, how does it work? And, I said. "I don't know. The fact is that it works. It's a useful test". And he said, "If you don't know it's not a worthwhile project and it shouldn't be funded". Despite, the fighting by the other two site visitors, one of whom was very prominent in ACNP and backed the research, it didn't go well in the study section. And, so I was without a grant but, happily, that's the only time in my thirty-six years in research that I've been without grant. I was thinking, what am I going to do? How am I going to get a grant? Then I met Joe Cochin on a bus going to and from some hotel at a meeting and we started talking about research and I told him about my interest in seizures and the brain lesions. He said, "Well, why don't you use morphine"? I said, "What in the world would I want to use morphine for"? He said, "Well, morphine causes seizures". He said, "Just do the same thing, only do it with morphine". Well, all right, I'll do that. And, I submitted a grant application for it.

- LS: To what agency?
- MA: It was to NIMH.
- LS: Before NIDA?
- MA: It was before NIDA. This was in 1966. That did very well and I got funded. And, so, I started working with morphine and one of the things we found is that the literature was wrong. Morphine was anticonvulsant. We kept going along those lines but, then, something interesting happened.
- LS: I'd be interested, but I think it's very important, particularly, for young scientists to understand that a surprising result, in general, is more useful than an expected result. You got your grant and you knew that you were expected to do some work with morphine, which you had heard would produce seizures and you made your early observations that, in fact, it was anticonvulsant. What went through your mind at the time?
- MA: Well, the first thing, obviously, was that we did something wrong. We sat down and we looked at the data and we said, "Well, this is right. OK, something's wrong with the animals". So we took another batch of...
- LS: There was a dose-effect function there?
- MA: Yes, there was a dose-effect function and it was crystal clear...
- LS: It was clear-cut what was happening?
- MA: And, we ended up repeating it a number of times.
- LS: Had the field confused withdrawal with the direct effects of the morphine?

- MA: No, I don't think that was it. What happened was that people quoted a paper that Bill Martin had written about this and quoted it incorrectly. They said that morphine causes seizures in rats and it wasn't rats. The experiment was done in rabbits and rabbits react entirely differently. Gus Maynert, from Hopkins, was one of my site visitors. And, afterwards we started collaborating on this topic and that's when we began to work with serotonin and norepinephrine with regard to the seizures.
- LS: That's interesting. That admonition was in your mind about looking at the mechanisms.
- MA: Oh, sure.
- LS: So, you had remembered that and when the opportunity arrived to examine the mechanism of the seizures you were there.
- MA: Yes, but I wouldn't say that the turndown of my grant application had a positive effect in anything except that it made me angry. I mean, being trained in pharmacology...
- LS: And, it might have been motivating.
- MA: Oh, absolutely, there's no question about it. My experience is that you get two types of responses when you get turned down on the grant. Unfortunately, it's becoming more and more common. Either, you get angry and you try and answer it and you fight harder for the grant or you say, "These people who are doing the reviews are crazy. They don't know what they're talking about and to say, to hell with them". And you give up. I know people that have done both. If I mention the names of the ones that gave up, you would know because they're not doing any research. But, the ones who fought are generally successful if they keep fighting.
- LS: So, there's an evolutionary biology operating here with natural selection. Persistence is what the Darwin of the grant world reinforces.
- MA: Yes, it does.
- LS: So, now you're into morphine and still organizing your research in the seizure field. When did you turn to drug abuse?
- MA: Well, it was in the seizure field because that was the primary end-point we used in looking at recovery from brain damage. And, in fact, we were the first to use the term, denervation supersensitivity in the central nervous system. Just using the term from the peripheral nervous system, we applied it to the central nervous system that led to a huge fight with the editor of *JPET* who said that I have no proof that it's the same mechanism. I said I was using "denervation supersensitivity" as an operational term and I threatened to withdraw my paper when they said, "What a miserable young guy this is". And, we got it in. So, it was the first use of the term and that's what we were interested in. What is

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the time course of the recovery from the damage? What leads to the supersensitivity or to the lack of supersensitivity? And, now, of course, we know tons more about it than we did then. But, to answer your question about getting into the drug abuse area, it really was the golden era of research and support, because at that point NIDA or drug abuse research was spun off from NIMH changing from a section to form a separate institute. I received a call from the people at NIDA saying, "We have money. Would you like to do some research in the field of drug abuse because you are working with morphine"?

- LS: Was this the Psychopharmacology Center with Dan Efron as Executive sSecretary, was he in charge?
- MA: To tell you the truth, I really don't remember at this point.
- LS: That might have been the precursor of the Center.
- MA: It was the precursor. I put together a group of six faculty members at Temple and we put together a grant application for the study of "Narcotic Receptors in Addicted and Non-Addicted States." That was in 1970. Opiate receptors hadn't been discovered yet, but being a pharmacologist I had to think in terms of receptors and we did know of a couple of antagonists of opium and, therefore, it met the criteria for receptors, as we knew it at that time. That's what got us started in the field. We spanned a pretty wide and diverse area within pharmacology, everything from work that Ron Tallarida, who is still a collaborator of mine, does in terms of the mathematical constructs and theoretical pharmacology, to a biomedical engineer. And, a whole group of us were doing that sort of work; four of us are still there and working on this project.
- LS: With the focus on opiate drugs at the time?
- MA: Yes, the focus was on opiates. We received the usual site visit and Bill Martin was one of the site visitors and Saul Schanberg was also a site visitor. At that time when money was more plentiful, it was much easier for a young person to get help in trying to get funding and Bill Martin was superb. I had proposed eight endpoints to use and determine how they all hooked up together. After we each presented our work he called me aside and said, "I want to tell you something". And, the person from NIDA said, "But Bill you are not allowed to say that". But he proceeded to say: "Pick four". So, I asked, "Dr. Martin, what do you mean, to pick four"? He says, "Pick four, because if you get to learn about even four, you are going to be a wonderful success." So, he says, "Think about it and write it up and send it to us". And, I did that.
- LS: You had to look hard at that list.

- MA: I certainly did and I'm still working on some of those four. He's an absolutely brilliant man, a remarkably strong influence on me and many other young scientists.
- LS: So, we're starting to identify factors in successful research, particularly, nationally funded research. The first you mentioned was persistence and the second you mentioned is focus. We will accumulate this list as we examine your career. So, you've got endpoints for your opiate research and you've got the funding. You've put together a rather large group and the other thing that impresses me is that, as a pharmacologist, you have understood that the concept of receptor is almost everything. So the title of the project has receptor prominently in it and you're thinking it's organized around receptor mechanisms. This must have been very refreshing to an emerging field, as drug abuse was at that time, to bring real science to the challenge of drug abuse. So, how did that evolve?
- MA: I think it's a natural course of events. If you've been trained in the scientific method in experimentation, it's almost irrelevant what you're going after. In the sense that you have any understanding of the current state of knowledge, you can design a proper experiment. Larry, when you evaluate a grant or you look at a paper that's sent in for review, I'm sure, and I don't want to insult you, you don't understand all the nuances of the technology that's involved with this specific project, but you can tell very easily whether it's in animals, one species or another, human or whatever, whether there's a proper design to the experiment, whether you have correct control groups, whether the end point is correct, whether the conclusions that you reach are based upon the facts. And, if you want to go out on a limb, you are at least justified in saying, "OK, I'm going to take a wild guess but, based on what I have, this is almost the beginning of a hypothesis".
- LS: Right.
- MA: You can do that to every aspect of an area, so the grounding has to be in proper scientific methodology. And, I don't care if it is psychology, pharmacology, biochemistry, anatomy or what have you, it's almost immaterial. But, I'll also say that one of the strongest influences on me was the fact that I did work with MDs during my thesis. I did work with them in subsequent years and still do and I took a number of clinical courses. I'll branch off into something for a second, if you don't mind. I think we train our students too narrowly. It's fine to get into a new technology, help develop that technology. It's fine, but if you can't see past that technology, your contributions are really limited and I think you have to think beyond that. And, in order to do that, you need a broader

exposure. Too many of our medical schools, today, are forcing the students to become narrow at much too young of age. We all become narrower as we go along.

- LS: Would you like to see broader and, even especially, clinical questions being asked?
- MA: Yes, I would.
- LS: And, that the research should, at least, start to provide the early leads towards solution to problems and disease?
- MA: I would. Every one of my pre-doc students is required to take a course, although a shortened course, in pathology. I'm the only one in my department who requires that.
- LS: And, would I be correct in saying then that, given those attitudes, you then looked at the question of drug abuse in a medical model and said, "Can this be construed as a disease and if it is a disease, how does one deal with the problem and how does one elucidate it"?
- MA: Absolutely. That's certainly the basis, no ifs, ands or buts. But, now I do something a little bit different. After years of doing nothing but chronic experiments where you're waiting a year until you see if you have any-thing, there's a certain attraction to doing acute experiments.
- LS: There's a lot of work in a chronic experiment. Was your thinking that these chronic experiments were vital experiments at the time that you were doing them?
- MA: Well, are you talking about some of the brain lesion work, are you talking about the research with morphine?
- LS: Well, that could be construed as a general question, but I was actually thinking of the drug abuse problem and why you focused on it. We will hear about the short-cut acute experiments, as well, but I'm interested as to why you said, "Hey, this is a chronic disease and we need to do chronic drug experiments in order to understand it".
- MA: Well, because that's part of the human equation. That's what happens in real life and I think that's where the influence of the clinical courses has been. As much as I am a basic scientist I don't want to lose track of the fact that what we're out to do is find things that answer the problems and the questions that come up in life. And, certainly, when we talk about drug abuse, we're talking about the chronic administration of drugs. You're not talking about somebody who tries a drug once. Has that person abused the drug? Yes. Is that person a drug abuser? Not in my book. So, we're talking about the chronic effects of drugs or the effects of chronic administration of drugs. And, I guess, my career has really been shaped by the fact that I've been interested in what happens in human disease and I've always considered that drug abuse is much

more than something like "just say, no", which is a nice phrase and sure, it's helpful to have that, but that's not the answer to the problem. That it's a very complex series of events that have occurred, not the least of which are the pharmacological properties of the drugs, certainly the environment, the genetics, socioeconomics, behavior and everything else that goes into it.

- LS: And, the long-term changes that chronic administration produces in the body's physiology?
- MA: Yes, and this led us to some of the work that we do now with the acute...
- LS: And, of course, many other workers, particularly some of the molecular people, are very interested in and distinguish clearly, between the acute reinforcing effects of drugs of abuse and the long-term chronic changes they may produce, particularly, in the brain.
- MA: Absolutely.
- LS: And, with your contributions with the chronic studies and the emphasis upon that, that puts us in this happier state of affairs, I think.
- MA: You know, I think it's a mix. What's nice in science is that you don't get overwhelmed with your own importance and your own contributions, because lots of people get similar ideas at the same time. Science reaches a certain point where you have a natural outgrowth of ideas and people begin to work on them. Some of our studies led us to conclude that there must be strong influences of the various neurotransmitters involved in that and the neurotransmitters must change with time, as a result of it. We became interested in what the endogenous opioids do and, so, we tried to...
- LS: So, you were fascinated at the time with the discovery that the brain has its own natural opiate system. This, immediately, had an important impact on your research?
- MA: Absolutely.
- LS: And, you were a believer real early, because there were skeptics real early. So it might be worth hearing a little bit about that, about your reaction to the Hughes and Kosterlitz claim. Well, first there were opiate receptors, but you had talked about drug receptors for a long time.
- MA: Right.
- LS: So, that was not a big stretch.
- MA: No, especially some of the work of Dr. Bill Martin...
- LS: But, the fact that there were endogenous opioids must have been interesting to you and I am curious as to what your state of credibility was when you first learned of this work.
- MA: Well, I had no doubts that there were endogenous opioids. I don't believe you had receptors sitting there. They weren't waiting there for

somebody to use the poppy plant. They had to be doing something. They interacted with some endogenous system. But, in studying it and studying some of the endogenous opioids and trying to look at their function, you begin to look at endogenously administered drugs to get some idea, so you give them morphine or you give GABA agonist or whatever. And, then you say, well, these aren't acting by themselves, so it leads you to the next level of complexity. And, people have looked at the neurotransmitters dopamine, serotonin, etc. In this regard, we chose a slightly different path. We decided to look at the neuropeptides and how they interact. So, we've been studying CCK, Substance P, neurotensin and TRH, and so on. And, we pick up new techniques as we go along. We now know a lot about how you get release of these compounds and what release is in terms of the opioids, what can block them and then you begin to ask questions. How does that play in? What's the initiating event vs. the reaction event? Which peptides are involved? So, you find out for acute drug administartion and then you say, "Well, that's all well and good, but what happens in chronic drug administrtaion"? And, that's something we've started more recently. But, then new things come up. And, the newest thing that we're involved in, and I'm using this as an example of new things that come up, it was recently discovered that cytokines exist in the brain and that they are produced by the glial cells. And, for most years, as you well know, the glial cells were there. What did they do? They outnumbered the neurons nine to one or ten to one.

- LS: There was a guy at Walter Reed, who wanted to glorify the glial cells and he got shot down by his boss, who was an anatomist who considered that a heresy.
- MA: There was a guy named Dick Orkand at Penn, who proposed that glial cells are involved in sodium-potassium balance and I was struck by, whatever happened to him. But, now, we know there were cytokines and some of the work that we're doing indicates that they not only interact with the opioid system in the brain, but some of their effects, in terms of fever, for example, can be blocked by an opioid antagonist. So the complexities are always there but at different levels. When I first started in the whole field of psychopharmacology, it was Hess' theory of the ergotropic and trophotropic systems, and you had acetylcholine...
- LS: That might burn up Brodie.
- MA: Yes. I mean you have these very simplified systems.
- LS: And, then, you had serotonin, norepinephrine...
- MA: Sure, sure, but the important thing is that we were right, not in the specifics but in the concept that you have a balance of systems.

- LS: Yes.
- MA: And, that's never changed. So if you thought of it, not in terms of norepinephrine or serotonin, but you thought of it in terms of the balances between systems, it still holds true. And, so that's when you and everybody else...
- LS: So, you're trained to organize your data.
- MA: Absolutely.
- LS: I wonder if we could switch topics a little bit because your contributions have not only been in basic science fundamental research contributions but you have made very decisive contributions in administration and in support functions for research in two important areas. I'd like to discuss those with you: Firstly your experiences as chairman of a study group, and secondly, your very important role as the Executive Officer of the College on Problems of Drug Dependence. So, why don't you talk about both of those and whether they interact with each other and what you're trying to accomplish in your roles in both, in terms of advances in science?
- MA: I was asked to show up as an ad hoc reviewer on a study section in 1976. I guess anyone who has ever been asked to do this, first time he or she is asked, feels this is a great honor before they realize the amount of work involved. But, it's a great honor and that was in 1976. I became an official member of the committee in 1978 and became Chairman of the Biomedical Research Review Committee at NIDA in 1980. And. I've since gone back and chaired a number of other committees and I now chair the Center Grants Committee. Let me put it this way, it's sort of a circular thing. I very, very much appreciated the help I got from people like Bill Martin and Saul Schanberg and Joe Cochin and some others, when I was trying to start in, what was to me, a new field. They went out of their way to be helpful rather than just critical without helpful criticism. So, when I went on the committee and then, especially when I became Chair, I felt it was my obligation to make sure that every applicant had a fair hearing. And, if the grant was lousy, it was going to be lousy, but if it was good, it was good and it wasn't going to be nitpicked to death, because there's no grant that can't be nitpicked to death. And, you have to keep sight of a broader importance than just a word here or there. This, especially, holds true in my book for the young investigators. You've got to get people started somewhere. So, it was a very strong influence, what happened to me, and the help I got from people and giving back to others. And, that's what I have tried to keep as my primary focus.

- LS: This was recognized when you were a committee member and is the reason that you were elevated to Chairman, that you took a critical but a constructive attitude toward the grant, with a particular eye on the young investigator, knowing that is the future of the field.
- MA: Yes and what made it easier was that there were a number of people at NIDA and NIDA staff, who felt the same way. I mean, you can't be a lone voice in the wind and if you are you would never really accomplish anything. You can be a lone voice for a while, but unless additional voices join you, you're not going to make it. And, they were receptive to it and I will mention Joe Cochin again. Joe was a strong influence on that and, in fact, CPDD has a yearly award honoring young scientists, the Joseph Cochin award, a very strong influence. And, another strong influence on that was a young executive secretary, as they were called at the time, Mike Morrison, who, unfortunately, died from malignant melanoma; he was my executive secretary. CPDD gives an award, the Michael Morrison Award every other year to somebody in scientific administration. His push was the same thing, that a fair shake on a grant review that is tough but fair, and a little bit of a boost towards the young group, people who will determine the future.
- LS: Tell us how the College on Problems of Drug Dependence began and tell us about your role in directing the College.
- MA: Well, the CPDD began as a committee and is actually the oldest research group on drug abuse, I think in the world, certainly in the United States. It began, I won't go back to the whole history, as a committee of the National Academy of Sciences and it was started in 1929. It split off and became independent in 1976, and was sponsored by twelve organizations, including ACNP, The American Society for Pharmacology and Experimental Therapeutics, The American Chemical Society, the AMA and so on. It became independent but still retained the name, "Committee on Problems of Drug Dependence". After a long series of changes, in terms of the executive committee and the board of directors and so on, the current system evolved. It became a membership organization four years ago if I'm not mistaken, with an executive committee, a board of directors and an executive officer. Joe Cochin was the executive secretary as it was called at that time and when he died in 1986, for a short period of time thereafter, Conan Kornetsky functioned in that position. Mary Jean Kreek worked on it as well and in 1986, I was elected to that position, so I've been in that position for ten years now. Let's call it a very close sister organization to ACNP in many ways, with the primary concern being drug abuse, as opposed to being

more general psychopharmacology. The emphasis is different, but the interests of the two organizations are very close in many ways.

- LS: I think we're at a point where we can wrap things up. Is there something, at this point, you might want to say, particularly, to the young scientists at this time when funding is as tough as it is and careers are tough but, at the same time, we recognize the need that the next generation must be trained. I wonder if you have some concluding views at a point in this field that some might be inclined to view dismally but, perhaps, you have an optimistic note.
- MA: Well, I don't know. I am both optimistic and pessimistic about it. We can't keep growing at the rate that we have. There are no ifs, ands or buts. Jobs for new PhDs or MDs doing research are fewer and farther between. The landscape changes; whereas, probably most graduates before, in these fields, ended up in academia, today, a much larger number ending up in pharmaceutical and biotech companies. I'm talking mostly about pharmacology, obviously, but also basic sciences, in general. There are different types of opportunities available, but it's not as easy. Somebody is not going to walk in and talk about what happened to the Philadelphia Eagles and give you a grant with a technician. And, the answer today, I think, lies more in group-research than in individual research. The techniques are too complicated. The equipment is too expensive. The space required is too great for one person to expect to be able to do it all by himself or herself, but groups, in collaborative efforts as you say, are awfully important and this causes department alarms. I'm a strong believer in departments. I think that's our real support system but, at the same time, I recognize that no department can spread itself so thin that it will have everything one needs to do research in all fields. So, you need interdepartmental cooperation, and inter- and intra- university cooperation. And, it works.
- LS: And institutes, which have to find a niche in a department-based medical school?
- MA: Yes, I am totally, irrevocably against a free standing institute. It has to be department based. If it's free standing, it's an invitation, in my book, for disaster, but department based, it can work.
- LS: Are you optimistic about dealing with the disease of drug abuse and do you foresee on the horizon that we will be dealing with cocaine abuse and opiate abuse in more effective ways?
- MA: Oh, absolutely. I think as our knowledge base expands, just to give you an example, the use of knock-out mice, to look at some of these, to understand in detail the transporter system and how you might be able

to block it, the contributions of molecular biology toward this are enormous. But, as long as we don't forget that molecular biology, as crucial as that is to its understanding, can only tell us what happens in vitro and then you've got to go to an in vivo system and then go back to the in vitro system. That's fine, but I, also, think that although, we'll come out with new medications, new ways of dealing with it, we're not going to find the magic bullet. You're not going to be able to give the drug and say, "Ah ha, there's no such thing as cocaine abuse; there's no such thing as craving; there's no such thing". Cocaine abuse and craving will be with us, but we'll be able to handle the problem, just as we handle lots of diseases, and I think we do have to think of it as a brain disease. I think we have to think of it as a public health issue and if we begin to put it in terms of the perspective that it deserves, that it's with us and it always has been, only now we say, "Hey, it's with us". So; therefore, it's more than it has been in the past. We recognize that we have to deal with the situation effectively and we can. I'm very optimistic about that. In my mind, there's no question that we will. But, at the same time, there'll be new drugs coming along that none of us can envision now, that the street pharmacologist will come up with. And, some of these street pharmacologists are awfully smart. We're going to have the problems, but we have to learn, you know, to deal with them and we have to take that out of the closet and not deal with something, "Oh, you can't talk about that. You know, that doesn't exist". And we have to get rid of the mentality that everybody can just stop when he or she wants to stop. That's not true. They're going to need help, whether that help is psychological, psychiatric, pharmacologic, or more likely the combination of all of those, plus some others, and I am very optimistic about that. I think there's every reason for optimism.

- LS: Well, with that positive and optimistic note, we conclude a fascinating interview with one of the pioneers in the pharmacology of drug abuse, Dr. Martin Adler.
- MA: Thank you.

HERBERT BARRY III

Interviewed by Thomas A. Ban Acapulco, Mexico, December 12, 1999

- TB: We are at the 48th annual meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico. It is December 12, 1999. I will be interviewing Dr. Herbert Barry III.* I am Thomas Ban. Let's start from the very beginning. Could you tell us where you are from and something about your education and early interests?
- HB: I'm Herbert Barry III, Tom. I trust that for you, I'm Herb rather than Herbert Barry III. I have been told that my parents both grew up in the New York area and that I was born in Doctor's Hospital in New York. They moved to Cambridge, Massachusetts before I was born. My maternal grandparents wanted me to be born in New York City. I grew up in Cambridge, Massachusetts for the first sixteen years, when my family moved to Brookline, Massachusetts. I went to college, undergraduate, at Harvard in Cambridge, Massachusetts. My father, all three uncles, and one of my grandfathers also had graduated from there, so it was a family tradition. I went to graduate school in psychology at Yale, where I got my PhD degree in 1957. I continued at Yale as a post-doctoral research fellow and then as a junior faculty member, doing full time research, sponsored by Professor Neal E. Miller. My first job elsewhere, in 1961, was at the University of Connecticut in Storrs. In 1963 I moved to the University of Pittsburgh, Department of Pharmacology School of Pharmacy. This was my first residence outside of New England. I have been in Pittsburgh ever since at the School of Pharmacy.
- TB: How did you decide to enter psychology and get involved in psychopharmacology?
- HB: It was quite an individual influence. My major in graduate school was experimental psychology and, essentially, it was what we called "rat running", using laboratory rats as models to test learning, memory and behavior, applicable to humans. My PhD dissertation was entitled "Effects of Strength of Drive on Learning and on Extinction".
- TB: So your PhD was in experimental psychology.
- HB: My dissertation tested a rather simple situation. The rats ran down a straight alley to get a food pellet. I measured the duration it took them, to the nearest hundredth of a second. When I was finishing my PhD degree, my psychoanalysis, which began in my first year in graduate school, was still continuing, so I had an incentive to stay in New Haven for a while longer to finish the psychoanalysis. I wanted to apply for a

^{*} Herbert Barry III was born in New York, New York in 1930.

post-doctoral research fellowship. I almost applied for a fellowship from the National Institute of Mental Health, NIMH, to be sponsored by Irvin L. Child, a developmental psychologist, to extend some of the research I had already been doing with him on child training practices in a world sample of societies.

- TB: Are we in the 1950s?
- HB: Yes, it was in 1957. Neal Miller, who was the major advisor for my PhD dissertation, had started doing psychobiology research. He said that psychopharmacology was a new and rapidly developing field. In 1957, it certainly was. He suggested that I apply for a post-doctoral research fellowship from NIMH in psychopharmacology. He felt that there would be a better chance of it being awarded and funded in that area. And I was fascinated by the topic of drugs.
- TB: You have been working with a conditioning paradigm so. Didn't you?
- HB: It was instrumental rather than classical conditioning, but it was a conditioned behavior. One of the hypotheses tested in my PhD. thesis was that a change in the rat's motivation, from a longer to a shorter deprivation of food, or from a shorter to a longer deprivation of food, would affect its running speed because of the change from the previous experience of running to the food pellet under the other degree of food deprivation. In my post-doctoral research fellowship with Neal Miller, I did a behavioral analysis of drug effects. We constructed an allev in which the rats had an approach-avoidance conflict and then we tested the effects of drugs on the rats' performance. We found that alcohol and amobarbital would decrease the avoidance more than it decreased the approach component of the conflict. The rat was intimidated by shock when it approached the food cup and got a painful electric shock at the cup. The rat therefore avoided the cup. Under the influence of the drug it became bolder or less deterred by the shock. That was the beginning of my psychopharmacology research.
- TB: So, you found that alcohol and barbiturates decreased the avoidance component more than the approach component?
- HB: Yes, and we also tested several other drugs. Chlorpromazine was one. We did a little bit of work with morphine.
- TB: And, all these drugs decreased the avoidance component with little effect on the approach component?
- HB: Yes. I was a post-doctoral research fellow for two years. During that time Neal Miller applied for a research grant in psychopharmacology with me as his co-investigator, not co-principal investigator. I became an instructor and soon afterward an assistant professor at Yale during the two more years I stayed with him on that project. It was quite

successful. We published articles in *Psychopharmacologia* and in the *Journal of Comparative and Physiological Psychology*.

- TB: What was your first publication?
- HB: It was Neal E. Miller and Herbert Barry III, Motivational Effects of Drugs: Methods Which Illustrate Some General Problems in Psychopharmacology. It was published in Volume 1 of Psychopharmacologia. Its citations included a couple of articles from 1935 and 1936 by Neal E. Miller and Walter R. Miles, which reported psychopharmacology experiments on rats.
- TB: In what year was your paper published?
- HB: In 1960. The manuscript was received by the Journal in October 1959. We subsequently published several other studies together. In 1961, I accepted a job as assistant professor of psychology at the University of Connecticut, where I continued research in psychopharmacology. In fact, I was principal investigator of a research grant that I applied for at the University of Connecticut.
- TB: What was that grant for?
- HB: It was on stress. The title was "Situation-Drug Interaction in Emotional Responses."
- TB: How did you induce stress?
- HB: One of the ways was by exposing the animals to severe painful shock prior to injecting the drug. Also, I was continuing some studies on approach-avoidance conflict.
- TB: You were probably among the first to do this kind of research in North America.
- HB: Yes, Hannah Steinberg did some similar studies in England. Neal Miller had been the major advisor of John J. Conger, who did a PhD thesis on alcohol. I was one of the early Americans to do laboratory animal research in psychopharmacology. I was offered a job at the University of Pittsburgh in 1962, during my second year at the University of Connecticut. The research project there was well funded by NIMH. The principal investigators, William J. Kinnard and Joseph P. Buckley, were professors in the Department of Pharmacology, University of Pittsburgh School of Pharmacy. They had been awarded a grant and Oakley S. Ray was expected to do the behavioral research on it. The title of the project was "Analysis of Psychopharmacologic Methodology." Since the emphasis was on behavior, a psychologist was needed for the project. Kinnard and Buckley were both pharmacologists. Oakley Ray was listed as the principal investigator when the grant was awarded. After a dispute with Joe Buckley, the Chairman of the pharmacology department, Oakley Ray decided to withdraw from this project. He had a job

at a Veterans Administration Hospital in Pittsburgh. After the five-year grant had begun, Buckley and Kinnard were looking for a psychologist to run the experiments and direct a large part of the research. They recruited me. Neal Miller had been a member of the committee that established and approved this project. I met Buckley and Kinnard, and the project seemed like a very good opportunity to focus on my research; I had considerable teaching duties and rather meager laboratory facilities at the University of Connecticut in Storrs. That university now has a medical school in Farmington with great facilities.

Although Neal Miller advised me against accepting the job, I accepted it and started in February 1963, at the University of Pittsburgh as a research associate professor of pharmacology. I was well aware it was funded by a research grant that might expire in four years. I expected it would be a temporary job, but I'm still there. It is ironic that when I accepted the job at the University of Connecticut, I expected it would be my long-term future career.

- TB: So, you have been for many years in Pittsburgh by now.
- HB: Yes.
- TB: What was you role in the project?
- HB: Bill Kinnard was the principal investigator and Joe Buckley, the Chairman of the department, was the person who really directed the project. I conducted the portion of the project that involved operant conditioning. We focused on trying to establish the optimal techniques for testing effects of chlorpromazine. My part of the research was on conditioned avoidance response. Chlorpromazine, as you well know, suppresses avoidance response. It does not interfere much, if at all, with the animal's ability to escape the shock. The animal waits until the shock begins before it presses the lever or makes whatever other response to terminate the shock. Avoidance performance is very much impaired.
- TB: Weren't some other people also doing somewhat similar research at that time?
- HB: Leonard Cook was doing research on conditioned avoidance in squirrel monkeys. I also know of an article by Geller and Seifter, published in Volume 1 of *Psychopharmacologia*.
- TB: Did you do your experiments in rats?
- HB: I did rats, yes, as did Geller and Seifter. George A. Heise also was doing research on conditioned avoidance in rats. I don't think he used chlorpromazine. He was one of the original investigators of the benzodiazepines.

- TB: Were you the first to establish in rats that chlorpromazine suppresses the avoidance response without having an effect on the escape response?
- HB: Oh, no. My research on the conditioned avoidance response used two levers. The animal pressed one lever to avoid the shock and a different lever to escape the shock. That technique was described by Heise and Boff in 1962 in an article entitled, *Continuous Avoidance as a Base-line for Measuring Behavioral Effects of Drugs*, published in Volume 3 of *Psychopharmacologia*. Prior to the publication of that article, Murray Sidman had developed the technique for conditioned avoidance. For two or three years at the University of Pittsburgh, I concentrated on that technique and also cooperated with colleagues on the project. One of these colleagues, Nathan Watzman, was assigned to do research on the effects of drugs on motor activity in mice. For a couple of years I worked closely with him, particularly on writing and publishing the findings of those studies.
- TB: Did you study the effect of drugs on spontaneous motor activity?
- HB: Yes, on spontaneous motor activity in a circular arena. We published several articles on it together in the *Journal of Pharmaceutical Sciences*. In 1966, the sponsors of the research project on which I was employed expressed dissatisfaction with the research. Their criticisms applied less to my part of the research than to other parts. We were advised not to apply for continuation of the prior program project. We were told that if we wanted to continue doing the same research, we ought to apply for it in a grant with a new name. The members of the review committee for that program project had changed, and the new members did not like the kind of research we were doing. That project therefore was terminated.
- TB: What did you do after the project was terminated?
- HB: I then applied for a research grant. And Joe Buckley also encouraged me to apply for a research scientist development award from NIMH at the same time. Both of them were approved and funded shortly before termination of the research grant on which I was employed. A few years later, in 1970, I was promoted from research associate professor, outside the tenure stream, to tenured professor in the department. In 1970, the same year, the Elsevier Company published a book on *Actions of Alcohol* that I co-authored with Henrik Wallgren. Our purpose was to summarize scientific knowledge about ethyl alcohol. I believe that book contributed to my promotion. Henrik Wallgren is a very distinguished physiologist in Finland. The Elsevier Publishing Company invited him to write a book summarizing scientific knowledge about alcohol. He was

asked to do it with a psychologist, preferably an American. Neal Miller recommended me to him. Wallgren wrote the invitation to me in 1963. I visited him in Helsinki in 1964, and we worked well together. It took us six years to finish this book, which consisted of two volumes. The original tentative title of our book was *Actions of Ethanol*. My father, Herbert Barry, Jr., asked me sarcastically if we used the word "ethanol" instead of "alcohol" for the purpose of minimizing the number of readers of our book. He was trained as a psychologist and then he became a psychiatrist. He and I published several articles together in the 1960s, on psychiatric implications of season of birth and on birth order in the family.

- TB: You published articles on the effects of alcohol with Neal Miller. Didn't you publish also some other papers on the effects of alcohol on your own?
- HB: My articles with Neal Miller were on effects of alcohol on approachavoidance conflict in rats. My earlier publications included a paper in 1968 on socio-cultural aspects of alcohol addiction, and another paper in 1969 with my father and Howard T. Blane on birth order of delinguent boys with alcohol involvement. All these papers were cited in my book with Wallgren. Our book included findings on the physiological, neurological, and behavioral effects of different types of alcoholic beverages. We divided the work on the book so that Henrik Wallgren wrote the initial draft of half of the chapters and I wrote the initial draft of the other half. He wrote the chapters on the physiological and neurological effects of alcohol, on alcohol metabolism, and on interactions of alcohol with other drugs. I wrote the chapters on voluntary consumption of alcohol and on behavioral studies on laboratory animals. I also wrote a chapter on alcoholism, which was the first of my series of papers on alcoholism. It dealt with personality characteristics that make a person either vulnerable or resistant to develop alcoholism.
- TB: So, you were involved in studying the effects of alcohol quite intensively?
- HB: Yes, I had done some initial studies on alcohol with Neal Miller at Yale and then I did some more at the University of Pittsburgh. I worked on the book from 1964 until 1970. I published articles on birth order of alcoholics in the 1970's, because as a psychologist I was very interested in social and developmental factors. This interest was concurrent with my research on laboratory animals in behavioral psychopharmacology.
- TB: Could you tell us something about your findings in your birth order study?
- HB: Alcoholics are more often last-born from large families of four or more children. That was our principal finding. Howard T. Blane and I

summarized results from many studies on alcoholic men in an article on Birth Order and Alcoholism; a Review, published in 1973 in the Quarterly Journal of Studies on Alcohol. Our interpretation of the finding was that the last-born child in a large family is customarily treated as the baby of the family. The mother does not desire to have the youngest child become assertive and independent. This induces a conflict that is especially severe if the youngest child is a boy. A general psychoanalytic theory suggests that many alcoholics are conflicted between being dependent and becoming independent. The children are unwilling to acknowledge their very strong desire to be dependent and taken care of and are also unwilling to act out their dependence. Intoxication is a way to be dependent on alcohol or another drug and, at the same time, to deny one's pharmacological dependence. For example, the person who is drunk will have fantasies that he is very powerful. He may get very pugnacious, saying, "I can beat up anybody else in this bar". This is our explanation of the finding that alcoholics are most often the lastborn child in a large family. An alternative possible explanation is that the last-born child is more likely than earlier born children to be hospitalized for alcoholism, not necessarily because of having a more severe drinking problem.

- TB: So while you did behavioral research you maintained your interest in psychodynamics. Did you finish your training in psychoanalysis?
- HB: My psychoanalyst suggested that we finish the analysis soon after the beginning of my post-doctoral research fellowship. He and I agreed that it was the appropriate time. I believe it was a good experience. I am skeptical about some of the Freudian psychoanalytic doctrines, but I have maintained an interest in the topic. I contributed a chapter on *Psychoanalytic Theory of Alcoholism* to a book on *Theories on Alcoholism*, published in 1988 by the Addiction Research Foundation in Toronto, Canada. The Editors of the book were C. Douglas Chaudron and D. Adrian Wilkinson. I enjoyed preparing the chapter. An unusual feature of my chapter was that I summarized Sigmund Freud's published writings about alcohol effects and alcoholism.

Ever since I was an undergraduate at college, majoring in Social Relations, I have been very interested in personality dynamics and developmental factors. My first rat experiment, in my first year in graduate school, compared the memory of very young rats with mature rats for previously escaping from an electric shock in a runway. My psychoanalyst pointed out that I was fascinated by the question of how well a very young individual would remember an experience compared to a mature individual. That initial experiment was unsuccessful but fortunately my subsequent experiments in graduate school were successful. That is a digression from psychopharmacology.

- TB: So let's get back on the track, what you were doing in Pittsburgh.
- HB: Several years before Henrik Wallgren and I finished the book on alcohol, I started doing research on the discriminative stimulus attributes of drug effects in laboratory rats. It is sometimes called drug discrimination. The human experimenter trains the laboratory rat to inform the experimenter whether it feels drugged or normal. A hungry rat is trained to press either of two levers to obtain a food pellet in a chamber that contains a food cup. After this preliminary training, one lever delivers food only if the rat has been injected with placebo and the other lever delivers food only if the rat has been injected with a drug. An equal number of sessions are preceded by placebo and by the drug. The interval between successive sessions is two or more days to permit complete recovery from the effect of the drug or placebo.

The rat gradually learns to press preferentially the lever that delivers food, depending on whether the session was preceded by the drug or placebo. In a training session of ten or fifteen minutes, no food is delivered in the first one or two minutes. We count the number of times the rat presses the two levers during this initial part of the session. After more than twenty but less than forty sessions, divided between the drug and placebo conditions, the rat in the initial interval without food usually presses more often the lever that will deliver food in its current condition. The rat therefore responds to the internal differential drugged or normal condition.

It is a technique that was initiated by Donald A. Overton. His first article on this technique, *State Dependent or Dissociated Learning Produced with Pentobarbital* was published in 1962 in the Journal of *Comparative and Physiological Psychology*. A more extensive report, State-Dependent Learning Produced by Depressant and Atropine-Like Drugs, was published in 1964 in Psychopharamcologia. Overton trained and tested rats in a T-shaped maze. Food was at the end of one arm under the drug condition and at the end of the opposite arm under the non-drug condition. My first publication on drug discrimination research also used a T-shaped maze. Alcohol was the drug discriminated from placebo. It was a one-page article I wrote with coauthors Eileen Koepfer and Joyce Lutch, with the title An Operant Procedure for Training Discrimination between Drug and Nondrug State, in 1965 in Psychological Reports. Koepfer and Lutch were high school students who did the research project under my direction.

Since primacy is an important factor in science, I can claim to have originated drug discrimination research in an operant conditioning box containing two levers. This apparatus has been used frequently in a great variety of studies. A novel technique was to establish drug discrimination in rats that had been trained to alternate the condition of the light in the chamber, on and off, by successive lever presses. Illumination was associated with food after alcohol injection for half the rats and after placebo injection for the other rats. Successful training was reported in my article Prolonged Measurements of Discrimination between Alcohol and Non-drug States, in 1968, in the Journal of Comparative and Physiological Psychology. In the same area of research, Robert K. Kubena and I published in 1969 two subsequent articles. Two Procedures for Training Differential Responses in Alcohol and Nondrug Conditions appeared in the Journal of Pharmaceutical Sciences; Generalization by Rats of Alcohol and Atropine Stimulus Characteristics to Other Druga appeared in Psychopharmacologia. Both articles are based on the Master's Thesis of Kubena. I was his principal advisor in this research and in his subsequent PhD. dissertation. I initially felt apprehensive about advising Bob Kubena to undertake a project that required maintenance and training of the animals for several months before obtaining useful data. There was meager prior information on this research technique. Fortunately, he conducted the initial experiment and subsequent ones very proficiently and successfully.

I continued the research on drug discrimination for many years, from 1967 to 1983 with the support of a research grant for "Behavior and Drug Effects during Chronic Stress" from NIMH. The principal use of the drug discrimination technique has been to test other drugs to find out if another drug is more similar to the training drug or to the placebo. Also, tests with different doses of the drugs can determine the minimum effective dose. In the early studies, Don Overton and I both showed that alcohol and a barbiturate could substitute for each other. Bats trained to discriminate either drug from the placebo make the drug response when tested with a sufficiently high dose of the other drug. A drug discrimination technique that I subsequently used was to train animals to discriminate between two different drugs, such as between alcohol and pentobarbital, instead of between either of the drugs and placebo. Although the discriminative effects of these two drugs are similar, they are not exactly the same. Differential discriminative effects are found in rats trained to discriminate between several doses of alcohol and several doses of pentobarbital.

I relinquished my animal laboratory in 1995. I am now writing some historical reviews of psychopharmacology.

- TB: What are you writing about on the history of psychopharmacology?
- HB: My most substantial work in this area was A History of Division 28. Division 28 is the division of psychopharmacology and substance abuse of the American Psychological Association. My historical account was published in 1998 by the American Psychological Association, in volume 2 of a book on Unification Through Division: Histories of the Divisions of the American Psychological Association. The book was edited by Donald A. Dewsbury. The very large American Psychological Association is organized into more than fifty divisions. Division 28 was founded in 1966. I was one of the founding members of that division and its president in 1981. The membership of the division is approximately 1000 people, a small percentage of the total membership of the American Psychological Association but a sufficiently large number of people to sponsor the division's programs at the annual meetings and to make substantial contributions to psychopharmacology.
- TB: How many members are in the American Psychological Association?
- HB: More than a hundred thousand, I believe. The American Psychological Association decided to publish several volumes containing histories of its different divisions. The Division of Psychopharmacology recently changed its name to "Division of Psychopharmacology and Substance Abuse". By the name change it tries to broaden its scope. More recently I co-authored an article with Donald A. Overton and John A. Rosekrans on the *Creation and First 20 Years ofthe Society for the Stimulus Properties of Drugs (SSPD)* that was published in 1999 in *Pharmacology, Biochemistry and Behavior.* I presided over the first meeting of the SSPD, in 1978, and I was in 1980 the third president of the organization. Several international meetings of that society were held in Beerse, Belgium, and sponsored by the Janssen Pharmaceutical Laboratories. The SSPD is a small society, with fewer than two hundred members, but I believe it is an integrative force for its specialty topic.
- TB: So, you were one of the founders of that society, and one of its early presidents.
- HB: Yes. I was one of the early contributors to that specialty topic.
- TB: Could you explain to us what it means when you say, "stimulus properties of drugs."
- HB: A drug effect functions as an unconditional stimulus. I remember having been told that Pavlov's term in Russian was mistranslated as "unconditioned stimulus" but should be translated as "unconditional stimulus".

The drug effect is an unconditional stimulus in the central nervous system. A stronger and therefore more effective unconditional stimulus is the rat's hunger. Food pellets constitute an unconditional stimulus. The unconditional response is eating food to alleviate the unconditional stimulus of hunger. The differential drug and non-drug conditions during the training sessions become distinctive conditional stimuli, associated with the differential conditional responses of pressing the different levers to obtain the unconditional stimulus of a food pellet. If a conditional response is learned under the influence of a drug effect, that conditional response is specific to the drug effect and to the function of the nervous system under the influence of the drug.

- TB: So the unconditional drug effect becomes a conditional stimulus?
- HB: Yes. Therefore, an individual animal or human can be trained to make differential responses and acquire different habits. One habit is acquired under the influence of the drug conditional stimulus. A different habit is acquired under the influence of the normal or non-drug conditional stimulus. It is like training the rat to distinguish whether it is drugged or normal. Pharmaceutical companies used this technique a great deal in recent years. Animals are trained to discriminate a prototype drug, such as an antipsychotic or an opioid. When a new drug of the same type might be superior, because it is effective at a lower dose, or has less, side effects, the new drug can be tested in animals that were trained to discriminate the prototype drug from the non-drug condition. The experiment determines what dose of the new drug is sufficient to cause the animal to make the same choice as the prototype drug.
- TB: Which are the drugs you tested with the employment of this technique?
- HB: Over the years at the University of Pittsburgh, I tested a great variety of drugs. I began with barbiturates and alcohol. Two graduate students who earned the PhD degree under my direction, Robert K. Kubena and R. Duane Sofia, were interested in research on marijuana. They did several studies on effects of Δ -9-tetrahydrocannabinol. Initially, in accordance with Dr. Raphael Mechoulem, who had originally synthesized the compound, we used the name Δ -1 tetrahydrocannabinol. Our articles included a statement that Δ -1 is a different designation for Δ -9.
- TB: So, you tested alcohol, barbiturates, THC with the employment of this technique.
- HB: Also morphine. One of my graduate students, Edward C. Krimmer, earned the PhD degree under my direction and became my principal colleague for many years. Our research included morphine as the discriminative stimulus.

- TB: Now, you worked mainly in animals. Did you do any research in humans?
- HB: Not in psychopharmacology. I have given questionnaires to humans, but not related to drug effects.
- TB: What did you study with the questionnaires?
- HB: The questionnaires are designed to measure empathic choices in hypothetical situations. This research was done with Helene Borke, PhD, who is accompanying me at this meeting. She has a PhD degree in psychology from the University of Chicago. The alternatives to empathic choices are emotional or rational choices. For example, if your fiveyear-old child has drawn with crayons on your wallpaper, how do you react? The empathic choice is "I realize you wanted to experiment with something new". The emotional choice is "I wish you had not messed up my wallpaper". The rational choice is "I will let you use the crayons only on blank sheets of paper".
- TB: What did you find?
- HB: We found nothing clear-cut or definitive as yet. The choices are highly specific to the situation. The questionnaires thus far have been given to students at Community College of Allegheny County, near Pittsburgh. Older students choose the empathic response more often and younger students choose the emotional response more often. We expected that females would choose the empathic response more often but there is very little difference from male students. We did find more empathic choices by females in the initial version of the questionnaire. Choices in that version were general traits not associated with a specific situation, such as "I am usually sympathetic" or "I am usually enthusiastic" or "I am usually logical." I believe that the specific hypothetical situations are more valid measures of empathy.
- TB: Are you still involved in this kind of research?
- HB: Yes, I have constructed many successive versions of the questionnaire.
- TB: Are you still involved in research in psychopharmacology?
- HB: Not now. Several years ago, for a couple of years, I participated in a project on alcohol effects with Seymour M. Antelman, Anthony R. Caggiula, and David J. Edwards. In 1991 I was co-author of S.M.Antelman, A.R.Caggiula, D. Kocan, S. Knopf, D. Meyer, and D.J. Edwards, in an article on *One Experience with Lower or Higher Intensity Stressors, Respectively Enhances or Diminishes Responsiveness to Haloperidol Weeks Later: Implications for Understanding Drug Variability, that was published in Brain Research.* In addition, I suggested ideas for developing novel apparatus or techniques, but they were not used.
- TB: You suggested developing novel apparatus or techniques to measure what?

- HB: Spontaneous activity of laboratory rats, I proposed a dark, enclosed place to measure the amount of time the animals ventured into the larger, illuminated arena. That apparatus might be a useful measure of the degree to which spontaneous motor activity measures boldness instead of fear. Conventional tests of spontaneous activity measure stimulation instead of depression of motor behavior.
- TB: Why did you decide to close your laboratory?
- HB: My relinquishment of my animal laboratory is partly due to other interests, including the research on empathy I have described, in addition to difficulty and expense of maintaining a laboratory animal facility. Another influence on me is the threat of animal rights activists, although I have never been personally attacked by these activists, and research on rodents is not a prime target.
- TB: Have you served on any of the committees of ACNP?
- HB: Several years ago I was a member of the ACNP committee on laboratory animal experimentation. My former dissertation advisor and colleague Neal Miller has been defending laboratory animal research very effectively and eloquently. As a laboratory animal researcher, I was obviously interested in that topic.
- TB: When was that?
- HB: I became a member of ACNP in 1986. Therefore, it must have been within the last twelve years. It was probably six or eight years ago.
- TB: Haven't you been involved in some editorial work?
- HB: Emphatically yes. I believe one of my major credentials for ACNP membership and a major personal contribution to psychopharmacology was my function as field editor for laboratory animal behavioral research for *Psychopharmacologia*, beginning in 1974. My title was Managing Editor, and I became Coordinating Managing Editor for the other Managing Editors in the western hemisphere of the world. Subsequently the Journal's name was changed to *Psychopharmacology*. I served as Managing Editor until 1991, for 18 years. I received more than two thousand manuscripts. More than a thousand of them were published in the journal. My predecessor was Conan Kornensky and my successor is Klaus A. Miczek. They are both members of ACNP. I regard Klaus Miczek as an especially excellent and effective editor. I felt glad when I was relieved of that task, but I enjoyed doing it and I believe that it was an important contribution to the field.

There is some equivalence between a journal editor, who helps to choose which manuscripts are published, and a member of a research review committee, who helps to choose which research-grant
applications are funded. I have had experience with both roles, much more extensively as a journal editor than as a member of a research review committee. Some people probably place greater value on membership of a research review committee, because they participate in determining the expenditure of thousands of dollars and the careers of the investigators who apply for research grants. I preferred journal editing, partly because the decision was primarily mine. I sent the manuscripts to two reviewers. I was strongly influenced by their opinions but it was primarily my judgment and opinion that determined publication. I also had the opportunity to improve the paper because my usual procedure was to specify needed changes and send the paper back to the authors if I believed the research report could be accepted. I very seldom accepted a manuscript without requesting revisions and corrections. In contrast to the decisions by an editor, a member of a research review committee negotiates or debates with other members of the committee. Another difference is that a grant application usually contains grandiose statements about what wonderful research is going to be done, but the proposal is not a reliable prediction of the quality of the prospective research. A manuscript submitted to a journal is a product of the research. Its quality is usually much better. Therefore, I prefer to read a manuscript submitted for publication than to read a grant application.

- TB: You have been all through your professional life with universities. What proportion of your time did you spend teaching?
- HB: The minority of my time was teaching. When I started at the University of Pittsburgh, in 1963, I was as a full time researcher. I continued to be obligated to do full time research as recipient of a research scientist development award for two five year terms from 1967 to 1977. Actually, I believe that I did more teaching during those ten years than before or after. I taught one third of a course for undergraduates, a general pharmacology course, and I gave lectures in other courses. I also taught two graduate courses. They were on biomedical statistics for many years and, for several years, on behavioral psychopharmacology. Subsequent to 1977, I have given less than ten hours of lectures per year. They were in team taught courses. Therefore, my teaching load has been negligible. I hope that I have contributed enough, by my research and journal editing, to make up for the fact that I did so little teaching. I have not been asked to do any more teaching.
- TB: You also had several graduate students, didn't you?
- HB: I was the principal advisor for five students who earned the Ph.D. degree. In1970, I was the principal advisor of Robert K. Kubena, in

1971 of James L. Perhach, and Duane R. Sofia, and in 1974 of Edward C. Krimmer, and Tsung-Ming Shih. I have also served as a member of the PhD dissertation committee for many additional students, including several in the Psychology Department in the University of Pittsburgh and in the Pharmacology Department in the Medical School of the University of Toronto in Ontario, Canada.

TB: On this note we should conclude this interview with Dr Herbert Barry III. Thank you, Herb for sharing this information with us.

JACK BLAINE

Interviewed by Leo E. Hollister Washington, DC, April 14, 1997

- LH: Good morning. Today 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 a MD, 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, 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. I chose medicine because medicine appeared to be an interesting field and was 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 in medical school 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. He taught a section on the opiate drugs and drug abuse, and I became interested in it at that time and then took a seminar from him later in the year. In my senior year of medical school, I received a Manealoff Traveling Fellowship to London where I had the opportunity to work with Griffith Edwards and Philip Connell at the Maudsley Hospital on drug abuse and also to work in a heroin dispensing treatment clinic in London.
- LH: Phil was the father of amphetamine psychosis, wasn't he?
- JB: Right. That was a wonderful experience and it furthered my interest in the field. I did my internship, a mixed medical internship, at UCLA Affiliated Hospitals. I finished my internship in July 1969. I hadn't really decided about a residency or what medical field I was going to go into. Sidney Cohen who I had met while at UCLA had recently left UCLA

^{*} Jack Blaine was born in New Brunswick, New Jersey in 1943.

to become the Division Director of the Division of Narcotics and Drug Abuse at the National Institute of Mental Health. That Division was the precursor of NIDA. That was during the Vietnam War. As an alternative to being drafted, I joined the US Public Health Service and went to work for what was then the Center for Study of Narcotics and Drug Abuse, in Sidney Cohen's division. And that's where I met you, I think, 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, although the name has changed several times.
- 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 that, I decided to go into psychiatry and psychopharmacology in particular. I went back for my psychiatric residency at the University of California, San Diego for three years. Following that, in 1975, I came back to NIDA. I worked from 1975 to '80 at NIDA. Then I transferred to the National Institute of Mental Health where I was in the Psychopharmacology Research Branch from 1980 to 1986.
- LH: That was Jonathan Cole's operation.
- JB: Jonathan 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 working there. I worked there for six years, from 1980 to '86, and then I returned to NIDA in '86. I became Chief of the Treatment Research Branch at NIDA, and I've been at NIDA 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 go to Jamaica to visit a research study on the effects of chronic smoked marijuana on humans being conducted at the University of the West Indies. That was an interesting experience.

- LH: We'll probably have to have another one. Marijuana is always so controversial.
- JB: It seems to be.
- 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 accepted by President Nixon.
- LH: Nor, I guess, by the present crew either.
- JB: 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 the Commission took your advice, but nobody listened.
- 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. At first, Dr. Arnold Mandel was the Chairman of the Department of Psychiatry, and Dr. Louis Judd was the Deputy Chair. They were running the Department together until Dr. Judd became Chairman. I had more contact with Lou than with Arnie. Also, I was fortunate to work with Dr. David Janowski who had come to San Diego when I was a resident. We did some studies together on the effect of smoking marijuana by pilots using a flight simulator. That was a very good experience.
- LH: Arnie was a colorful character, wasn't he?
- JB: He certainly was. During that time period he was the psychiatrist for the San Diego Chargers football team.
- 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. 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. 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 Janowski 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 1975.
- LH: Who was running it then?
- JB: At that time, Bob DuPont, MD was the Director of NIDA, Bill Pollin, MD was the Director of the Division of Research, and I was in the Clinical Behavioral Branch, led by Pierre Renault, MD.
- 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 that he came to me almost in tears, and I said to 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. NIDA was working on LAAM and naltrexone in 1975.
- LH: It's incredible.
- JB: NIDA got finally both on the market.
- LH: You were working on LAAM in the 1970s but it wasn't until two or three years ago that 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 head of The Special Action Office for Drug Abuse Prevention (SAODAP). Jerry thought it would be an easy thing for the government to get a drug on the market.

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 and marketed, the government embarked on a series of studies first sponsored by Jerry Jaffe and the SAODAP. These were the Phase II studies of LAAM. There had been a number of small clinical trials with LAAM that showed that it was an effective and safe drug compared to methadone. SAODAP and the VA sponsored the early 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 try to get drug companies in the project, but none was interested. Jerry Jaffe and others, like Avrum Goldstein, tried very, very hard to interest the companies. I think at that time Eli Lilly marketed methadone. Endo had the rights to naltrexone; but naltrexone hadn't been approved either. I don't think methadone made a great deal of money. Methadone had all the negative associations of being a drug for heroin addicts. So no pharmaceutical company was interested in LAAM.

- LH: At that time, I think, methadone was being made largely by Monsanto, wasn't it?
- JB: Maybe.
- LH: A chemical company rather than as a pharmaceutical company.
- You're probably right, but I thought Lilly was marketing it, but I am not JB: sure, Leo. To get a drug company interested, the government advertised for a contract to conduct the Phase III study of LAAM, compile and submit the NDA to FDA and put LAAM on the market for the treatment of heroin addiction. Unfortunately, the government underestimated the task. I think the initial contract was a two-year contract for \$2 million, a very small amount even at that time. Bob DuPont was very, very supportive of getting LAAM on the market. He really wanted to be available to the treatment programs. 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 and available to many addicts. The smaller part of the study was a comparison study, a random assignment to methadone and LAAM, and the larger part of the study was an open trial in many clinics across the country in order to treat thousands of heroin addicts.
- 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 detracted from the amount of time and effort 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. The initial contract intended to put women on LAAM, but early on there was some question about a mutagenicity laboratory study in some, I don't remember which, cell preparation. It wasn't an animal study. That kept women who could become pregnant from going into the study as planned and made it more difficult to reach the intended sample size. So the study took longer than intended. I think about 6,000 people entered the study. Thus, the contract needed to be reissued. That became a political nightmare because NIDA was trying to contract to John Whysner, MD who had a small consulting firm in Washington, DC. He had coordinated the original contract that had been awarded to his firm, Whysner Associates, competitively.

LH: Who was that again?

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JB: John Whysner. He was a physician who had toxicology expertise, and had actually worked briefly at SAODAP. He put together a group including an advisory board that could carry out the contract, coordinate and conduct the clinical trial, and set up heroin treatment clinics across the country to provide the treatment. Whysner Associates was competitively awarded the initial contract.

Generally, data developed under a government contract is the government's data and is in the public domain. Because LAAM was not under patent any more, the question was how would whoever obtained the NDA have an exclusive market for LAAM. The concept that the government lawyers devised was that the contractor would be given the exclusive rights to the data in exchange for the cost-sharing the contract costs.

In the initial contract Whysner Associates relinquished the profit that could have been earned as the cost-share for Whysner Associates. Whysner was given the rights to the data generated under the contract for this cost share. When the contract was going to be reissued again, Whysner didn't have enough money to continue his company's operation if he continued to relinquish his profit. The government was in an untenable position where it felt like they had to continue this cost-share. The contract wasn't awarded again. Whysner Associates had the data generated under the contract.

- 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 and in his files, but had not been analyzed or put together in an NDA. Years later, the government actually negotiated to purchase that data from Whysner and, more recently, NIDA proceeded to do another Phase III study of LAAM and successfully submit the NDA permitting the marketing of LAAM.

- 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 in the late 1980s or early '90s, NIDA formed its Medication Development Division and brought together the expertise to actually proceed with a NDA after NIDA had the data. The staff of the Medication Development Division went to the FDA and requested to use the data that had been purchased from Whysner and inquired about what would be necessary to obtain an NDA and market LAAM. FDA noted that the data on LAAM was from the late 1970s. They felt that there had to be a study done with current addicts who were using other drugs, especially cocaine that wasn't in very much prominent use back in the 1970s.
- LH: A more naturalistic situation.
- JB: The study previously done was a naturalistic study, but it was done in 1975 to 1978. This new study was done in the early 90s.
- LH: Who did that? Walter Ling?
- JB: Walter Ling was certainly a key 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. The government advertised another request for proposal for a contract I guess in the early 1990s or late '80s, 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 LAAM. He was the one who put together the group and worked with FDA and NIDA's Medication Development Division. The NDA for LAAM was finally approved after all those 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 Bradford, that he and BRI were able to obtain the NDA approved for naltrexone as a treatment for heroin addiction as well.
- 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.
- The experimental data looks very good. I think what has happened with JB: naltrexone is that the studies that were done to get the approval were carried out in very controlled clinical trial programs, at the University of Pennsylvania by Joe Vopicelli and Chuck O'Brien and at Yale by Stephanie O'Malley. Both of those centers do a fair amount of psychosocial behavioral interventions with the medication treatments. I think naltrexone was done in the context of a significant amount of high quality psychotherapy or substance abuse counseling. Naltrexone seemed to work very well in that context. I think that now naltrexone is being prescribed mostly by general practitioners and internists in private practices with very little counseling involved, and because of that, my guess is that it is not being taken as prescribed. I believe that even if the medication works pharmacologically, just don't hand somebody a pill and expect that they are going to take it the way they're supposed to take it and that it works. Additional follow-up is required. You need at least clinical management, and maybe even some psychological or 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 μ receptor antagonist be effective?
- JB: I don't know the answer to that question, but I believe they think it's because the opiate receptors and the dopamine receptors interact, and that causes the modulation of the dopamine receptor decreasing the pleasurable effect of alcohol and reducing craving for alcohol. 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: Few opiate addicts will take it. Well, some researchers are working on changing 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 in the late 1970s and involved with naltrexone, he felt that naltrexone wasn't a medication for all opiate addicts. Naltrexone was more appropriate for a subpopulation of opiate addicts who were highly motivated or in the early stages of their addiction.
- LH: Like in O'Brien's study.
- JB: Like in Chuck O'Brien's and Jim Cornish's studies; people who, such as physicians or other professionals who have something to lose and have a lot of strengths and psychosocial support. Also, for people who might be on parole or probation, who would lose their freedom if they use drug. 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 but nobody has actually studied this. Also naltrexone could be useful in the population of people who are chippers, but want to stop and are not opioid addicts yet. I think naltrexone would have some promise. The population it has been used on mostly is people who had beeen on detoxification from opiates, or those who have done well on methadone and are being tapered off it or are being switched to buprenorphine. These are very difficult populations to work with, at best.
- 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 well. They don't like it. It makes sense that if you blocked the endorphine system people might not feel as happy as they normally do.
- JB: Some opiate addicts report mild dysphoria when taking naltrexone, but that certainly isn't something that is common with naltrexone. Whether that is some kind of withdrawal...
- LH: ...or protracted abstinence...
- JB: ...it's unclear. But naltrexone hasn't been used successfully in opiate addicts. NIDA is now funding some studies with naltrexone in combination with behavioral therapies. For example, Bruce Rounsaville 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 they are meeting with some success. The addicts are reinforced with some vouchers of monetary value for providing drug-free urines. They don't actually get money, and they have to spend the vouchers on socially reinforcing items.
- LH: Like M&Ms.
- JB: Like movie tickets or items for their children.
- LH: How do you motivate kids without M&Ms?
- JB: Right. The vouchers can be spent on movie tickets or for gas or rent or things like that. 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 encourage people to take naltrexone. The value of the vouchers adds a little bit more motivation for continuing to take naltrexone and providing drug-free urines. The other side, you know, if you're dirty you go back to jail but 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?
- I've been involved with cocaine through funding research grants to JB: study medications and behavioral therapies to treat cocaine addicts. Unfortunately, I can't say that anyone has been too successful with medications for 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-1980s NIDA has been testing anything that might possibly work for cocaine, and NIDA is 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, looking for useful ones. They have put together a system of investigators who can now test promising drugs to come up with the right one. I think NIDA has the will and the capacity to be able to do it. NIDA investigators have been more successful finding behavioral therapies and counseling approaches that are helpful for cocaine addicts.
- LH: Is NIDA looking for a cocaine substitute or a cocaine blocker?
- JB: I think NIDA is looking for anything that would work. At this point, there hasn't been a focus on the substitute, although I think investigators are beginning to look at agonistic-like drugs that may be like a methadone

for cocaine. Obviously, there have been some thoughts about a cocaine antagonist. As you well know, the trouble is that cocaine works at the dopamine receptor and people probably need dopamine function to feel normal. So I don't know that an antagonist for dopamine would work. It may work for cocaine, but it would be bad for the individual. There has been some recent work to show that dopamine and cocaine work at a slightly different site on the reuptake pump. Possibly, if the cocaine site could be blocked but not the dopamine reuptake pump, that might work. Researchers are looking for drugs that might do that.

- LH: 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. I guess Tom Kosten has come up with a similar result.
- JB: Well, Tom Kosten tried bupropion in New Haven. I think it was a small open study. There were positive effects. This was in a population of opiate addicts who were on methadone but also were abusing cocaine, and he gave them bupropion in that context. Based on that small study, NIDA supported a three-site collaborative study. I know Walter Ling had one of the sites. I think Chuck O'Brien had another site as did Tom Kosten. And, again, in methadone-maintained opiate addicts who abused cocaine, bupropion was not effective. I was recently told that bupropion was being tested in cocaine addicts. An open study showed some positive results.
- 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 Medication Development Division is pursuing is finding a drug for the craving and relapse prevention.
- LH: That's hard to define.
- JB: The target behavior would be to prevent the compulsive drug use. It would not be an agonist or antagonist. This type of medication would be called a relapse prevention drug. Treatment programs are able to get cocaine addicts clean for a short period of time. They are able to stop taking the drug for weeks or sometimes even months; but there certainly is a strong tendency to relapse back to cocaine. It's unclear,

what is the neurobiological underpinning of cocaine craving and of the compulsive desire for the drug. A medication that would affect these behaviors might be different than an agonist or an antagonist.

- LH: 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 for anything else. 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 of NIMH?
- JB: I was working primarily with Bob Prien in the affective disorders section.
- LH: Was that the lithium study?
- JB: Bob 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 involved with that study. I was working with Bob on electroconvulsive therapy, which was the area that I was in charge of 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 for mania.
- LH: What was that, a comparison between ECT in bipolar depression versus unipolar depression?
- JB: Most of the studies that NIMH supported at the time were studies of different wavelengths or different pulse or sine waveforms or unilateral or bilateral electrode placements or energy levels of electroconvulsive therapy. There had already been a few sham ECT studies done in Europe, showing the advantage of ECT over sham ECT. So it wasn't believed that it was ethical in the United States to give somebody an anesthetic without giving actual treatment. NIMH supported grantees to do studies using low currents or sine wave versus brief pulses with different intensities, different electrode placements, to look at cutting down the side effects.
- LH: Unilateral versus...

- JB: Unilateral versus bilateral electrode placement, to see if the effectiveness of ECT could be maintained while decreasing the memory and confusion, 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: Bilateral, and 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 that drugs do have devastating effects on many people's lives. It is important that as clinicians and scientists, we work on finding treatments for the people who come to us and try to encourage people to come in for treatment so that they can have more functional lives. The daily functioning of many of the people who are addicted to these substances is very dramatically impacted in a negative way. 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, that is shifting more funding to prevention and treatment. I suspect that emphasis is still needed on the supply side to keep the flow of drugs out of the country; as well as to discourage the inventive chemists in the country from making up new abusable, 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: Probably drugs will always exist in society 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. It has become so much a part of our society!
- JB: That's true. Many people can use those drugs without problems, but many 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 partly in NIDA's purview as well as the National Cancer Institute's, and the Institute of Heart, Lung, and Blood's. So it's sort of split. Interestingly, I think that the physical harm from tobacco is very clear, causing heart disease, emphysema and cancer, and yet many, many people still become addicted to it and stay addicted to it because of the psychoactive effects 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: It is both the drug and the way the drug is administered.
- LH: You have to separate out the drug addiction from the smoking addiction.
- JB: With tobacco, people are more bothered by the physical harm that the tobacco causes than the addiction to the psychoactive substance, nicotine.
- LH: What thoughts do you have about marijuana, which is currently a drug of controversy?
- JB: I still think that, in some way 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 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 to think 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: I think Dole and Nyswander showed methadone to be useful for treatment of heroin addiction in the late 1960s and its use in narcotic treatment programs expanded in the 1970s.
- LH: So we haven't come a long way since.
- JB: We have made progress, but still have a long way to go
- LH: You have had an interesting career, Jack, shepherding all these things through the twirls of the government bureaucracy.
- JB: It has 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 and still enjoy a high level of regard, you know....
- JB: Thank you. I have been fortunate over the years to have worked with many others such as Pierre Renault and Lisa Onken at NIDA and Bob

Prien, Nina Schooler and Jerry Levine at NIMH who have had long and distinguished careers in the government and are well regarded in their fields.

- LH: It's a thankless effort. I want to thank you for coming this morning.
- JB: Thanks very much. It was my pleasure.

KANELLOS D. CHARALAMPOUS

Interviewed by Thomas A. Ban Acapulco, Mexico, December 14, 1999

- TB: We are at the 38th annual meeting of the American College of Neuropsychopharmacology in Acapulco, Mexico, at the Acapulco Princess Hotel. It is December 14, 1999, and I will be interviewing Dr. Kanellos Charalampous* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Let's start from the beginning.
- KC: I grew up in Greece, and I lived there until the age of nineteen. I grew up during difficult times. In 1940, the Nazi forces invaded Greece, and in 1944, when the Germans were still occupying the country, the civil war was already in progress. Communist guerillas tried to take Greece. My family was religious and right wing, and we were exposed to quite a bit of danger. My father, a physician, was practicing in an area controlled by communist guerillas. Since he did not join them, we were looked at as enemy. The civil war ended in 1949 and the same year I finished high school. I went to Athens to attend simultaneously the University of Athens and Panteios University. I studied philosophy, theology, and political science.

I came to the United States on Christmas 1950, directly to Texas, without knowing anything about Texas. In January 1951, I started college at the Texas Christian University, majoring in biology and chemistry. I graduated in 1954 with a double major. During my college years I took several courses in marine biology and received a fellowship to study oyster mortality. In those years there was a legal battle in Texas between the oyster growers and the oil companies. The oyster growers complained that the drilling offshore was killing the oysters. The Judge asked the opposing parties to bring forward research findings. Biologists were hired by the opposing parties to pursue research as to the cause of oyster mortality. I received a stipend from Humble Oil Company and went to Virginia Marine Institute as a member of a team of biologists on the defense side. I had my oyster trays in the James River. I also took a course in fish biology at William and Mary.

During my junior year in college, I decided to apply to medical school. Since I was a foreigner, I could not apply to state schools. I had to apply to private schools and I was fortunate to be accepted by Baylor College of Medicine in Houston. In 1954, I started medical school and graduated in 1958 with an MD. After the first year in medical school I

^{*} Kanellos D. Charalampous was born in Athens, Greece in 1931.

had to work because I could not receive any money from home. I got a clinical clerkship in the Houston VA Hospital, and was assigned to assist two psychiatrists. One was Dr. Charlie Gates, who was doing a study with chlorpromazine, and the other was Dr. Alex Pokorney, the director of psychiatry at the Houston VA Hospital. I did the statistical evaluation for their studies. Actually, in Houston, studies of chlorpromazine had begun before 1955. In 1953, Professor Eugene Khan at Baylor, a student of Emile Kraepelin, had read in the French literature the papers of Laborit, Delay and Deniker, and he communicated this information to John Kinross-Wright, a Professor of Psychiatry at Baylor. John Kinross-Wright began clinical investigations with Thorazine (chlorpromazine). Kinross-Wright was also studying another compound, NP207 that was abandoned later, because it caused pigmentary retinopathy. Kinross-Wright was a very good clinician. He started a psychopharmacological research center at Baylor that was one of the six psychopharmacology centers at the time in the United States.

When I was a student at Baylor I did a fellowship with Dr. William Spencer, a pioneer in rehabilitation. The study was on the oxygen consumption of polio patients using respirators. I also assisted Professor Arthur Keats in the clinical evaluation of new compounds in the control of postoperative pain.

Between 1958 and 1959 I completed my internship at the city hospital of Houston. At Baylor Medical School I had two great professors. One was Hebel Hoff who discovered the physiograph. The other great professor was Michael E. DeBakey, my professor in surgery. As a freshman, these professors impressed me with the idea that the complete physician should be a clinician, a researcher, and a teacher. I was debating whether to stay in the United States or go back to Europe. I decided to stay in the United States and thought that the new frontier should be in brain diseases.

I started my residency in psychiatry at the Baylor College of Medicine and affiliated hospitals.

One good thing that happened in Texas in 1949 was the establishment of the Psychiatric Institute in Houston. It was a state facility. The plan was to upgrade the Public Health System in Psychiatry in Texas with an institute for research and training. The original plan also included the establishment of two other Institutes, one in Dallas and one in San Antonio. These however, were not funded. The one in Houston was funded and was directed by William T. Lhaman, who later became Professor and Chairman at Cornell. Dr. Lhaman put together a very good program for the Psychiatric Institute and in the 1950s he encouraged Dr. Kinross-Wright to develop psychopharmacology. The program in psychophysiology at the Institute, directed by Neil Burch, was also a strong one. He was pursuing research in sleep and did period analysis of EEG.

I had an elective in research while I was a resident. I had to make a decision whether I should work with Dr. Neil Burch or Dr. Kinross-Wright. Dr. Neil Burch was very easy going and Dr. Kinross-Wright was aloof. I decided that psychopharmacology would be more interesting to pursue. Dr Kinross-Wright gave me a drug to work with that had only been studied in small animals before. It was the enanthic ester of fluphenazine. I gave it to dogs first and then to monkeys. In 1962 I took it to the psychopharmacology unit at the Texas Department of Corrections in Huntsville and carefully, I gave it to human volunteers. I concluded that fluphenazine enanthate, in doses of 25 mg given in one cc. of sesame oil, when given to patients with schizophrenia would decrease their symptoms. I also found that its clinical activity could last up to two weeks. These observations were followed up by a controlled study first in which fluphenazine hydrochloride was compared to fluphenazine enanthate, and later by a study of fluphenazine enanthate in maintenance therapy and relapse prevention.

When I finished my residency, I joined the faculty of psychiatry at Baylor and was appointed as associate chief of the psychopharmacology center at Baylor. This center had several inpatient units but no outpatient unit. I suggested to Dr. Kinross-Wright that we complement the center with an outpatient clinic. One day, unexpectedly, he said, "Let's go to Austin and talk to the Superintendent of the State Hospital". Patients from Houston had to go 164 miles away to Austin for their psychiatric inpatient care. We visited with the Superintendent, Dr. Sam Hoerster, a sensitive and caring physician and he agreed to send the patients from Houston upon discharge to our new outpatient clinic. I directed the clinic for three years from 1963 to 1965. Controlled studies confirmed that aggressive aftercare with medication maintenance could reduce re-hospitalization significantly.

- TB: Did you publish your results with fluphenazine enanthate?
- KC: Those results were published in 1964, and then some of our later results were published in 1965. In 1963, I had also started to do basic research. I was interested in studying mescaline. I went to the nuclear medicine department, got experience in isotope studies, and got my license to do isotope studies from the Atomic Energy Commission. I used isotopes in clearance studies primarily with newer antipsychotics but also with antidepressants. I did clearance studies with tritiated protriptyline,

thioridazine, haloperidol, and mesoridazine. I used ¹⁴C in my studies with mescaline and did the definitive study on the metabolism of mescaline in man. Those studies were published in *Psychopharmacologia* in 1965 and 1966. I presented the data also in one of the early symposia at the ACNP meeting in San Juan, Puerto Rico.

- TB: Could you tell us something about your findings?
- KC: We identified all the metabolites of mescaline, and then, we tried to see if any of them were active. That was not the case. By the time I completed the studies with mescaline, a report appeared in literature by Arnold Friedhoff on a "pink spot" he found, allegedly in the urine of schizophrenics only. He claimed that it was not present in the urine of non-schizophrenic patients. From the literature we surmised that the "pink spot" was dimethoxyphenylethylamine. We got the substance, got it isotope-labeled, and gave it to human volunteers. We found that its largest metabolite in the urine was an acid. We studied it also in plasma and spinal fluid. I gave dimethoxyphenylethylamine to human volunteers and found that it has no activity. I gave it in a dose as high as 11 mg per kilogram of body weight. To decelerate the breakdown of the substance I pre-treated the subjects with a monoamine oxidase inhibitor. There was no activity. These findings were published in the Journal of Pharmacology and Experimental Therapeutics. Two years later Arnold Friedhoff published a similar study in mice. To my surprise our paper was not included in his references. In any case, the hypothesis about the role of the pink spot in the etiology of schizophrenia could not be substantiated.
- TB: So, you were the first to study the effects dimethoxyphenylethylamine, and among the first to question the theory that schizophrenia is the result of an endogenous, toxic, catecholamine metabolite.
- KC: Right. As you recall, in those years there was also a great deal of interest in the study of indoleamines and β-carbolines. In the Psychiatric Institute, there was a biochemist who was studying β-carbolines. This particular line of work had not proved useful. With Dr. Kinross-Wright at Baylor, we did several studies with phenothiazines, tricyclic antidepressants and hallucinogens. I did not take part in any of the studies for the defense establishment. Altogether, I participated in about one hundred clinical studies. Many of these studies were not published because of the desire to publish only controlled studies, or those with positive results. I think we made a mistake. They were primarily late Phase I and early Phase II studies. In retrospect, we should have published more of them.
- TB: Can you recall just a few of the drugs you worked with at the time?

KC: Most of them were phenothiazine analogues; many were antidepressants and indole amines. We did some studies with dopa decarboxylase inhibitors together with monoamine oxidase inhibitors and we did studies with methyldopa and α-methyl-paratyrosine. We did also some studies with GABA.

In 1965, we had a new Director at the Psychiatric Institute, Dr. Shervert Frazier. Dr. Frazier initiated significant epidemiological studies in the state hospitals in Texas. Prior to his arrival, a new law, House Bill 3, for the care of the mentally ill had passed in Texas. The law was signed in 1963 by the governor of Texas, John Connally. John Connally had considerable sensitivity for psychiatric disorders. He did, I think, two great things for Texas. He created a board of higher education for the state that upgraded the university system. He also created a very strong basis for subsequent development in computer science and industrialization of the state. Also, he used House Bill 3 to upgrade the mental health system in Texas by appointing Dr. Frazier, mental health commissioner. When Dr. Frazier permanently returned to the eastern United States, Dr. Kinross-Wright succeeded him as mental health commissioner.

I decided to leave Baylor and went to Oklahoma to work with Dr. Jollyon West, a flamboyant psychiatrist. He had, before my arrival, inadvertently killed an elephant from the Oklahoma Zoo, overdosing him with LSD while trying to produce a model psychosis. The elephant had two convulsions, fell over, and died.

In the department of medicine at the University of Oklahoma, there was a strong clinical pharmacology division. Doctors Colemore and Clark had a clinical psychopharmacology program in the prison system at McAllister, Oklahoma and another one in the Central State Hospital in Norman, Oklahoma. I participated in some of their studies.

When I was informed that Dr. Jollyon West was moving to UCLA, I decided to leave Oklahoma. I went to Dallas and joined Southwestern Medical School, ostensibly to help with the development of a psychiatric research institute. I continued with my studies in psychopharmacology there, and did some research with benzodiazepines. One of the substances I worked with was clorazepate. I had negative findings. This particular drug did not prove to be successful in the market place.

- TB: In what dosage did you use clorazepate?
- KC: I think I used up to 30 mg; I thought it would be sufficient. While I was in Dallas, I became the Clinical Director of the Woodlawn Hospital, an affiliate of Parkland Hospital. It was a seventy-bed hospital for the psychiatric care of adolescents.

Before I went to Dallas, I made a trip to Geneva to meet with officials of the WHO drug abuse section. From there I went to Turkey and Greece and Morocco to study marijuana/hashish and to interview both users of hashish and health care professionals. When I came back to the United States I gave a number of talks about marijuana/hashish. I had also gone to the British Museum to study the six volumes of the Royal Hemp Commission, a report on India's use of marijuana. With this information I invited a panel of experts for a section meeting of the American Psychiatric Association in Boston in the mid-1960s. I invited the most significant persons in the control of drug abuse in the United States. These people came happily to Boston to discuss the dangers of marijuana use. While the meeting was going on, the doors burst open and students from Harvard and Boston University came in and the meeting was dissolved.

- TB: What did they do?
- KC: They started yelling at the government officials. The pandemonium disrupted the meeting. I had also collected a large amount of literature with the idea to write a book. After this experience I felt the subject was too emotional to deal with.
- TB: Tell us more about your work with marijuana.
- KC: When in Turkey, I interviewed 13 hashish smokers. Twelve of them said that they would be terribly unhappy if a son of theirs became a user. Clinicians on the other hand had a different view. They felt the issue to be a societal one and not a medical one. In the 1970s, I wrote articles about drug dependency and drug abuse. I felt that the control of drug abuse should not be exclusively with the judicial system, because control without rehabilitation would be futile. The health care community should have active participation in the rehabilitation of the chemically dependent.
- TB: So, you did a lot of reading on the subject, interviewed users and those who treated the users.
- KC: Exactly. There was a professor in Athens, Dr. M. Strigaris, who had written a monograph on hashish. This physician was a student of Professor Lewin in Heidelberg, who had written a monograph on mescaline. Professor Lewin had encouraged Dr. Strigaris, psychiatrist from Greece to study hashish. When I went to Greece in 1966, I visited with Dr. Strigaris. He gave me his monograph and I had an extensive discussion about his clinical experience. In Greece, the prevailing opinion was that the user was going to decline psychologically.

In Greece, in the 1960s, there was a rediscovery of folk music, the boozooki music, otherwise known as rebetico. Musicians of this genre

used to smoke marijuana and hashish. A famous boozooki player, Vassilis Tsitsanis, used to smoke marijuana and I went to interview him. His personality was intact and his musical skills were undiminished.

Professor Gerald Caplan of Harvard University had a grant from NIMH to train psychiatrists in Community Psychiatry. He was using a systems approach for mental health consultation. I joined the class from 1968 to 1971. I enjoyed this fellowship and I believed there was going to be a future in Community Psychiatry in the United States.

- TB: When did you return to Baylor?
- KC: In 1972, I was invited to return to Baylor, and was asked to be the Director of Community Psychiatry in the Department of Psychiatry. Shortly before I got to Baylor, 2 of my colleagues had died. One was Dr. Moody Bettis, the head of Community Psychiatry.

There was another program at Baylor in need of leadership. The Department of Transportation was giving grants to several universities in the United States, some grants to study engineering aspects of vehicular deaths and others to study the effects of alcohol on drivers. My friend and colleague, Dr. John Finch, had applied for a grant to study the behavioral effects of alcohol on driving, DWI offenders, and rehabilitative initiatives that would help to separate drinking from driving. Unfortunately, Dr. Finch and his family perished in a fire in New Orleans inside an elevator of a hotel. When I got to Baylor, I was asked to direct this particular grant. As it was a large grant, I had to recruit several persons. According to protocol, I tried to create relationships with important community resources, such as the probation department and the DA's office. I developed diagnostic facilities for rehabilitation. The project did not receive the attention of the judicial system we were hoping for. A typical DWI offender would get a probated sentence without the judges sending them for rehabilitation. The defense lawyers did not support the idea of any conditions as part of probation. We tried to persuade the judges, separately, with no success. It became clear to me that "law and order" is not the avenue for the control of drug abuse. We found that DWI offenders were mostly not social drinkers. We found that fifty-seven percent of them were alcoholics and would repeat the offenses many times because of alcohol dependence. With this knowledge and several good professionals as part of the grant, we did some studies to find the best tests for early diagnosis of alcoholism in the general population. I decided to locate one of the early clinical inpatient programs for the rehabilitation of alcoholics in a large general hospital. Despite some early resistance, this program thrived and became a valuable teaching experience for students and residents.

At Baylor, I also started an anxiety-depression clinic for outpatient studies.

In 1973 I received a grant from NIMH to study cyclic nucleotides in the brain after alcohol and morphine administration in animals. With my associate, Bill Askew, PhD, we generated several publications, one of them in the *Journal of Pharmacology and Experimental Therapeutics*.

- TB: Didn't you become Chairman of a department in Texas?
- KC: In 1978, I became Chairman of the Department of Psychiatry at Texas Tech, a new medical school. I tried to develop a modern department of psychiatry and I stayed there as the Chairman for two years. After attending a number of seminars in medical economics, I became aware that the practice of medicine in general and psychiatry in particular was to be changed radically. I decided then to return to Houston. It was 1980, when I went to full time private practice. I also assumed the position as director of an acute admissions center for individuals who had severe psychiatric problems. They had to be evaluated and likely committed to a state facility. When I visited that center I found that patients sent there would be left for two whole weeks without any kind of treatment, during which time they would regress to the extent that the center would look medieval. I had been exposed to something I read in medical literature, and saw when I had visited psychiatric hospitals in southern European back in the 1950s and 1960s. I inquired from the legal services of the State Department of Mental Health whether it would be permissible to give the patients medicines without delay. The answer was no. No medications could be given because these patients were there involuntarily. The judge had to see them first and decide about their disposition. The legal services department added that in an emergency, it was permissible to give medication. I started evaluating the patients, carefully assessing their clinical status. After assessing their status as emergencies, I started prescribing antipsychotic medications and the facility was transformed. The staff started group therapy and art therapy, and many of these individuals did not have to be committed any longer. The administration of medication would permit them to go home. I organized, in Texas, a society for psychiatric administrators, hoping to help forestall the consequences of managed care. With managed care, the stigma of mental illness has returned. In that regard, we have regressed. On the other hand, we now find greater collaboration between neurology and psychiatry. In my clinical practice, I found that it was good to thoroughly evaluate my patients, together with input from internal medicine and neurology. Recently I decided to guit practice and do only some teaching in psychopathology and psychopharmacology.

I also supervise residents at the Medical School of the University of Texas in Houston. I decided to study as well the history of psychiatry in Texas. Many of the individuals, who started the psychiatric societies in Houston in 1954 and at the state level, have died.

- TB: When did Kinross-Wright die?
- KC: Dr. Kinross-Wright died in October 1999. Many psychiatrists, who had studied with Dr. Titus Harris when he was the Chairman of Psychiatry at Galveston, have died by now. In 1954 Titus Harris organized the first symposium in psychopharmacology for the American Psychiatric Association. Dr. Kinross-Wright was the main speaker.
- TB: When you say history of psychiatry in Texas, do you mean history of psychopharmacology?
- KC: I was talking essentially about psychopharmacology. Psychopharmacology in Texas started with Dr. Kinross-Wright. Progressively, the emphasis changed by stressing aftercare, and the comprehensive treatment of drug dependence.
- TB: You probably had many associates. Would you name a few of them?
- KC: Yes, in my research, I had some excellent collaborators, like Wayne Tansey, Bill Askew, P.C. Johnson, T.J. Skinner, W.K Huber, A.H. Vogt, A. Hug, L.E. Walker, S.A. Brown, M.L. Clark, and B.J. Zung. I had the good fortune that several of my residents choose psychopharmacology as their elective. A few of them became academic psychiatrists, e.g., Chris Sermas, George Keepers, and George Freemesser. Other associates became interested in alcohol rehabilitation. When I was at Texas Tech, I had several individuals who were interested in drug rehabilitation but I had no program. After we started a chemical dependency program, we trained outstanding counselors. A few of them came from the ministry. Some of them were priests, who had left the church, but had a great interest in the treatment and rehabilitation of patients. I am convinced that my choice of psychiatry and research in psychopharmacology was a very good choice. In the beginning, colleagues involved in psychoanalysis were somewhat resistant of our initiatives in psychopharmacology. The departments where I was, like Southwestern in Dallas, and Baylor in Houston, have developed productive centers in neuroscience.
- TB: You contributed, to many areas of the field. What would you consider your most important contribution?
- KC: Both basic research and clinical research are necessary for psychiatry. Additionally in order to give comprehensive and continuous care, you have to collaborate. You have to bring in many other colleagues from other mental health fields. That is something I learned from Dr. Jolly

West in Oklahoma. I felt on occasion that I lost some time by studying Community Psychiatry, but in terms of the importance to patients, I feel very happy that I developed a number of clinical centers and aftercare clinics.

- TB: So, you consider one of your important contributions to the field is the establishment of centers for clinical and basic research.
- KC: Yes, because the question is how to apply research findings to patient care. Dr. Kinross-Wright had many good initiatives. For instance, he had started a large center in the prison system. When Dr. Frazier followed him, we developed relationships with the state hospitals. Later on, I revamped the unit for the criminally insane and tried to introduce more diligent work in assessing and documenting psychopathology, creating a clinical chart. The mental health system has decreased in its scope and incarceration has exploded. Seventy percent of those individuals are there for drug abuse and very little rehabilitation is taking place. I feel that mental health and psychiatry should be given a greater priority in public health. The ideas of Professor Gerald Caplan, in Community Psychiatry need to be applied.
- TB: Do you think that those centers you established could play an important role in the community?
- KC: Yes, because the centers proved themselves. The centers became very popular among the public. The clinic I started in Houston became so big that it took over the Psychiatric Institute and compromised research. As a result, the Institute was taken from the state psychiatric system and given back to the psychiatric department of a medical school. I feel that a balance has to exist in academic medicine, and in psychiatry between clinical work and research. You cannot teach psychiatry in theory only. I think one of the things that I learned from great physicians like Michael DeBakey and Denton Cooley is that research has to move concurrently with clinical excellence. I felt that I was very lucky to have professors of that caliber in medical school.
- TB: Am I correct that you said that your current activities are restricted to teaching?
- KC: Yes.
- TB: So you have retired from your other activities?
- KC: I retired from clinical practice.
- TB: When?
- KC: Very recently.
- TB: You have been teaching all through your professional life. Have you been teaching also in departments outside of psychiatry?

- KC: Other departments in medical school do not want psychiatrists in their teaching programs. They want psychologists. We have this competition between psychologists and psychiatrists.
- TB: Do you feel very strongly that psychiatrists should do the teaching?
- KC: Very much so.
- TB: Wereyouteachingprimarilypsychopharmacologyandpsychopathology?
- KC: Psychopathology, community psychiatry and psychopharmacology.
- TB: So, you feel your greatest contribution was that you implemented a comprehensive system for psychiatric services in Texas?
- KC: Yes. As we know, the American society is changing. We have very many immigrants. We have people who really have difficulty in communicating. We have individuals with problems of self-esteem. We have difficulties in education, and people have problems in planning their future. The role of psychiatry is not simply to deal with symptoms, but to assist in personality development and life planning.
- TB: You are a member of many societies. When did you become a member of the ACNP?
- KC: I submitted my application in 1964, and I became a member in 1965. I became a member of CINP more recently. I have been a member of The Society of Neuroscience and of Biological Psychiatry from the 1960s.
- TB: Did you serve on committees in these societies?
- KC: I served on many committees, but mostly at the state level, in administrative committees and planning committees. Recently I received the award for "Excellence in Psychiatry" by The Texas Psychiatric Society. I served on committees in the Texas Medical Association, the Texas Psychiatric Association, and the APA. I was a member of the state mental health board for eight years. For four years, I was the chairman.
- TB: You have also published many papers?
- KC: Yes.
- TB: One of the early papers you mentioned was published on a long-acting phenothiazine preparation. Would you like to talk about that?
- KC: Yes. I feel the long acting preparations help the patients with compliance. When Squibb developed fluphenazine enanthate, the first long acting medication, the company did not market it well. However, when other long acting preparations came along the distribution and use of long-acting preparations improved.
- TB: Is there anything you would like to add?
- KC: I want to express my gratitude to this society, the American College of Neuropsychopharmacology, for promoting balance between basic and clinical research. When I was taking my boards in 1965, I had to

take exams in basic and clinical neurology. One third of the exam was in neurology and I really enjoyed whatever knowledge I had learned. It seems now that neurology is coming back. It took practically fifty years for neuroscience to become involved.

- TB: Well, thank you very much. Hope you will continue teaching for many years to come.
- KC: Thank you very much.

JEROME H. JAFFE

Interviewed by Leo E. Hollister Las Croabas, Puerto Rico, December 1, 1998

- 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?
- I got into both, more or less, by accident. I hadn't planned to go into JJ: medicine. I became involved in Psychology as an undergraduate, much influenced by Hubert Hamilton, the Chairman and Professor of Psychology at Temple, a wonderful man, but, I think, under appreciated by others. He studied animal behavior, and I got very interested in it and I thought I wanted to do research in psychology. He advised me, this was back in 1952 or '53, there was not much support for that and that if I wanted to do research I should probably go to medical school. And there were others who were influencing me in that direction. It was not something I had looked forward to, but I decided to apply to medical school and then found out that you had to have taken an exam a year before. I hadn't done that, so I was left with some time before I could apply, so I continued with some of the research I was doing and took a Master's degree in Experimental Psychology. Just about that time, chlorpromazine came out, and reserpine. The era of psychopharmacology was beginning just as I was making that decision and the work I was doing on animal behavior looked like it would apply in that way. 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.
- LH: 1954. Boy, you really came in just at the hour.
- JJ: Exactly at the beginning. I remember they were still talking about chlorpromazine as an antiemetic. 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 they were of the analytic

^{*} Jerome H. Jaffe was born in Philadelphia, Pennsylvania in 1933.

school and I was used to using scientific methods to decide what is true. I challenged them and they did not like that very much. I would ask questions that did not fit very well with what was being taught.

- LH: Conflict between philosophies.
- JJ: Yes. But, some time in 1957 or '58, I was in the library and came across Abe Wikler's book, and that was a magnificent literature review.
- LH: Oh, you mean that paper bound, The Relationship Between Psychiatry and Pharmacology?
- JJ: Yes, the paper bound, *The Relation of Psychiatry to Pharmacology*.
- LH: That was a classic.
- JJ: It was a classic. By that time, I'd had a summer Fellowship in psychopharmacology. There was one professor of pharmacology, an assistant professor at the time, Sydney Ellis, who felt I had some promise and allowed me to work in his lab for the summer doing some research, and that was a good experience. Then, Wikler's book came along and I was pretty well set that psychopharmacology was where I was going to go. It was just about the time that I had to choose my internship and I thought, Wikler is at Lexington and so that's, obviously, the place to go to study - in the Public Health Service with Wikler. But, I didn't know enough about the bureaucracy of the Public Health Service. After I signed on the dotted line. I realized that I had committed myself to the clinical division and that if they ever sent me to Lexington it would be to help staff the hospital. I hadn't realized that Wikler was in a separate division, the Addiction Research Center, which was administratively guite distinct. After my internship at the Public Health Service Hospital on Staten Island, I applied for the psychiatry residency, which was at Lexington, and was assigned there. At least that much was fortunate and I did get to meet and interact with Wikler during my time there.
- LH: Lexington was the playing field of all those giants in the field.
- JJ: Abe Wikler, Harris Isbell, Bill Martin were there. There were also people doing good 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 was. I was still interested in psychopharmacology in a general sense. After I did one year the PHS wanted me to complete my residency there, for another two years. At the time, the more time you put into residency training, the more time you owed them. I looked

at what Wikler had done with his career and I spoke to others, and it was clear that he studied basic science before he really got into psychiatry. I decided that I wanted to study more pharmacology before I got into dealing with what was then the dominant dynamic perspective of psychiatry. Sydney Ellis, with whom I had stayed in touch, suggested that I look into Al Gilman's department at Albert Einstein. Now, that was kind of awesome, because we had used Goodman and Gilman as a textbook. So, when I decided I was going to leave the Public Health Service I applied to what was then an interdisciplinary program, in the neurosciences, I think, at Albert Einstein, and much to my surprise they said they'd like to have me come there. That was very nice. I met Seth Sharpless and Murray Jarvik, and it was really a new world for me, really bright, sharp minds. Al Gilman said, "What you would like to do"? Well, nobody ever said that to me before, what would I like to do? I got to talking with Seth 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. We began to elaborate the notion that maybe some aspects of opiate withdrawal or withdrawal in general were due to denervation supersensitivity or, at least to functional reductions in neural input. And that was great. We elaborated on it and we came up with a series of experiments, and that's sort of how I proceeded.

- LH: I see in 1969, you and Sharpless wrote a book chapter on *Withdrawal Phenomena as Manifestations of Disuse Supersensitivity.*
- Well, actually, we started long before 1969. We began this work in JJ: about 1961. We got our first experiments done and published abstracts in The Pharmacologist in 1963 on barbiturate withdrawal denervation supersensitivity. But, just as we were about to say, "Isn't this a terrific idea", Emmelin 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 postsynaptic 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, but it was intracellular changes that probably accounted for some of the changes in sensitivity. But, then, some other things happened.
- LH: Now, this is about the time that a number of theories emerged that still are, I guess, standard in the development of tolerance and dependence.

I think, Avram Goldstein, Joe Cochin, and Lew Shuster, all three of them, presented one almost simultaneously.

- JJ: And, they all presented at a meeting that Abe Wikler convened on the addictive states. The Proceedings were published in 1968. I think it took place in 1967. We, also, presented the notion of supersensitivity as one of the phenomena that might explain withdrawal. 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 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, nearly everything that came up at Einstein that had to do with addiction was referred to me, even though I was still a post-doc and, at this point, a Fellow in pharmacology. I decided that while I was studying this denervation supersensitivity, I ought to go back and finish off the residency in psychiatry. I had done one year at Lexington. I managed to do it all simultaneously, so by 1964 I had finished the residency in psychiatry, and was still working with Seth Sharpless and teaching in Gilman's department. Then, it seemed like the world was changing. Addiction became a major issue. I got involved in clinical work. 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 now an antagonist that allowed one to test Abe Wikler's theory, which was a theory of conditioning phenomena as explanations of withdrawal.
- LH: Conditioned abstinence and withdrawal.
- JJ: Yes. Possibly you could block the reinitiation of physical dependence with an antagonist. After a while, there would be no reinforcement of drug using behavior. 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 1967, but even then the notion that there really was a receptor wasn't particularly clear. This was '64. We knew that cyclazocine 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, get some cyclazocine from the company, and I had all these opiate addicted patients who knew me at Lexington and were back in New York calling me up, saying, "Don't you have anything

that we could do; what kind of treatment can you offer"? We actually tried cyclazocine, and published on the work in 1966. That was the first clinical trial on cyclazocine ever done. And, the amazing part was, here was a drug that didn't give you any real reinforcement. As a matter of fact, it had some aversive qualities.

- LH: It was a mixed agonist and antagonist, wasn't it?
- Yes, it was, but people wanted to guit heroin badly enough that they JJ: would try it and that didn't surprise me. I met a lot of people at Lexington that were, I thought, likeable people. I didn't have any of these bad images of addicts that the world had because I had met so many of them. So, somehow, by 1965, I was deep into the notion of working on addiction; I mean both clinically and 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 post-synaptic changes. I was also trying to do some limited clinical work to see whether addicts do, indeed, develop so much tolerance to opiates that you have to escalate the dosage. I did a study that was never published, where we were providing intravenous opiates to a select group of addicts. I was visited by the Bureau of Narcotics about every two weeks. They were quite respectful, but they wanted to know exactly what I was doing. Then, again, fate intervened. Just about that time, I heard Vincent Dole give a talk, and met Vince and Marie Nyswander. Then I tried giving patients methadone instead of intravenous opioids, and there was something very, very different about the addicts' behavior, so it sort of confirmed what Vince had found out. On a single oral dose of methadone, they felt different, and treatment 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 there was an issue of people coming back every day, and I did what was probably the first ambulatory stabilization on methadone at that time. This work was all done at Einstein. When I had left Lexington, Wikler, Isbell, Frazier, and Martin gave me reprints of all their work - about twentyfive years worth of them - and I had read them all, because I'd been asked by Al Gilman, in 1963 or '64, to write a chapter on addiction for the Third Edition of Goodman & Gilman s The Pharmacological Basis of Therapeutics, which came out in 1965. I was the first person to write on both opiates and drug addiction for that multi-authored textbook. I was pretty junior, so I tried to read everything I could and I read all of those papers from Lexington, and I came across a drug called I-alphaacetyl-methadol (LAAM). It had been totally forgotten. People thought it was too toxic. 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 burden for the patient. So, I thought, gee, isn't this wonderful? And I wrote up a grant application and it was pretty good, but then I wondered where I would do this treatment. I'd done the cyclazocine work, actually, in Sam Barondes' office. He had this little, tiny room, maybe eight seats outside of his lab, and he'd allowed me to use that to do a little group therapy with the cyclazocine patients, but I couldn't imagine having people coming back there every single day to pick up the LAAM, and I didn't think it should be given out for self-administration. I tried to find space where I could do this study. This was, I guess, about 1966. Nobody in our psychiatry department was interested in addiction and it was not something that they wanted to get involved with. At the time, Enstein had an empty TB hospital at Bronx Municipal, and I tried to get one room there, but they told me they couldn't find any space. They had empty floors and rooms filled with old iron lungs, but they couldn't find any space. I was not about to put in the grant application if there was no place where I could actually implement it. Again, chance intervened and Danny Freedman asked me to join his department at the University of Chicago. That came about because by chance I had put on a symposium on drug abuse at Einstein and Danny was the obvious man to talk 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 Schuster and Paul Blachley.
- JJ: Yes, that was in, I think, '69. What happened was this. I had the drug because I knew Paul Blachley. He had a supply left over from the analgesic trials he conducted in the early 1960s. This was now the mid-1960s, and we were going to collaborate on the first clinical trial, but there was no place at Einstein where I could implement it, and I don't think he had enough heroin addicts out in Portland at that time. Danny Freedman met me during the symposium I organized, and shortly afterwards when he had accepted the Chairmanship at Chicago he offered me a position there. I accepted because there were some things I wanted to do and I could see that Einstein was not supportive. One of the things that I wanted to do was to study LAAM, which is what we called it at the time. I got out there by 1967, and the rest of my Chicago story has to do with creating the Illinois Drug Abuse Program.
- LH: But, before we leave LAAM, isn't there something of a frustration for you to be one of the first people to use it and, then, find that it took another thirty years before it come into general use?
- JJ: It was only about twenty-four years, I think.

- LH: Well, I thought LAAM came into general use only a few years ago...
- JJ: Well, I think it was only from about 1968. Well, it was a tremendous frustration, but I guess you learn that government doesn't always see things with the same sense of urgency as the clinician does. And, as you recall, I got an opportunity to actually expand the use of LAAM, briefly, in the early seventies, when I was in government in a position to do so. And, then, for a variety of reasons, it was put on a back burner and only in 1993 or '94, I think, did it get approved for use.
- LH: I think so. I had a little later date in mind, but it was somewhere in the 1990s.
- JJ: But even after that it still had to be approved at each State level, because it was still a Schedule I drug; so, although the Federal Government approved it, it took work at every State legislature to get it 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 about addiction that was different from that of most 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 thought that whatever its origins and he had some views on its pathogenesis, once it developed it was *sui generis* - it was a thing unto itself. I always said, and I wrote in an obituary for Abe, that 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 and to summarize them and 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 a quite humorous man, easily approachable, but 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 what 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 interesting thing about him, is that he'd actually set out to study with some of the best people in the world. 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, no.
- JJ: He learned Russian; he read Russian. There were equally impressive people that he'd taken Fellowships with, really great physiologists, some of them at Yale where he spent six months studying neurophysiology. When you look at his early work, you see 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 where he took these sabbaticals to study. They were not actually 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 range of knowledge of remarkable things.
- LH: Well, you were lucky to have had him as a mentor. Okay, so Danny invited you to come to Chicago.Then...
- I guess he invited me in early '66, just at the time that I was concluding JJ: that Einstein really did not have enough interest in addictions to help move the obstacles out of the way so I could start a clinical program. And, with some reluctance, I said, "yes". Then, Danny was asked by the Governor's Drug Abuse Advisory Council to provide them with advice on what to do about the addiction problem in Illinois. By this time, I had become familiar with at least five major ways you could deal with heroin addiction. There were maintenance approaches, methadone and LAAM. 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 Daytop Village on Staten Island. David Deitch, the Clinical Director, was guite courteous to me and I'd learned that there was something special going on here. This is not psychotherapy, but it works. People changed and they got better. There was also compulsory treatment. And, then, of course, there was detox. We had detoxed lots of people at Lexington. I took care of about 3,000 people during my last year there.
- LH: But, the recidivism rate was very high.
- JJ: The recidivism rate was very high, but it wasn't a hundred percent. Some people got better. Now, why? And, given that you have all these approaches, how do you decide which one to use? Do you 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 Governor's Drug Abuse Advisory Council when Danny sent me there as a consultant in his place. Danny had many, many interests, as most people know. He was a major mover and shaker in the world of psychiatry and, particularly, in the research aspects of mental health. He didn't attend all of those meetings, so, I was sort of the representative of psychiatry at this meeting. They first considered civil commitment. That was the thing in 1966. The Federal government had just passed the Narcotic Addict Rehabilitation Act (NARA) in 1966, which would have required people to stay six months at Lexington, after which they would have supervision. Illinois was considering that; and they were considering therapeutic communities. They had not considered methadone, and they were just debating which of these things should they do? And I said. I don't see that there can be much debate because 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 by developing a program that would compare the different treatments. 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 it turned out it was novel. But, it was absolutely logical. How do you decide on which of several treatments you use? You do an experiment. Well, apparently, States and governments don't usually do that, but the Council pondered this idea and no matter what they came up with, they also concluded it was logical. And, so, they put in a bill to the State legislature. This was in early 1967 or late '66. It asked for money for a drug abuse treatment program that would compare different treatments. They asked for what was then a lot of money, about a million dollars. That was big money back then. What I was told by the Chairman of this Advisory Council was, "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 my Research Career Development Award to study tolerance and physical dependence. 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 and limited experience with treatment. I was still finishing up in New York, but I had been going out to Chicago over several months as an advisor, I guess from mid-1966 to the beginning of '67. During that time

I began meeting a lot of people in Illinois who were addicted, or who had partially recovered, and they were decent people. 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 might give you some chlorpromazine or something like that. That's all they had. There were no long or short term facilities. There was nothing. So, I felt it was sort of on my shoulders whether or not that situation in 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 agreed to do it. That put me in the position of starting with a team of one. How do you get enough people to implement three or four different treatment modalities so that you can compare them? That was not going to be an easy task, and within a year it became guite apparent that you cannot be competent in a laboratory, build that laboratory, pursue that research, be the head of a state government program and, also, the only clinician implementing that program, trying to train everybody else who comes on board. 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 of trying to build this Illinois Drug Abuse Program (IDAP) 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. So, I was the Director of the Illinois Drug Abuse Program and built those programs. We did a lot of innovative things and Danny was very supportive, actually, except about giving back the money.
- LH: That is so hard to get.
- JJ: Well, I didn't know that. I mean, you have to remember, I was only about thirty-three at the time. I didn't know how hard it was to get money. I'd never had any difficulty with that before. I was on a postdoctoral fellowship 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 of Chicago 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?

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- JJ: Yes, 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, a detoxification unit where we could use cyclazocine after detox, and I recruited some people in to start a therapeutic community. We didn't get any help from Synanon. They were not interested in being looked at or evaluated, so we started our own therapeutic community using people who had trained in those methods, found a place to house it, and began to build that program. And, within a year we had a model of a therapeutic community; we had detoxification; we were using cyclazocine because there was still no other antagonist, and we had methadone on an ambulatory basis. Within the second year, I was able to recruit some good people to the program staff, including Bob Schuster and Patrick Hughes.
- LH: Ed Senay?
- JJ: Ed Senay was already at the University of Chicago. 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 in the Department of Psychiatry running the Consultation Liaison service. And, so, we were doing all these things, and within a year we had conducted the first experiments on LAAM. Things were really moving along and we continued to innovate, build and expand IDAP, and we actually did do a study 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. They usually knew what they wanted and you couldn't assign them to something else, even if you have a monopoly and the only treatment available. The ethics of it, I think, argued against such assignment.
- LH: Different strokes for different folks.
- JJ: Well, the point is that, we were trying to find out what was the best for them, 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. Some 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. We did that for awhile, but it became so apparent that the attrition rate was so high that when we started to look at the data we concluded, this data doesn't mean anything. And, this was all before they talked about "intention to treat" as a major design issue in psychopharmacology. But it was intuitively clear. I tried to present that

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data; Paul Blachley had a conference where we showed the preliminary stuff, and 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 I continued to run IDAP and the amazing thing was, we didn't think there were as many drug addicts in Chicago. The number of people who came forward seeking treatment was incredible, really quite surprising. We had waiting lists, and as a result it seemed not that the research should become secondary, but that the research had to take a sort of a parallel role. Our responsibility was to expand because people were getting better. You could see lives change, people who had been in and out of Lexington, and in and out of jail, changing their lives. This was sort of unusual because it deviated from the 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 great insight we got from the therapeutic communities about maintaining this very sharp bright line between who's staff and who's a patient is that you sort of generated what happens in the jail. It's us versus them. But, if you blur that line, some of the former patients became staff members, and really high ranking staff members, eventually, you didn't get that. 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 IDAP 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 on the faculty and to run the program. As the Director of the Illinois Drug Abuse Programs, I was nominally a State employee, but Danny actually was, in his own way sort of like the forward line behind some kind of running back or quarterback, in that he found space for us and got the University of Chicago to back us. The University has a lot of power in Chicago. I didn't realize how important it was at the time, but there's no question that it was a necessary part of our success.
- 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 the South 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 a study on cannabis together, and a few other things.

- LH: Well, somewhere along that line, you must have attended a CINP meeting and when Tom Ban asked me to review the proceedings of that meeting and I looked over what you had to say about substance abuse, 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 to that CINP meeting. Abe kept on re-entering my life. This was in 1966 or '67. Abe asked me to come to it. I wrote a paper and we talked about all the ways that people were approaching the problem of addiction, from civil commitment, compulsory treatment, to detox, and so forth. I said, "You know, the mission is to find out what works best for whom". And, I guess we're still at it, in one way or another way, and I don't know that we've actually solved that simple problem of giving a patient a straight answer about what will work best.
- LH: Well, that's true of all psychopharmacology. You could use a dart board.
- JJ: It may be so, but 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 try something, maybe that's a good enough 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, that was an interesting paper. I'm surprised so that anybody remembers that paper...
- 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 Programs actually became one of the models of treatment. Remember, the States were putting up money to say this is really the way it ought to go. New York was putting up money, but its great thrust was to build large facilities for civil commitment. New York City was putting its money into therapeutic communities. Then, under Henry Brill's influence, actually, with Vince Dole, New York made sure that they had enough money for methadone. I should mention that in the interval between my leaving Einstein and going to Chicago, Vince Dole invited me to spend six months working with him. So, I went down to The Rockefeller Institute and worked with them, and got to know those people reasonably well. Vince and Marie were very kind to me. What happened then was that the government, I guess this must be about 1968 or '69, was finally implementing a small piece of

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the 1966 NARA Act. By 1968 they were giving grants for community based treatment. Well, we at the University of Chicago were ahead of the curve. Still, we got one of those grants. Now we had money from the Federal Government for community based treatment and from the State government and I suppose we were viewed, because we had gotten this early start, as a place where new grantees should come and see what we were doing. The unique part of our programs in Illinois, what made it distinct from what was going on in New York, was that there was no sense of bitter rivalry among different modalities. There were people working in our methadone programs who came from therapeutic communities; if someone working in a methadone clinic needed to learn how to do group therapy, we would send them 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 that if someone didn't want to come to them they shouldn't just say, well, go out and die on the street. They'd say, why don't you go into 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, about how we're going to deal with the problem, how we're going to help the most people. And, that was very different from New York, where there was bitterness between methadone and therapeutic community and even civil commitment proponents. Some of that persists even today. In fact, there's a kind of a resurgence of that bitterness between different treatments. In New York, the mayor is saying, methadone is not appropriate. I guess this happens from time to time. So, people would come to visit IDAP and we would show them what we were doing. For example, Griffith Edwards came from the Institute of Psychiatry in London early on; Beny Primm came from New York; Bob DuPont came from Washington, DC; I think Herb Kleber came, too, from Connecticut. We were happy to show them what we were doing. We didn't view this as a sort of academic exercise so much as a practical application of what we were learning about a public health problem. They all went back and built their own programs. Bob DuPont built a scaled up version with some help from the White House. It was a major program in Washington, DC. It was mostly methadone, as I understand it, but his support came through the city of Washington, DC that in turn, was encouraged by the White House to do something about crime. I guess this was in 1969; Nixon was elected President in 1968.

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 to get started, but you can ask him about that. But, there's no question that there were some people in the White House who were interested in Bob's program. Once they got the Controlled Substances Act finished, there were people on the White House staff, Jeff Donfeld and Bud Krogh, who were saying to higher-ups in the White House, that 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. Jeff Donfeld was sent out on a reconnoitering mission to look at programs and Bob DuPont told him to be sure to go to Illinois. I'm not sure he would have done that otherwise. I'm sure he visited New York and saw those programs, and I guess he visited a number of places. He came out to Chicago and I treated him pretty much the way we treated anybody else who came 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 and made his report. 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. 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". 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, number one; and number two, who could keep their mouths shut that long. But I tried, I called people. I didn't think it could be done in six weeks. I persuaded Donfeld to give us eight weeks. Finally, I was able to put together a fascinating group. I got Sid Cohen, Jack Mendelson, and Jonathan Cole. There may have been other ACNP members. I also got Jack O'Donnell. Helen Nowlis was part of that group, as well. It was a really fascinating group and we got together on weekends and tried to write this report as best we could. Ed Brecher, who wrote the Consumer Reports book, Licit and Illicit Drugs, came on board sort of as our scribe.
- LH: He was a very good reporter.
- JJ: Yes, he was. We met over four or five weeks and we wrote up the notes of our meetings, then we wrote a report, and then Ed Brecher and I worked for another two weeks to put it in some kind of neat form. We didn't have much, if any, secretarial support. We typed it up and sent it

in to the White House, and it differed substantially from the report that the White House had solicited from government agencies. At the time, the dominant thinking was more sociological, that addiction springs from poverty, deprivation, and joblessness, and that unless you do something about that, unless you change society, you can't do much about addiction. 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. Remember, we're moving now into 1971. Vince Dole had been expanding methadone treatment. We at IDAP had been expanding it. Other people had been expanding it, 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, thousands of people have said they would rather have that treatment than continue using heroin, the government was saying it's only an experiment; at least that's what NIMH was saying. I could go into the personnel involved in writing the report NIMH sent to the White House, but I'm not sure that's really germaine.

LH: Don't mention names.

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JJ: Our report said, look, if you have this much money, the first thing you need to do is to stop the pretense that something that has been used in five to ten thousand people for five yers ws used only in a small experiment.is being used to treat is based on a small experimemt. You ought to make iavailable to those who need it. Then, there were a lot of other recommendations, including the establishment of some entity in government, not just a little piece of NIMH, that has both the intellectual capacity and the staffing to look across what the government is doing about drug abuse; what's happening in terms of prevention; what is done about treatment research; what are you doing about finding out what works; what is done about basic research? 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. That's pretty much what our concept was and that's what we recommended, and I think Jonathan Cole would probably have the same memories of it, and Jack Mendelson, as well. They were key people and there wasn't very much dissent in the group. We all saw it that way. Of course, we had to deal with marijuana, LSD, and all the other drugs, as well. We sent the report to the White House in December and didn't hear much, except that I got a brief thank you note from President Nixon in January of 1971. In April, I got a call from the White House to come to Washington. By that time, I guess, I had become one of their go-to experts on drug abuse. At that meeting they asked me what I would do about the heroin use by our military in Vietnam.

- LH: Oh, dear, that was a hot ticket.
- It was a hot issue. We had not known about it when we had written JJ: the report in late December, 1970. There was no mention of a problem of drug use among military people in Vietnam; it was a total shock. Then two Congressmen, Steele and Murphy, reported that they had visited Vietnam and that fifteen percent of our servicemen there were addicted to heroin. That's a big number. At the time, they were going through demobilization, bringing back a thousand servicemen every day to a country that didn't have adequate drug treatment if it was needed. Most people who wanted treatment could not get it. There were dire predictions about what happens when heroin addicts make other heroin addicts. I mean, there was this myth that heroin addicts would run rampant through society, and some in Congress were talking about expanding a major compulsory treatment program, civil commitment for two years for everybody who used drugs. The military had tried everything it could, but it could not bring heroin use under control, and they could not control the supply.
- 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. We did not know what would happen when they got back. Nobody knew.
- LH: Well, you know, there's something that nobody has ever brought up. Where did they get this ninety-five percent pure heroin? You know, that's not easy to make.
- JJ: Well, apparently it was coming across from Laos and Cambodia. There was still traffic through the Golden Triangle and they just weren't cutting it very much, but that was the situation. And, I had some notions about what to do. It was almost self-evident in the way that it was self-evident how you compare treatments. First of all, I found out that the military was offering amnesty to anyone who volunteered 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. So, one of the issues was how could you identify those people who were dependent, deter those who were not already dependent, and get some idea if the numbers being bandied about, fifteen percent addicted, had any relationship to reality. What I suggested to the White House was a method that would

accomplish all of those objectives by getting the epidemiological data, using a slight deterrent, and identifying those people that required treatment. It was fairly simple and I don't know why it wasn't obvious to the military. I said they should do urine testing and detoxify anyone found to be dependent. After a while, they should begin random testing to give the message that you really can't use heroin with impunity, and that somebody who's used should be put into treatment if needed, or put under a condition so that should they test positive again in the following six weeks, there is an adverse consequence such as you might have in an employment situation. They thought that sounded good. But then I pointed out that they'd have to make some changes, because as the Code of Military Justice stood, somebody found to be heroin positive could be subject to court martial, and to dishonorable or bad conduct discharge. Those were serious consequences for drug use. I said that the Code of Military Justice would have to be changed and the testing would have to be considered a medical procedure.

- LH: Now, by this time, had you been appointed to this special office?
- JJ: There was no talk of a special office.
- LH: Were you still a consultant?
- I was only a consultant. I was still Head of the Illinois Drug Abuse JJ: Programs. I was just giving some advice, suggesting what they probably ought to do. Now, I had one special tool that 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 that sort, but I had learned a little bit from Vince Dole about rapid screening. I was coming back from a CPDD meeting and I sat next to Avram Goldstein on the plane. Avram told me about an invention called the FRAT (Free Radical Assay Technique) machine, which could do an identification of heroin in a minute. Avram had one machine. He said there were no others at the time. I said I'd really like to get one for IDAP, and I ordered one using my State of Illinois hat, so I knew there was one being made that would be ready soon. So, when I spoke to the White House I knew that the urine screening I proposed could be done using these machines. And, if you could do one a minute, you didn't have to have sixty gas chromatograph machines in Vietnam. The White House bought into this proposal, and they soon sent me to present it to the military at the Pentagon. They were not very receptive to my ideas, said they didn't need to do all this, but maybe they'd get around to it some day. I, on the other hand, was pretty sure this was what the President wanted done and that he wanted it implemented right away. He didn't like the idea of addicted people coming back untreated to no treatment,

so I told the assorted generals at the meeting that I knew they were pretty busy with the war, and that if they just would get me a telephone I'd find some civilians who could get the job done. I was pretty serious. I wasn't intentionally being disrespectful, but they were shocked. Nobody ever says that sort of thing to the military. 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, President Nixon might fire someone". That wasn't what I meant at all. But, Nixon had that reputation. If he doesn't like somebody who can't get it done, they're gone. So the generals took a break from the meeting. They 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, just on the chance notion that this proposal might go through. I called up the company and asked if they were to put people on double time and have them working around the clock, how long it would take to make another machine in addition to the one that I had on order for the State of Illinois. They said it would take about two weeks, and I told them to go ahead and do that. I said, "I can't tell you what this is all about, but I'm calling from Washington". So, when the military agreed to the plan, I already had the company's Vice-President, Bill McGlashan, ready to go to Vietnam with a consultant and with these machines. And the most amazing things happened over those two and a half weeks. I also learned that if policy is to be made that spans not just treatment within HEW, but also the Veterans Administration, and the Army, and numerous other agencies, it had better be done at the level of the Executive Office of the President, so that the person put in to coordinate it all can have authority over all the agencies that would be affected. And that's the origin of the Special Action Office for Drug Abuse Prevention.

- LH: And, you became the first Drug Czar.
- JJ: Yes, I became the first Drug Czar, but that's another story, totally unexpected, not predicted. Basically, what they did is look at the 1970 report and say, here's what we need to do. We need to fund research; we need to evaluate treatment and set up a coordinating office. Sometime, I guess, in early June, I got a hint that they were going to develop this idea. I thought it was still going through HEW with some new funding. But at a meeting with Congressional leadership at the White House that I was invited to attend, the President announced a major initiative on drug abuse and the establishment of a new Office within the Executive Office of the President. And then he said, "Dr. Jaffe is going to run this". I was absolutely dumbfounded and nobody says, "Mr. President, who

told you that"? I had been in Washington to consult with Krogh and Donfeld, and I had not even planned to stay over. There was a press conference the next day. Somebody went out and bought me a shirt, they bought a shirt that was too big and it looks a little odd pn the press pictures, and I was sort of thrust out in front of the Washington press corps, not at all prepared, and I was asked what I was going to do. I could have said, "How do I know what I'm going to do"? But, I knew what we had to do because of the nexus between crime and addiction and treatment. I said, and I don't know how these things happen, but it came up without much thought, "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; 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 became the central thing that we wanted to do, at least, over the first year or so. I mean, there were lots of things that needed to be done, but to expand treatment to the point that there were no waiting lists was a goal. In addition, what came with it, was the great opportunity to put a real scientific base into treatment, because the amount of money that was going into the basic science of studying drugs of abuse at that time was minimal, probably no more than three or four million dollars. A lot of government money was going into 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 we were not there to punish people for past sins. We said, just make sure this money - and, we put up, I guess, 20 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, most of the money that NIH was calling drug abuse money was being spent on Jerry Levine's research. And if we moved all of that, then, there'd be no psychopharmacology research. So we let them keep it all and we put up new money that was to be used only for drug abuse research. And, so, we kept the psychopharmacology budget intact. Sol Snyder has said that was the money that allowed him to move ahead with his opiate receptor research. It's very gracious of

him to say that, and if it's true, that's terrific. But, what we knew is that if you're going to make progress, you need to have basic and clinical research funded for real. And, so, we put all of that into place and we started the change of that Division of Narcotics in NIMH into what ultimately became NIDA. It was a transition that began on the first day of the Special Action Office.

- 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 you were able to emphasize treatment for addiction that we've now got interdiction.
- JJ: Well, you know, the pendulum swings. It's much easier to fight some external enemy than it is to say there are some aspects of life that are difficult to deal with and the best we can do is provide 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. 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, I think, a very-diluted form of what we had in the early 1970s, 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 are available the more likely people are to use them, but, to say that treatment doesn't work is not just short-sighted, it's simply ignorant. It's just not so. Treatment for dependence is probably as effective as it is for any other chronic illness, and certainly it's as effective as it is for most of the other psychiatric disorders that we have. But, we did get a lot accomplished in terms of psychopharmacology during those early years of SAODAP, certainly. We initiated the studies of LAAM. We got CPDD, which was then a committee of the National Research Council, to study naltrexone. Those are major accomplishments. And I think

another accomplishment was getting Lee Robins to carry out a major follow-up study of the natural history of heroin use among returning Viet Nam veterans. There were a lot of obstacles to getting that done. We actually assigned someone specifically to make certain that there were no roadblocks in Lee's way. I think the Department of Defense was very uneasy about doing a follow-up that might show there were dire long term consequences of the heroin addiction in Vietnam. I had spoken to the President about this, and he said that I should find out what happened and in fact, that I should write a book about it. I felt I had been given direct authority, so any time the generals put roadblocks in Lee's path after we designed the study, I would call up, directly, from the White House, and open those paths again. I think that was a critical study. It's a landmark and I was pleased to have been able to see that one through. 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 a press conference on Lee's study on their turf, 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 been telling how awful these people were and they should have their buttons stripped off and be dishonorably discharged. So, on the way back, he said, "Say, that was a very attractive, very intelligent informative guy that was showing us around", and I said, "Yes, Sir, he's on 40 mg 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. 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 will be using it and with what consequence, for how long?
- LH: You have to do market research.
- JJ: In a sense, yes. You know, we had to do these initial estimates of prevalence. The Household Survey had to be continued. DAWN (the

Drug Abuse Warning Network) had to be initiated. I mean, all of this had to be done, and he instantly grasped it. 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 Robins' Viet Nam follow-up study would never have been done if he hadn't been so direct in saying, "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.

- LH: Now, your career has always alternated between the academic role and the public service role. Since then, you became Director of the Addiction Research Center.
- Yes, but before that I returned to academia for about ten years, first at JJ: Columbia and then at the University of Connecticut. One of the things I had written into the first National Strategy on Drug Abuse and that I argued with DEA about including, alcohol and tobacco. The DEA guy said, "Well, you deal with illicit drugs". I said, "No, we're going to deal with all drugs". I finally got it in, but it was just a bare mention. When I wrote my first chapter in Goodman & Gilman, in 1964, I had a little section on nicotine; alcohol was in there as well. Al Gilman was not happy to see nicotine labeled as an addiction and he shortened that paragraph. using his prerogative as editor. He was a chain smoker. So, when I left SAODAP and went to Columbia, I sort of wanted to explate some guilt about not having been able to really speak about the whole range of the addictions. I thought I would like spend some time studying tobacco dependence. A lot more deaths were associated with chronic tobacco use than with opiate use, and I wanted to know more about it. How does this drug use compares to the others? How is it different? And, at Columbia, we spent some time studying tobacco addiction, treatment of tobacco use, effectiveness of treatment. I was able to work with Bob Spitzer and we were the people who put, for the first time, tobacco dependence into DSM-III. Before that, the only mentions of tobacco, if you really want to look at it, in all of the psychiatric textbooks, are as a psychosomatic disorder of the pulmonary tract. It was fascinating how little concern there was in psychiatry about tobacco smoking as an addiction or nicotine as an addiction. So, having gotten that in, defending that for a while and studying that, I then found that it was very difficult to start smoking cessation clinics in New York. Fortuitously, Roger

Meyer had taken the chairmanship of Psychiatry at the University of Connecticut and he invited me to come there. He thought all the big insurance companies would be happy to help me continue the smoking work. Well, it 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 drugs, and I was feeling, reasonably well-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 lose the skills to work on the molecular or even the physiological level. I know I felt that way. I think we got a couple of things done, but nothing remarkable. Then, when Bill Pollin asked me if I would be interested in coming to Head the Addiction Research Center, which was in the process of moving to Baltimore, I felt that was a nice closing of the circle. I mean, I started out as a medical student wanting to go to the Addiction Research Center to work with Wikler, and although I wound up in the same building, it was to work on something else. Here, now, I was being asked to come back and Head the Addiction Research Center. 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. Anyway, I got the job and moved to Baltimore, and spent a few years in that position. By that time, the mid-1980s, cocaine was the great threat to the national well being and we began to reintroduce studies of cocaine at the Addiction Research Center for the first time since Isbell gave them up. Isbell had given up cocaine and I don't know why he thought it was so risky and deadly that he said it was a dangerous drug and you just don't want to do an experiment with that. I didn't feel we had very many options. We had millions of people using it and I thought we ought to find out what you can do about it. Shortly after I got to the ARC, Bill Pollin decided to retire as Head of NIDA. Ian MacDonald, who had been a classmate of mine in medical school, was head of ADAMHA. He and Bill asked me to take on the Interim Directorship of NIDA while still remaining as Director of the ARC. It was tough, but I agreed and during the time that I was there we got a few important things done. We got NIDA involved in AIDS; there had been a reluctance to do this. We got it involved in workplace testing, so that all of the testing that is now done, in terms of employee programs and such 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 a priority then. And,

then, I was delighted to return to the Addiction Research Center when Bob Schuster took over as head of NIDA, and I was there until about 1989. Then, during Fred Goodwin's tenure as head of ADAMHA and a period of reorganizing various offices, he asked Beny Primm, who had a large treatment operation in New York, to head up a new office whose primary purpose was to expand treatment again for the whole country. It was called the Office for Treatment Improvement (OTI). Beny and I had been friends from way back in the early 1970s. In fact, he had gone to Viet Nam with me when we were sent to inspect and report back to the President how the urine testing program was working. Beny asked me to help get OTI set up. So, I returned to the bureaucracy with the notion of expanding treatment and I stayed in it in various roles in various offices until about a year ago. I put up with it as long as I could. I guess old fire horses have to retire to the pasture sometime. About a year ago, 1997, I said, I've had about enough of government, 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 and followed it, 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 that, maybe is the major achievement. By putting that funding in place, initially, by writing the legislation that enabled the creation of NIDA and deliberately increasing its research base over those crucial two to three years, I controlled the budget for 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 that now the addictive disorders represent a major area of neuropsychopharmacology.
- LH: Oh, yes.
- 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, I'm a consultant to some small companies. I'm a Professor at the University of Maryland. I teach something I never thought would exist, Addiction Psychiatry as a sub-specialty. So, I do that, and I'm also doing some work on tobacco research, 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.

DONALD R. JASINSKI

Interviewed by Leo E. Hollister Washington, DC, April 15, 1997

- LH: It's Tuesday, April 15, 1997, and we're here in Washington, DC, to continue a series of videotaped interviews with people, who know something of the history of psychopharmacology. Among 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 the series.
- DJ: Thank you, my pleasure.
- LH: Probably interesting to figure out how and 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 and 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, the growth of research in science and the medical school faculty was prosthetizing 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.
- DJ: And, Klaus had trained so many number of people in neuropsychopharmacology and one of Klaus' claim to fame, as many of his people have described him, was that Klaus had his 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. And, Klaus had attracted a large number of people. In pharmacology, what I found fascinating was the lectures. It was a superb course. Coming up once a year to give our lectures on addiction was Harris Isbell. So, I became

^{*} Donald S. Jasinsky was born in Chicago, Illinois in 1938.

interested in pharmacology and I had a summer Fellowship in pharmacology. 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 from medical school. I did my internship at the University of Illinois. Just prior to this, at the University of Illinois, I worked very closely in neurophysiology with Sid Smith but Sid went off to become Chairman, at the University at Buffalo. I never really had the hands to become a good neurophysiologist, so I decided that, perhaps, I should be a clinical pharmacologist. When I told about my interest to become a clinical pharmacologist to Unna he wrote a letter to Harris Isbell, but Isbell had retired in 1963.
- LH: I didn't know that.

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- DG: In 1963 Isbell and Wikler had gone over to the University of Kentucky where Isbell had started the University of Kentucky Medical School. Harris went over as Professor of Medicine and Abe Wikler went over as Professor of Psychiatry. 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; he had been one of Klaus' students. So Bill interviewed me and said, yes, there was a position, a two year position, 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. Then, I spent the year in Lexingtand helping Bill Martin to run the Human Research Unit. It was a wonderful learning opportunity. So, I had a one-on-one mentorship with Bill Martin, at this time. Since Harris Isbell and Abe Wikler went over to the University of Kentucky and Frank Frazer had gone to work for Eli Lilly, 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, probably, fourteen months, Bill wanted to know whether I wanted a permanent position and I said, yes, so I got 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 Program. I was only twenty-nine or thirty years old.
- LH: My, that's a rapid ascent.
- DJ: 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 get involved also in Harris' experiments. I ran them. And, so, I had a very broad based sort of experience at the time. The period from 1963 or '64 to the mid-1970s were the most productive years.in Bill Martin's department.

- LH: Bill was impressive wasn't he?
- DG: Yes, and I was doing the human experiments to show that the new concepts, like multiple opioid receptors can applied in human pharmacology. We had gone on to develop drugs for treatment. We had studied methadone, naltrexone, naloxone, and amphetamines.
- LH: You studied cannabinoids too.
- DG: Well, there was an interesting round about way to the cannabinoids. Harris had gotten interested in cannabinoids and had worked out a relationship with Professor Kortha in Germany. Kortha was isolating active principles from cannabinoids, from hashish. And, they used to ship them to us in vials, which were freeze dried. And, since they were extracted from plants, they were considered biologic substances and not drugs, so they were not subject to the IND regulations. So, Harris had designed an experiment; and I actually ran it. What we did was we took the vials, added ethanol, put the substance in solution, and drew it up with a syringe. Then we injected it into a cigarette and after the alcohol evaporated we would let subjects smoke the cigarette. We had gone through cannabidiol, tetrahydrocannabinol, δ -8, δ -9-tetrahydrocannabinol, a whole series of these and found the one, which was active, was δ -9-tetrahydrocannabinol.
- LH: Of course, this was before Raphael Mechoulam's synthesis.of THC.
- DJ: Yes, yes.
- LH: So, you did a natural exchange. How were you sure of the compounds?
- DJ: We had a very, very sophisticated organic chemist, and he identified them. 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 until we got a hallucinogenic response. 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 a study on cross tolerance between LSD and tetrahydrocannabinol. So, we made our volunteers tolerant to LSD and, then, gave them tetrahydrocannabinol, and found that they were not cross tolerant. So, it was two different mechanisms. And, we did these studies; we never thought anybody would be interested in these studies. At that time,

there was not much interest in marijuana research. This was probably in 1968, or '69, somewhere in that era.

- LH: I think we got some of the synthetic stuff around 1965. Then, I dug out some synhexyl from Abbott, which had been in the freezer up there for twenty-five years; and we did a comparison between THC and synhexyl.
- In about 1960, right after we did our studies the Illinois State Medical DJ: 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. This was in Chicago and I remember it was held at the Sherman House in Chicago; I grew up in Chicago. So, I had written up a paper in abstract saying that tetrahydrocannabinoidol was a hallucinogen with a mechanism of action that was different from LSD. So, I had written this abstract that was sent in ahead. I'd gotten a call, they wanted me to come up and attend a press conference. At that time, as a federal scientist, you had to have clearance for a press conference and there wasn't time to get clearance to do this. So, I said, no, I didn't particularly want to talk to the press. This was a very interesting pro vs.con conference with the attendance of Timothy Leary and a number of other people, who were pro-hallucinogen at the time. So I find myself with all these...
- LH: ...mystics...
- DJ: ...with all these mystics. I remember staying at the Sherman House at the meeting. 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 got delayed. It 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 had calls from 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.
- DJ: So, this was an interesting period of time. I never thought of a tetrahydrocannabinol and marijuana issue, at that time. For me it was straightforward research which we had done by experiments. I, then, 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 done.
- LH: Oh yes, and a lot of them involved synhexyl.

- DJ: I wrote this up and there was another symposium at the New York Academy of Sciences where, I addressed the topic of "What We Do about Marijuana and Its Addiction Potential". And, I had looked at this straightforward and pointed out that there were a number of things we didn't know, because the experiment hadn't been done. I did that at the conference in New York that was hosted by Stan Yollis. It must have been, in the '70s, sometime. Interestingly, we just had to revise these data because people are now interested in this data, again. It's amazing, there was, recently, at the joint meeting of the clinical pharmacology societies, the American Society for Pharmacology and Therapeutics and American Society for Clinical Pharmacology, a symposium, which was on the marijuana issue, on control of marijuana and I was one of the speakers. It was about a month ago. So, this has gotten to be sort of interesting, again, this whole idea and it has gotten revisited. And I'm thinking that we will see more of it.
- 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 and 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: I was interacting with people like Harris Isbell, Bill Martin, and Abe Wikler. I got to interact with them. To keep the relationship with the National Academy of Sciences, the KM Programs of Drug Dependence, and the Abuse Potential Studies, I got to interact with Nathan Eddy and with Moe Sievers and Moe Sievers did some nice things for me.
- LH: Moe Sievers was a Dean of Pharmacology.
- DJ: Yes and among all those people, I think the inherently smartest was probably Harris Isbell. Harris was a very smart man. He was very soft spoken and very quiet. That was in the days when people used to smoke. In company, he used to smoke a cigarette and although he was very quiet before you know it, he would become the center of the conversation. People would be relating to him. Women would find Harris a person who they would talk to and he would relate well to them. Harris had no trouble giving people opinions. He was a wonderful lab chief. He was a father figure. 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. 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 and Bill Martin, were 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 I used to feel inadequate.
- LH: You just stepped in at the right time.
- DJ: Oh. Yes, I was fortunate on this.
- LH: Boy, you learned.
- DJ: I was fortunate, yes. And, I had this wonderful opportunity. It was there. And, they were constantly looking for people to bring into the area.
- LH: Well, I remember that, almost simultaneously, when I published the first paper on THC and synhexyl, Andy Wile published one in *Science*. Andy wanted to get away from the 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, the history of Laxington goes back to the 1920s.
- LH: To Cliff Himmelsbach...
- DJ: Well, to Himmelsbach and to Larry Kolb, Sr. Most of the people 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 he got interested in the addiction problem and was really instrumental in getting the Lexington Hospital opened and the research roling. He became the first Director of Lexington. The Lexington Hospital opened in 1935. Kolb recruited Himmelsbach, who was a young medical officer and sent him off for training, for a few years. They had a 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 written-up?
- DJ: No. In 1975, at its 40th anniversary, there was a anniversary symposium, and there's a book, which was published, in which a number of people reminisce. I mean, if you interweave these stories, you look at

the tradition of Lexington and get the idea that you could do controlled experiments in addiction. If you look at Himmelsbach's experiments from the late 1930s, 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 are properly generated; a hypothesis tested. Good science that 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. My major job was to do the Human Abuse Potential Studies and the screening of drugs 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. We would get our compounds very early; the pharmaceutical companies couldn't tell us no because it was necessary for them to have our findings to get their drugs through the system. So, we got our hands on all sorts of interesting drugs. And people looked at this as applied research. When Bill inherited this program, the first drug he assessed was cyclazocine which was a potent antagonist of morphine; it didn't look like morphine, and it produced some hallucinogenic activity as well as dysphoric responses in the addict populations. And when Bill gave it chronically, he showed that it produced a withdrawal syndrome, which was not like the withdrawal syndrome with morphine. And, then, Bill asked a very simple question, namely that if they became tolerant to the agonist effects of cylazocive, did they become tolerant to the antagonist effects of morphine. So, he gave it, chronically, and showed that they did not become tolerant to morphine's antagonist effects. It was this finding that led Bill to the formulation of a multiple opioid receptors theory. It was the idea that cyclazocine was an antagonist at µ and an agonist at, what we now call K receptors.
- LH: He gave them the original names, didn't he, μ and K?
- DJ: Originally he called them nalorphine type and morphine type but that is another story. We had looked at these drugs and knew there were two receptors, at least, and we could explain the action of opioids. The term, opioids, was coined by Bill. We would also train graduates at the University of Kentucky. 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 to study in humans. So, he put the young man to work, studying and comparing all these agonists, antagonists.
- LH: And, he, also, did some rather simple animal preparations, as well.

- DJ: It was really mainly research in humans. It was human data, which we had generated. Pharmaceutical companies industries were producing agonist and 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: Was that the famous Lasagna study?

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- DJ: Actually, Harris and Frank recognized that nalorphine in volunteers produced some morphine-like effects. And, it was Klaus Unna, the pharmacologist at Merck, who had done the work on nalorphine. He did the basic pharmacology and Klaus wanted Merck to proceed to develop nalorphine as a morphine antagonist. When they didn't want to do that Klaus left and went to work at the university. There was a relationship between Klaus and Harris through the study of nalorphine that started back in the late forties.
- LH: And, that was the beginning, of course, of the whole concept of using a mixed agonist amd antagonist.
- Naloxone was fascinating. We gave it to volunteers and we went up DJ: to huge doses and saw nothing, no changes. And, then, we gave very small doses to morphine dependent individuals and that would precipitate abstinence. My project with Bill was working out how to measure the relative potency of the antagonist. So we would assay for precipitated withdrawal. And, then, we did these studies comparing this with agonist effects. What we found was that naloxone had virtually no agonist effects in humans. And, this was interesting, because it was clear evidence that you had a competitive antagonist. And, that was probably the second paper I ever wrote in medicine. It had huge implications. We gave naloxone around the clock in very large doses by injection for, I think three or four weeks, and showed no changes and showed no withdrawal symptoms. And, when we were looking at this we realized that we had a competitive antagonist and realized also that you could explain a number of the effects only in terms of multiple receptors. The next experiment which I did was a study of the interaction of cyclazocine and naloxone showing that larger doses of naloxone could antagonize cyclazocine. This was really what crystallized for us, these phenomena in humans with naloxone, ideas which led to the multiple opioid receptors. Then, we found a partial morphine agonist, a Parke-Davis compound called Profadol. If we gave people large doses of morphine to make them dependent, and then gave a partial agonist, it wouldn't have sufficient activity. If you lowered the level of morphine dependence, the same drug could now have enough activity. We had

two partial morphine antagonists, Profadol and I think B4507 was the other drug.

- LH: I always thought 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 also synthesized naltrexone too.
- DJ: Naloxone was very expensive to synthesize, and, since it was apparent that naloxone was not going to be an analgesic, Endo had no interest in developing it as an antagonist. When we studied the substance our conclusion was that this would be the drug of choice as a morphine antagonist. In those days, we were looking at structure activity relationships and there were a couple of things we were aware of. One was that most of the antagonists were derived from morphine by substitution on the nitrogen atom. Cyclazocine had been a cyclopropylmethyl substitution. And, in man but not in animals cyclazocine produced effects which lasted for twenty-four to forty-eight hours. The substance was also well absorbed, orally.

There were also other ideas floating around and we looked at them as well. Abe Wikler had looked at conditioning in the Pavlovian response and found that the withdrawal syndrome and drug craving could be seen as conditioned phenomena.

The other project I worked on with Bill was the idea of protracted abstinence. The idea was to keep people abstinent by producing a chemical blockade by cyclazocine 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, but, if we gave it orally, it had a very high first pass metabolism and its' effects were gone within about three to four hours. So we thought to try the N-allyl substitution that was made by Endo. So, Bill took a trip up to Endo to meet Harold Blumberg and Alan Pater and as soon as they got an IND, we did all of the Phase I and generated all the human data. So, I gave the first dose of naltrexone by injection, which was .001 mg. Eventually, we wound up giving 50 mg, but we had done this very carefully. We looked at this and we showed that, unlike naloxone, it was very effective, orally. The cyclopropylmethyl did protect against the first pass metabolism. It produced a very long lasting compound in man, which lasted twenty-four to forty-eight hours. So, then, we did the other experiment, which was to give naltrexone, chronically, and, then, give morphine, chronically, on top of that and we showed that we did not get physical dependence in the withdrawal syndrome. So, Bill said, "What dose should we give"? I said, "Well, maybe, 25 mg, if we look at this". Then, he said, "Let's be safe, let's double it".

So, we picked a 50 mg dose to do these studies. We gave people 50 mg 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 done about 1969 or '70. I have memories of this, because we published our findings. Then people wanted to know how the dose of 50 mg tablets was standardized because when it went on to development, the 50 mg dose became the dose. It was actually never standardized.

LH: Lucky hunch.

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- DJ: That was a very interesting time in history, because it opened up research in many areas.
- 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 was the relationship between narcotics and asocial criminal behavior. We were dealing with people you would call psychopaths in the old days, now, you call them character disorders, anti-social personality disorders, and we were interested in their response to morphine. We knew we could change the personality of these people with morphine, make them feel much better and be much nicer people. We were interested in general in a biologic approach to the concepts of addiction. And, we did interesting experiments, which never got clear recognition. We hypothesized that there was a, what you might call a state or a trait, which made these individuals much more susceptible to morphine.

Science is affected by the society. We had, in the last century, beginning in probably the 1860s or 1870s, the growth of the Abstinence Movement, the Prohibitionist Movement. It hit its' heyday in this country, in the 1910s and '20s. 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. I was struck by listening to General McCafferey 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. We had another thing, which was an outgrowth of this, which transcended everything; it was the idea of Marx's philosophy 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, suffered a great deal, but it was not entirely in response to their environment. Environment contributed, to their suffering, but there was probably something else there as well. We're now ending that era. I think this era of Marx's philosophy has passed. Our friends in molecular biology, I think, are going to the opposite extreme where everything is considered 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: Yes. I think that marijuana was controlled on the basis of two hours of hearings before Congress and it was controlled because a number of states in the southwest and the northeast had already controlled it at a state level.
- 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; it was used by the Mexican laborers. It was a very short hearing. 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, so it became a controlled, basically 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, that there are inconsistencies 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. I suppose, that one is one of the best examples. The twenty-five year old war on drugs seems not to have been very effective.
- DJ: Again, going through the 1960s and '70s, people were convinced that there could be a social solution. I think we, now, accept much more, that we people are varied and, in terms of brain chemistry and some of us may be born with a tendency toward anxiety.and some of us may be born with a tendency toward depression. But we don't approach addiction yet in the same way. Many of us believe that addicts, have personality disorders, impulsivity, low mood states. They have poor self-image and I think it shold be a mission to develop an appropriate pharmacology for these people, but we don't do it.
- LH: So, there is an addictive personality?
- DJ: Yes. Well, I think there's a propensity towards addiction. You know, you take a number of people and expose them to any sort of drug that's reinforcing, some are getting into trouble and other people are not

going to get into trouble. What distinguishes those who get into trouble from those who don't get into trouble? What is different about them that get them into trouble? If you look at those people we used to see in prison. We see personality disorders and we all know that the addict sociopath with an antisocial personality disorder is the one who causes havoc. And, we tend to separate those people from the "recreational user" and from those who get addicted in the course of treatment for pain. I don't know whether they should be separated. Obviously, certain people, if they're exposed, will get into trouble with the drugs. Most kids during their college years drink and consume huge amounts of alcohol, and some, probably, do drugs, but then they reach maturity. When they get to be twenty-three or twenty-four, they're out of college, stabilize and all of a sudden they don't do it any longer, because it makes them fat or just don't want it any longer. And, they change their drug taking behavior. Yet, some don't change and persist. What makes the difference? Is it entirely environment? Is it genetics? Is it induced behavior? Is it learned behavior? I have no idea.

- LH: Well, it's a tough problem, but I don't think anybody had much more experience on the pharmacology of these drugs and in searching for drugs to prevent heroin abuse or prevent cocaine use, as you do. Should we go the methadone route, a drug that substitutes, or should we go to naltrexone route, a drug that blocks the pleasue?
- I think there are other alternates now than those. But, most of our cur-DJ: rent drugs for heroin and opiate treatment emerged out of the research at Lexington. We have now dzugs which would modify the opioid receptor; we have drugs which act as an agonist or drugs which act as anantagonist at the opioid receptor. Then, people would argue with me; that if you take an addict sociopath, and give them opioids, are they better off on the opioids or off the opioids? In the methadone program we are using a µ receptor agonist. But we measure efficacy from methadone in terms of retention and treatment. We don't measure efficacy in terms of the changes we produced in the individuals. To me, one of the great lapses in our field in reflecting back on this, is that this idea for using drugs for opioid addiction, and using antidepressants, both emerged about the same time in the early 1960s. Nobody would approve the use of an antidepressant without a placebo controlled study showing its effectiveness. For an antidepressant you have to do a placebo controlled trial. We have a large number of antidepressants and we know that antidepressants work. This did not happen with the treatment drugs for opiates. The idea of doing controlled studies was resisted. Methadone, you know the story as well as I do, was approved, originally

by the FDA on the basis of clinical experience and 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 sort of switched as to the way we look for treatment drugs. At least, with cocaine, we have a hypothesis that the reinforcing effects of cocaine are dopamine related; the hypothesis 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 an antagonist to dopamine. So, we've been looking for dopamine antagonists. Whether this will result in a cocaine treatment drug, I don't know. Whether you can find a drug, which is a selective dopamine reuptake inhibitor or blocker, that will be an effective cocaine treatment drug, I don't know.
- 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; the idea was to get a partial agonist to substitute for methadone? Methadone does everything that heroin and morphine do including producing respiratory depression, respiratory deaths. We also knew that it was awfully hard to get off methadone because the withdrawal syndrome was much longer lasting than the withdrawal syndrome of heroin. So, buprenorphine came along as an analgesic to be assessed for abuse potential. And, I remember this very clearly, because it had like naloxone, naltrexone and cyclazocine, the cyclobutylmethyl substitution. And we were doing dose ranging studies in our addict volunteers.who used to have jobs and I remember one individual who used to work as a clerk who on the next day after he was given the drug looked at me and said, "You know, Doc, I still feel that drug". Buprenorphine was a partial µ agonist which was orally effective and had long lasting effect that could be used as an alternate to methadone. It also had limited physical dependence capacity and lessened ability to produce respiratory depression as a partial agonist.

I thought that the use of methadone was the wrong way to go. Buprenorphine was a drug which clearly had lesser potential to create public health and social problems in toxicity. It could also be used along with other psychotropic drugs, to treat people, for example along with antidepressants and along with antianxiety agents.

- 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?
- I missed that; sometimes in retrospect, you realize you're a dummy. DJ: But the Medical Director of Endo, Ralph Jacobson, told me a story that there was a navy aircraft carrier, which was out in the ocean, and one of the men on the airraft career was found comatose and when they injected him with naloxone, he woke up. And, he swore that he hadn't done any drugs. All he had done was drink the medicinal store of alcohol. Bill did a study and we knew that naloxone will reduce some of the effects of barbiturates. And, there are a number of people, who had tried naloxone, primarily to antagonize alcohol and barbiturates, but they were "vague" experiments. The findings weren't really clear, one way or the other. The findings with naloxone in opiate addicts is really striking, because you have somebody who's experiencing opioid agonist effects and you give them a dose of naloxone and those effects are gone. It just reverses it. You could never get a complete reversal in case of barbiturates as you get with the opiates.
- 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, the changes, what I see, since we have stopped as a group, training clinical investigators, is, that now it is molecular biology. The problem is that molecular biology, which does wonderful things, sometimes doesn't necessarily mean it's going to work in a disease state or a clinical situation. So, I'm still active as a clinical investigator and my services are in demand. And, I'm beginning to see that most of drugs in medicine came about from somebody fooling with the drug and trying it at some disease state. Chlorpromazine is a classic example. Chlorpromazine, benzodiazepines and all of these drugs came about because somebody tried it in a diseases state. It's been fascinating to watch people develop drugs which effect for example agonists, serotonergic agonists or antagonists. But to develop these drug they have to run a dozen or two dozen clinical trials in different sort of disease states. I think we're beginning to see people getting back into clinical investigations at the human level. That's my view. And, there aren't many of us left, who do these human pharmacologic experiments.
- 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 another and did it with enormous success, far more than some of us would have predicted.

- It was another interesting part of history, if you like stories. Bill Martin, DJ: once it was clear that Lexington was closing, did not want to leave. So, Bill became Chairman of Pharmacology at the University of Kentucky, so I was made Director in about 1976 or '77. And, then, I spent the next two years getting 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 which I thought, at the time, was really a straightforward trivial experiment. The very simple idea was that heroin affected less than one percent of the population but that 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, in terms of research activities in this area. So, it was the idea of doing research with nicotine at the Center. The issue was that at the time the Cancer Institute was getting all of the money for cigarette smoking and Bill Pollin, as an institute director of NIDA, wanted to get some of this money for research. So, he sent a memo on this to us and I suggested that we should study the abuse potential of nicotine as a lead to define addiction to nicotine in terms of a behavior. It was guite obvious that there were certain people who had a compulsive use of tobacco, who couldn't stop, and by that definition, nicotine was addicting. The question was, whether the mechanism of nicotine addiction was similar to the mechanisms that underlie the addiction to opiates and other drugs. So, I started with this project. At that time, most people didn't think nicotine was an addictive drug. Smoking was a habit. And, the first thing I did was to recruit Steve Goldberg, who had been a pharmacologist up at Harvard. Steve was expert on monkey self-administration and he showed that nicotine was highly reinforcing for self-administer.
- LH: Were these the first self-administration experiments with nicotine?
- DJ: There have been others, but these were the first to show that it had a reinforcing property. Then, we moved up to Baltimore and I had rebuilt the lab and the first experiment that was up in Baltimore was as a request from Bill Pollin. Bill said, "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 a controlled study of clonidine vs. placebo in opiate withdrawal. And, then, my friends down the hall, George Bigelow, Roland Griffiths, and Maxine Spitzer, had been doing
some stuff on cigarette smoking wuth a guy named Jack Henningfield. So, I said, "Jack, you want to come and have a Fellowship with me in Intramural Research"? He said, "Sure". Sol said, "We really should do something about nicotine's reinforcing effects". The first thing he did was review the literature and wrote a paper showing how nicotine and heroin were similar in what they did. We got some pure nicotine, from a reference lab and we would put nicotine in a solution and did a rising dose response curve. We'd give nicotine by injection, in the vein and what we discovered was that it was a very short acting drug. But we also learned that its effect was similar to the effect of cocaine or heroin. Now, these were addicts, who'd had intravenous experience, and we're giving them nicotine. So, we must have done a hundred people, this way, over the years. So, in the next experiment we tested whether one of the trace amines in nicotie use was a sort of pathway for amphetamines. I had written a protocol and gpt an IND to do phenethylamine infusions in humans. And, as it happened, when we moved up from Lexington I said, "Jack, let's see if people will self-administer nicotine. So, we took people, who were smokers and we sat them in a room for two or three hours and we put the catheter in the vein, hooked up to a syringe, and to a lever. So, we did that with these people and it was amazing. Almost all of them pretty soon were injecting nicotine, just like puffing on cigarettes. So, we clearly produced these results and showed nicotine was reinforcing. We had a scientist from Japan, my friend, Tomogi Onagida, and we arranged for a young man to be trained in clinical research, a Japanese fellow and this young man was measuring the effects of nicotin on blood pressure, heart rate, pupils, and subjective feelings. 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 are very short acting. So, it's a very hard thing to measure effects, which last one minute., But we worked out this project and published the paper and showed that nicotine was typically reinforcing and that it produced changes in the the same scales as heroin. Then, we did studies in which we measured self-administration and subjective effects. And, it is to Bil Pollin's credit that we have a 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.and on the basis of data, he got, eventually, on the package that cigarettes are addicting. And he really led this battle up through the Public Health Service with Congress about the addiction potential of nicotine. And,

ours were straightforward experiments, which had been classic abuse potential experiments we had done with dozens of drugs.

- LH: Well, it's too bad that 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 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.

HERBERT D. KLEBER

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

- AT: I am Andrea Tone, and I am interviewing this afternoon Herbert Kleber.* It is the 42nd Annual Meeting of the ACNP and we are in Puerto Rico. Thank you for joining us.
- HK: Thank you, Andrea.
- AT: Why don't you tell me a little bit about your family background and your education?
- HK: I was born in 1934 and grew up in Pittsburgh, PA. My family on my father's side was from Lithuania, from Vilnius, and on my mother's side from Russia, and they both came to the country in the first decade of the century. My father went into the family luggage business after he grew up, although he had always been interested in medicine and in fact had a pharmacy degree, started medical school, dropped out, and I think because of that from an early age I was either consciously or unconsciously being programmed to be a doctor. The family was a prosperous middle-class one, the luggage business was doing well in those days. I went to a public high school, Taylor Allderdice, and was very active in a number of things.
- AT: Such as?
- HK: Well, I was head of the student council, the prom committee, president of my fatrenity and did very well academically. Before high school, one of the very important formative experiences was my grade school. The principal of the grade school was getting her PhD, and was doing research on bright children, so she developed a "special class". She pulled the 5 or 6 brightest kids out of each class from fourth grade on and we all met in one big room from fourth through sixth grade and basically went as fast as we could and as we chose to. By the time I finished grade school, sixth grade, I already had finished at least a year's worth of algebra, had a lot of biology, history. When I started public high school in seventh grade I repeated a lot of what I had already learned. At times, I got very bored with the repetition but I think that was a terrific experience in grade school. It really stretched you, and saved you from the tedium of a lot that was going on. Before I was in that special class, I found myself getting very bored. You do 20 arithmetic problems in which you repeat the same thing that one or two would have taught you. So, often I didn't bother doing the other 18 because I already knew the principle of it. Getting into that special class probably helped me from getting thrown out of grade school.

^{*} Herbert D. Kleber was born in Pittsburgh, Pennsylvania in 1934.

AT: What about high school?

- HK: The high school was an interesting one. I'm Jewish and the grade school was predominantly Jewish. This was a prosperous Jewish area of Pittsburgh called Squirrel Hill. The high school was very different. It was divided both ethnically and socio-economically, so that the Jewish kids going to the high school tended to come from prosperous families wore nice clothes to school, and were going on to college whereas the non-Jewish kids tended to be the sons and daughters of the miners and steel workers, often immigrants from Eastern Europe, and they were not going on to college. They were going to the mills and the mines when they finished, and so there was a lot of tension, culminating at times in riots in the school. At times you would walk through the halls and your books would be knocked out of your hand and you would be surrounded when you were trying to pick up the books. You would be kicked and the .books would be kicked away. And they would do it just long enough until you were late for class, at which point you were then sent to the principal's office for being late. And you learned how to survive in those kinds of situations. I was small, about 5' 6". And I survived in a couple of ways. One, I learned how to use a knife, which was useful in the after school fights. Two, I was a very fast runner, which was probably even more important in terms of avoiding some of those after school confrontations. And three, by being elected president of my homeroom, I became someone that the other kids felt needed to be protected. So, even the kids that normally would delight in picking on the Jewish kids didn't pick at me because I was their president, and so they had to protect me, make sure that I was OK. An ability to adapt that has served me well in academia. As I said, I did well in high school but did not know much about colleges. My parents wanted to send me away to private school but I refused to go because I was having much too much fun in high school in spite of the above problems. I really knew very little about getting into college or taking the college boards, so I only applied to two schools, Haverford and Dartmouth, both of which were very difficult to get in. When my friends asked, "Why don't you apply to some safety schools?" with the usual cockiness of youth. I said, "Well, if I'm not good enough to get into those schools, maybe I won't bother going to college".
- AT: Why did you apply to those two?
- HK: Even though I didn't know anything about colleges, and my parents didn't either, my mother, who was head of her local Hadassah chapter, asked her friends what schools her bright young son should apply to, and they gave her names, and she sent away for all the catalogues,

mainly the Ivy League schools. I had never heard of the Ivy League up to that point. And I looked through them, and I said, "Well, Harvard, I'm not sure I want to be in a big city like Boston". So, I threw away that catalogue. And New Haven seemed like a very unattractive city, so I threw away the Yale catalogue, as well. But Dartmouth and Haverford both appealed to me. They were small schools in lovely settings, had good course selections, and I thought they would be interesting places to go to for college. I was accepted at Dartmouth and went there. In those days, you didn't visit the colleges in advance. Or at least, my friends did not visit the colleges. The first time I saw Dartmouth was when I went there in September and enrolled. Very few kids from my school went on to the Ivy League so I knew no one there. I had my interviews in Pittsburgh with representatives from Dartmouth and from Haverford.

- AT: Did you have an aptitude for science at that point?
- HK: Not particularly, with the possible exception of chemistry. I tended to get good grades in everything, but I can't say that I had a better aptitude for science than for anything else. That became obvious once I was at college as a pre-med.
- AT: Can I ask you at one point you had said that your mother and father had pretty much programmed you to go to medical school, but at what point did you personally decide that?
- HK: In my sophomore year in college, I called my father one weekend and said, "Dad, I 'm planning to drop pre-med. I really don't like the science courses. I love my literature courses. I love philosophy. I'm really not interested in the science courses". And he said, "Look, you're over 13. You've been bar mitzvahed. It's your choice. I'll be up on the next plane". And sure enough, that weekend he came up, and we had a long talk, and we agreed that if I would stay pre-med for the remainder of that year, I would do it with his blessing. Then I took my first psychology course and I really liked it. And I said, "OK, I'll go on to medical school and be a psychiatrist".
- AT: That is interesting because we know that so many psychiatrists have said they became psychiatrists only after trying other things first, but you had committed to this pretty early on.
- HK: And made a mistake when I started medical school letting people know that.
- AT: Why was that a mistake?
- HK: Because of the attitude then about psychiatry in most medical schools. I graduated from Dartmouth in 1956, did well academically and went on to Jefferson Medical College, which was not my first choice because of

their psychiatry department. But, in any event, I went on to Jefferson, and I assumed that one could be open and honest about wanting psychiatry. I was in some ways naive about the world. At one point, I still remember vividly the anatomy professor saying, "It's very important that you learn the origin and insertion of this particular muscle, except, of course, if you Mr. Kleber are going on to psychiatry". So, that was the attitude in those days...

- AT: ...toward...
- ...toward people going into psychiatry. Jefferson prided itself on its HK: anatomy department. They had twice as many hours of anatomy as most other medical schools, and you learned anatomy very well. I used to drive my professors crazy because I have very poor spatial relations, but very, very good visual memory. So we would study by reading Gray's Anatomy and one of us would open a book and say, "Page 928", and I gave the topic on the page. And the other guy had to rattle off what was on that page. So, I knew my anatomy very well and on the written exams I did terrific. On the practical exams, where you walk around the room and there are little strings around various nerves or muscles or whatever, I often didn't have the foggiest notion what they were, and so I would look up and start flipping pages of the book in my mind. And the professor would say, "No, no, no. The specimen is here. Look down here". And, so I tended to get A's on the written and D's on the practical, which did not thrill the anatomy professors because they were convinced that it was because I was not adequately studying my cadaver.
- AT: Why this prejudice against psychiatry? Was it specific to Jefferson, or do you think it was part of a larger bias in the medical curriculum across the United States then?
- HK: I think in the 1950s there was still a lot of strong feeling that psychiatrists were not real doctors. My father was happy that going into psychiatry kept me in medical school, but I have to admit that the poor man was not thrilled when, after I graduated, I actually went through with it and started psychiatric training. "I spent all this money sending you to college and medical school, and you're not going to be a real doctor? You're going to be a psychiatrist"? So I don't think it was just Jefferson. I think it was a common prejudice at the time. I ended up going to Yale for my residency and the department was still quite analytic. Even the people who were very big on biologic psychiatry had to pay their dues by being in the analytic institute. Gerry Klerman, who was one of the great scientists in ACNP and one of my mentors after I finished my residency until he left Yale and went back to Harvard, was also an analyst.

Danny Freedman, who was president of ACNP, one of its founders and one of the pioneers of biologic psychiatry, was my key mentor during my residency days and for many years after, and he was an analyst as well.

- AT: So your training in medical school leaned largely to analytic principles?
- HK: No, they hated Freud. Jefferson was very organic-based in terms of psychiatry. I think Freud and the Freudian followers were barely mentioned at all in psychiatry. The textbook, which was a British one, was very much the kind of organic psychiatry that was being practiced in England rather than the Freudian-based psychodynamic psychiatry that was going on here. And they stuck to their principles. They didn't like psychiatry. They didn't like psychoanalysis. And they tried to come up with a psychiatry that was as close to their conception of what a doctor should be as in the rest of the medical school. Ironically, at that time, I was still enamored of psychoanalysis and, in fact, had two years of a personal analysis. I thought it would give me a jumpstart on becoming an analyst but it mainly convinced me that I didn't want to be an analyst.
- AT: When did you get interested in pharmacology?
- HK: In medical school I got very interested in pharmacology and, in fact, had my own grant and my own little laboratory in pharmacology with Professor Bob Manthei. I was studying the effects of nicotinic acid and nicotinamide on insulin hypoglycemia, which I got into because of my interest in psychiatry. During one summer as a psychiatric aide at one of the psychiatric hospitals, where they were still doing insulin coma therapy, there were some patients they had trouble bringing out of the coma. Just giving them more glucose did not help. So I became interested in that problem, studied it and wrote a small grant application to one of the drug companies, Lederle, which no longer exists. I was a Lederle research fellow while doing that research with mice and debating after medical school whether I should get a PhD in pharmacology or go on to psychiatric residency or do both. I finally decided that I did not need the PhD in pharmacology to do the kind of research that I wanted to do. One of my memories was when I gave my first paper at a FASEB meeting based on that insulin study. I had practiced it down to a T, gave my talk and handled the questions and answers. Then, at the last question, a man in the audience said, "Well, Dr. Kleber, what temperature did you run the study at? You didn't mention it". This was significant because the study involved insulin metabolism. And I was floored, because I could only think of the temperature in Fahrenheit, and since this was a scientific meeting, I did not want to give it in Fahrenheit, I was trying desperately to convert Fahrenheit to Celsius in front of my large

audience. I came up with a number and everyone seemed satisfied, and as I walked back to the seat, I passed the man who had asked the question, and he said, "It must have been pretty warm in there, wasn't it". And, I said, "No, no. It was air-conditioned". And he looked a bit oddly at me. When I got to my seat, Bob Manthei said, "I spent a fortune air-conditioning that lab and you just told them you carried out that research at 96 degrees". So, I learned you don't try and make those conversions on stage.

- AT: Going back, wasn't it very unusual for someone early on in medical school to be contacting a pharmaceutical company for money to do research?
- HK: The idea for it came from Bob Manthei. He said that my idea was an interesting research project but he didn't have funds to support it. If I wanted to do it, I would have to bring in my own funds, and suggested a number of places where I might apply. So I did. It was the first in a long string of grants, that haven't been less than a million a year since 1970. It was a good experience, I loved doing the research, and I used to come in on one weekend day as well as during the week. By then I knew a bit more about how to figure out which schools were best and I decided that the two best places to learn psychiatry in the United States were Yale and Menninger, with Penn a distant third. My mentors convinced me that if I wanted to live on the east coast, Menninger was not the place to go. It was fine if I wanted to live in the west or California, but if I wanted to practice in the east, I was better off going to Yale or Penn. My internship, in those days internship was separate from residency, was at the University of Pittsburgh because I knew that I wasn't going to live in Pittsburgh, and this was the last chance to be in Pittsburgh with my family and give my parents a chance to spend more time with their grandchildren. The hospital gave me minimal time off to apply for residency. So I had to work the regular workday, and then I drove all night, because I didn't have the money to fly, and I drove all night from Pittsburgh to New Haven, got there around 4:00 in the morning, found a motel room, and my first appointment was at 8:00 in the morning. I was late for this first interview and a little punch-drunk from having only three hours of sleep. At the end of the first interview, the interviewer said, "Now, I just want to tell you that Yale is a very competitive and difficult place to get into, and we get many, many applications, and half of them we can get rid of very guickly, and then with a great deal of difficulty, we can get rid of another quarter, and the final quarter it's just like throwing them up the stairs and see where they land. So if you don't get in, don't feel bad". And, I said, being somewhat punchy

from lack of sleep, "Don't worry about it. I'll see you here next July". And, then, of course, going home, driving back to Pittsburgh, I thought, "You, idiot. Why did you say anything as stupid as that". But the interviews must have gone reasonably well, and I did get into Yale and had a wonderful three years of residency there. Shortly after I began my residency I signed up for the Public Health Service (PHS), because in those days they were drafting doctors out of their residencies. But you could sign up for the PHS, Commissioned Officer Reserve Deferment, and I signed up for this plan and negotiated when I signed up that they would send me to NIMH because of my research background. About three months before active duty, I get a letter from the PHS saying, "We are looking forward to your coming in July; you've been assigned to the Public Health Service Prison/Hospital in Lexington, KY, where they treat narcotic addicts". And I said, "There must be some mistake. We had an agreement. I was supposed to go to NIMH". And, they said, "Well, go to NIMH and see if they still want you". So, I went down there and they said, "Yes, we'd love to have you". So I called the Public Health Service and they said, "Great. Just tell NIMH to send someone to Lexington in your place". They didn't want me that badly.

- HK: During residency my area of research interest became student use of psychedelic drugs. I was spending a year at the student health service and it was the time of Tim Leary and Richard Alpert at Harvard and the whole psychedelic revolution and I was seeing youngsters coming in, taking these drugs, some of them talking about what a wonderful experience, others clearly having bad side effects from the drugs, and that became an area of interest of mine.
- AT: What kind of drugs were they taking?
- HK: Primarily LSD, or peyote, some of them were taking morning glory seeds, which contained
- LSD. I'm trying to think whether any of them were taking psilocybin at the time. My memory is no. Heavenly blue morning glory seeds had the most LSD, supposedly, in the seeds. And so my second research paper was the first one was on the insulin work on prolonged adverse reactions from students' use of hallucinogenic drugs. And then when I went to Lexington, I got very interested in narcotic addiction. So when people say, "How did you get into the field of addiction?" my answer is, "I trusted my government". That's, how I ended up at Lexington, and that's how I ended up dealing with addicts.
- AT: Up until that point, this was not something that you had wanted to pursue.

- HK: I didn't see any addicts during residency. I mean alcoholics, yes, and these youngsters experimenting with the psychedelics, but I really didn't see any heroin addicts, and cocaine was not around much then. There was some marijuana, but the marijuana explosion was just sort of beginning, and we would see some people in trouble with it, but not very many. So, I really had no experience with addiction.
- AT: You mean, in high school there was no marijuana?
- HK: I smoked a little marijuana when I was in high school, which was unusual. It was not around much. But my friends were musicians so I smoked occasionally. And when I went to college, it never occurred to me to look for it, so I never had any marijuana after I graduated from high school. I didn't find it all that interesting anyway. And there were not very much illegal drugs around then - it was mainly alcohol. Remember I graduated high school in 1952. This was the era mainly of drinking. Most of the things you did were alcohol-related, not other drugs.
- AT: Could you get back to thinking about narcotic addiction, treating narcotic addiction at the time you arrived in Lexington?
- HK: I spent the first couple of months there devouring everything in the library that they had there because I knew nothing about addiction and the rest of the people there didn't seem that they knew that much either. A lot of them were there for two-years like myself. Some of the great people in addiction had gone by then but George Valiant was there when I was there. Everett Ellingwood, Fred Glaser, Jerry Jaffe had been there before me. Marie Nyswander who started the methadone program with her husband, Vince Dole, had been at Lexington. So a lot of the people who ended up doing the work in the field of addiction in the United States had gone through Lexington as part of their public health service. Basically in those days it was psychological therapy. My job, the two years I was there, was heading up the Receiving Unit, which admitted and detoxified all the patients that came. Lexington was unique. It was more of a hospital than most prisons and more of a prison than most hospitals. Basically it was a minimum-security prison that held about 1,000 people, of whom, one-third were volunteers. It was the only prison that ever mixed volunteers and prisoners doing up to 10 years. That led to lot of problems, but that could take up the whole interview. Se we won't get into it. But, part of my job was trying to figure out who would benefit from, basically, psychological therapy, which was all we had to offer. We would decide which individuals would benefit from this therapy. We always had specialized groups, enough doctors, nurses, and pharmacists that I could run a group of just health professionals. We always had a lot of jazz musicians. I really enjoyed

working with the addicts. But certainly wasn't encouraged that what we were doing helped very much. The statistics were pretty clear that about 90% of the people that left Lexington relapsed within the first 30 to 90 days after they left.

- AT: Can you tell me a bit more about the population at Lexington?
- HK: It was predominantly white. The black addicts tended to be from the big cities. Lexington took all the addicts east of the Mississippi and all the women from anywhere in the United States. Fort Worth, Texas, took all the men west of the Mississippi. So, addicts from Chicago, New York, Boston, Philadelphia, Pittsburgh, a lot of them minority, primarily black and Puerto Rican, were sent to Lexington. A lot of the white addicts were also from the big cities, but also every southern town had their "good old boys" who were primarily addicted to cough medicine, codeine, prescription pills, and to paregoric. Paregoric is camphorated tincture of opium. The camphor does nothing therapeutically. It is put in there to keep people from abusing it because it tastes so bad. The addicts quickly learned that if you put it in the freezer, the camphor froze, so you threw away anything that froze and then you were left with the tincture of opium, and you boiled that and you got rid of the alcohol. Now you had pure opium and you could smoke or inject it. There was also a small group of Chinese addicts. When Lexington first opened in the mid-1930s, about a third of the patients were Chinese. But by the time I was there, there were very, very few Chinese. The people who were there in the 1930s were primarily those who had come over and left their families in China and had come here, hoping to make enough money to send for their families. They worked very hard and when they weren't working they were using opiates. That generation pretty much had died out by the time that I got to Lexington. It was mainly whites, partially from the southern towns and partially from the north, and blacks and Puerto Ricans primarily from the northern big cities.
- AT: You said that the only treatment available...
- HK: ...was group therapy. It didn't work very well.
- AT: Were they "psychologically minded"? Did you feel that they had some interest in learning why they used drugs and perhaps an interest in doing something about it?
- HK: A few did. It was out of that frustration with the existing therapy for this population that I decided to try LSD therapy, which I had read extensively about, and Lexington was doing LSD research at the time. So I submitted a proposal to the review board, which quickly turned me down. Then George Valiant taught me an invaluable lesson, because they had turned him down for what became his classic 10-year follow

up of Lexington addicts. His advice to me was, "Herb, if you want to get your research approved, get on the review committee". And so I got on the committee that reviewed research, which was what George had done, and that is how my LSD project got approved. And the company gave me the LSD, so I didn't need money. At that time there were two schools of thought. You had people who had taken LSD themselves, therapists, who thought that LSD therapy was incredible. And then you had therapists who had not used LSD themselves who said that it was a waste of time, and so I thought I would do the perfect controlled study. I would do a double-blid controller study with a group of volunteer patients assigning them randomly to LSD or placebo. The placebo was either 10 or 15 mg of dextroamphetamine, I don't recall which. My plan was to do the group and then take LSD myself, under supervision from experienced people there, and then I would repeat it with a second group of patients and see what happened. As I was nearing the end of the first group, Sandoz recalled the LSD because LSD had become a street drug by that time and they felt they were getting a bad reputation. Even though it wasn't the research drug that was leaking into the streets, they decided they didn't want any part of it. So, they recalled all of the LSD, but I had enough to finish the first group, and I had enough that I could have taken some myself. But I no longer had a scientific rationale for doing it, and although I had curiosity, I decided it wasn't worth it because the scientific rationale wasn't there. So I didn't take it, and I sent the remaining LSD back to Sandoz. I never published the study because I never could do the second group. When I was ready to leave Lexington, I debated between going back to Yale or accept the offer from the University of Massachusetts in Amherst to work there in the student health service, heading up the mental health part. My familv was hoping I would take the Amherst job. They liked that quiet way of life. And so, I visited, and I remember my Yale colleagues were sending me lists of potential research projects and the fellow from Amherst was sending me envelopes stuffed with autumn leaves. I accepted the Amherst position. I went up there to look for a house, and found myself getting more and more depressed. Now, I never get depressed. I am 99% of the time upbeat. But I was really getting depressed and came to believe I had made the wrong decision. I called Yale and said I would like to come back and discuss the possibility of returning there. And they said the offer is still open, and I ended up at Yale. I think one of the reasons was Gerry Klerman. He had come to Yale from Harvard and was Director of the newly opened Connecticut Mental Health Center. Many of the older members of the department at Yale were somewhat

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hard to deal with, except for Danny Freedman. Fritz Redlich, who was the Chairman, was a master manipulator. I remember when I had my interviews; the first one of the day was with Fritz, and then the exit one was with him again. And he said at the beginning of the day, "We would like to have you back, and are willing to offer you \$14,000 a year and an instructorship". The interviews had gone very well and the end of the day he said, "So, what were we talking about this morning"? And, I said, "We were talking about \$16,000 and an assistant professorship". And, he said, "That's exactly what we were talking about". I asked him later why he did that. He said, "Well, if you didn't think you were worth more, why should I pay you more or give you a higher position". That was the Yale tradition. As my friends used to say, "We know the administration is behind us, we're just not sure what they're doing there". Or, as one of my friends in the physics department put it, "The University behaves in such a way that you can work there unencumbered by institutional loyalty". But, be that as it may, I went back in 1966 and I stayed there until 1989 and had wonderful and productive years there. My first couple of years back at Yale, I ran the whole outpatient programs there, and then I ran an inpatient unit. I ran the psychiatric emergency room at Yale-New Haven Hospital. But I was a marked man because I had been at Lexington. The doctors were sending me their addicts. Parents wanted me to speak at PTA meetings. Addicts kept showing up at my door, and I finally decided, "Well, maybe this is something I should try". So I decided what I would do is continue my LSD therapy. I wrote a grant to NIMH for LSD therapy, and the project officer who was Roger Meyer, said, "It's a nice grant, but you don't have any treatment program. How do we know that you will get any addicts? Write a grant for an addiction treatment research program and we may be interested in funding the LSD on top of it". So, I did. And then again Roger called me and said, "This is an unusual year. We happen to have a little money. If you were to design the best treatment program for addiction, and do it in a way that built in research to evaluate it, what would it look like"? So, I designed it, and NIMH funded it. Of the six community-based programs funded then by NIMH and overseen by Roger Meyer, only the Yale Program remains. Roger and I were friends over the ensuing decades and research collaborators. He is one of the most astute and thoughtful analysts of addiction research in particular and psychopharmacology research in general. The most difficult part of getting the grant was getting it out of the department. The Acting Chair, Fritz Redlich had gone on to be Dean, Ted Lidz, did not want me to submit the grant. He said, "It's too much money for a young faculty

member". It was \$500,000 a year for five years, which back in 1968 was a lot of money. And he said, "You're too young to have that kind of money, and I don't think it's a worthy area to do research. If the government has that kind of money, they should better send it back to the treasury and lower our taxes".

- AT: Times have changed.
- HK: Only partially. There is still prejudice against drug addicts. I figured that I wasn't going to convince him, so I tried to figure out who could convince him. He had an executive committee of six people, I met with each individually, found whether they had either a personal or scientific interest in the substance abuse problem, and he was outvoted 6 to 1. The grant was submitted, and it was approved, and I have never had less than half a million dollars a year since that time. The first grant contained everything that we knew about treating addiction at that time. That is, there was a therapeutic community, modeled after Daytop Village in New York; a methadone maintenance program; an outpatient drug-free program for adolescents; an outpatient program for adults; and a storefront outreach run by a community organization of recovering addicts. We also had a research division to study all this. Ironically, I never got around to doing my LSD research, and to this day have not done it. But the unit kept expanding and improving treatment; because we kept discovering that it wasn't enough. The outpatient day program wasn't enough for adolescent drug abusers. The results weren't adequate. We even tried "alternative highs", such as sailing. The Coast Guard would follow our boat to make sure no one drowned! They were too young to put on methadone, so, I thought, well, we do have naloxone, which is a narcotic antagonist, used by injection. But if you give enough orally, you can get some absorbed. Now remember, the standard dose for naloxone in the emergency room might be 0.4 mg and I was giving 800 mg a day, orally, and getting an 18-hour blockade, and using up the world's supply of naloxone. The company, Endo, was having a fit but continued to supply it without cost to us. The naloxone was given as part of a day program at the end of the afternoon so that the only time the adolescent wasn't blocked from opiates was on weekends if they didn't take their take home dose.
- AT: So at this point you had already switched from the idea that therapy wasn't adequate to looking at medication treatments.
- HK: That's correct. I had learned at Lexington that there was something going on that wasn't going to be able to be reached by the best dynamic therapy that we had. Marie Nyswander, the co-founder of methadone maintenance, talks about that a lot in her book, about doing

psychoanalysis or psychodynamic therapy with addicts, and getting nowhere. That's when I became interested in doing biologic treatment. Not that I don't believe that some people can be helped by therapy, but it is not going to be by the classic dynamic therapy. It is going to be by new techniques such as CBT or the structured, confrontational, rigorous work of the therapeutic community. That's why, I have always been a big believer in the Phoenix House or Daytop kind of model, and feel that a comprehensive program should have everything. There is no one right answer. As I try and tell my young faculty that if anyone tells you they have *the* therapy for addiction, they're lying either to you, themselves, or both. There is no one therapy. This is a heterogeneous group of people, and you need as many arrows in your quiver as possible.

- AT: So therapy should be tailored to the individual.
- HK: Absolutely.
- AT: If it is not, it probably won't be adequate?
- HK: You got it.
- AT: First of all, compared to other people in your field, what would you say your key contribution has been to the issue of narcotic addiction? What have you stood out for?
- HK: Probably the use of medications for treating addiction in general, not iust narcotic addiction. I believe I have made two other major contributions: First, the idea of a multimodality approach, that there is no one right answer for addiction; and second, that psychopathology is very important. If you treat the addiction and don't treat the psychopathology, the individual is going to relapse. If you treat the psychopathology and don't treat the addiction, you are not going to treat the addiction. Regardless of why the individual got addicted in the first place, by the time you see him, treating the so-called root cause won't work. Just taking away the "cause" is not enough. You now have a disease on its own. If you are aware of what some of the problems are, you need to address them, but you also need to address the fact of addiction as a separate disease, a separate disorder, from any underlying psychopathology. Our group at Yale did a lot of work in trying to elucidate what that psychopathology was. Finally, and perhaps most important, we did a lot of work trying to develop different pharmacologic approaches. We were, I believe, one of the oldest methadone programs in the country. We pioneered both new ways of inducting patients onto methadone as well as better ways of treating them. People who started our program, if they were not employed, they spent six weeks in a very intensive day program where we tried to break the code of the streets. If they were employed, they came in a number of evenings a week. We believed

a very intensive approach early on is critical in treating the addict. Methadone is a medication, not a treatment. It has to be embedded in the appropriate treatment approach. That was one of our contributions, because a lot of the New York methadone programs basically gave drugs rather than a comprehensive approach.

- AT: Is methadone not enough for heroin addicts then?
- HK: No. A lot of them just were basically treated with methadone. Their philosophy was similar to the Hong Kong model where you had 10,000 people on methadone and 11 social workers! You don't end up helping the patients reach their full potential as a human being. We also disagreed about whether you had to stay on methadone life long. Doctors Dole and Nyswander felt that you needed life long methadone. We felt that the problem was that it was very hard to get people off methadone, and so one of the things we started in the mid 1970s was trying to develop better ways of detox. In 1978, we found that clonidine was the first non-narcotic drug that could adequately treat opioid withdrawal.
- AT: Would you say that clonidine decreased the length of time on methadone?
- HK: Yes, in some cases, but we found that clonidine was good, but it wasn't good enough, and we moved on to more rapid methods of detoxification by combining clonidine with naltrexone. I should mention the naltrexone story, because that's an interesting bit of history. We moved on from the agonist naloxone, as described earlier, first to cyclazocine, which lasted longer but had too many side effects, to naltrexone, which had just been developed by Endo. DuPont then bought Endo, and DuPont decided that there was really no profit potential in naltrexone. They decided to discontinue it. This was around 1972 or '73, I believe. I called contacts that I knew at the Washington Post and the New York Times, and I set up a press conference for three weeks hence, and called the company and said, "You have three weeks to change your mind or we hold a press conference talking about how unpatriotic DuPont is. Soldiers are coming home from Vietnam addicted to narcotics, and DuPont is putting profits above our boys' lives". And, a week before that period was up, they caved, and they continued with naltrexone. We were one of the centers that then helped develop it as an antagonist for FDA approval. I've always believed it was important to have antagonists as an alternative treatment to agonists like methadone and buprenorphine. Also, as mentioned earlier, we went from clonidine to a rapid clonidine detox, where you combine clonidine with naltrexone. The naltrexone precipitated the withdrawal and the clonidine ameliorated it. If you titrated properly and put a few benzos in, you could get

someone off heroin in two and a half to three days and have them maintained on naltrexone. Dennis Charney, who is President of ACNP this year, was one of the young faculty members, who collaborated on that research with me during his days at Yale. The original clonidine work was done primarily by Mark Gold, Gene Redmond, and myself, and was based on the pioneering work of George Aghajanian, a pioneer member of ACNP, on the locus coeruleus. For that research, the four of us were awarded in 1981 the APA's Foundation Funds' Award for Research in Psychiatry. Then we began to move on to lofexidine, but the company was not interested in it as a better agent for withdrawal.

In the late 1980s, we began research with the partial opioid agonist, buprenorphine. My first buprenorphine paper was in 1988, and now buprenorphine has finally been approved by the Food and Drug Administration about a year ago as the first opioid type drug available for office based prescribing for the treatment of addiction. Our program at Columbia is doing some very innovative work with buprenorphine. To finish up the 1970's, in the mid 1970s we showed that methadone was safe, even when given for long periods. Our study showed that patients who were on methadone continuously for five years were fine as far as their various organ systems. In the late 1970s we began to collaborate with Myrna Weissman, then at Yale, who was very interested in depression. We began also to develop probably the best cadre of young researchers that I think any substance abuse research program had in the country. Scientists such as Bruce Rounsaville, Tom Kosten, Rich Schottenfeld, Frank Gawin, Stephanie O'Malley, and Kathy Carroll, all of who have done important seminal work in the treatment of addiction. Other important scientists, such as Ray Anton, Bob Swift, and Mark Gold, have continued in the addiction field but went elsewhere. One of the things I have always been most proud of was the young scientist that I mentored and brought along, both at Yale and now at Columbia.

Also, in the 1970s and 80s, we kept adding to our treatment programs. When an adolescent day program wasn't enough, we developed an adolescent therapeutic community. When that wasn't enough, we developed our own therapeutic school. We developed our own medical unit because we felt our patients were not getting adequate care from the doctors at Yale in New Haven. We developed our own vocational training program. So whenever we saw a need, if we couldn't get it filled, we just developed it. And of course before dong it we researched it. We began in 1981 to develop medications for cocaine. Our research was built on the foundation of our cutting-edge treatment programs.

And we wrote papers about how to do it, how to improve it. One of the things that made it possible was that in the early1970s I developed our own foundation, the APT Foundation, Addiction, Prevention, Treatment Foundation. This began because we put in a grant that required a match and neither Yale nor the State of Connecticut was willing to match it. I went to the key movers and shakers in New Haven, the key leaders of the black, Jewish, Italian, Irish, Puerto Rican communities, the bankers, etc., and I said, "I want to set up a foundation to help prevent and treat addiction among our youth and young adults. I know you are too busy to be on the board, but would you suggest someone that would be speaking for you". And, interestingly enough, many of them said, "I'll be on the board". So we had a senior editor of the newspaper, the head of a large bank, the key leaders of the community from the various ethnic groups. New Haven is a very ethnic city. And so whenever Yale gave me grief, which they usually did, I would say, "Why are you talking to me? I don't run APT Foundation. Talk to the President of the board". Yale kept trying to get us to shut down our programs. They were very afraid that if the federal or state money dried up, that there would be a lot of pressure on them from the community to continue the programs, and they didn't want to be put in that bind. And then, of course, once APT got very active, they were very unhappy about the overhead they were losing, because by the time I left Yale in 1989, APT was probably bringing in 3 or 4 million dollars a year in grants, and we had another three or four million going through Yale, but it meant that Yale was losing a couple a million a year in overhead.

- AT: Would you say the research you were doing at Yale had a ripple effect?
- HK: We helped do some of the pioneering work in the pharmacologic treatment of addictions, first, narcotic addiction, and then in the early 1980s, cocaine and most recently marijuana. We developed a number of grants to try and develop biologic treatments for cocaine at a time when practically no one else was doing it. The group at Yale helped develop naltrexone for alcoholism, although honors for first developing it go to the Philadelphia group under Chuck O'Brien. Stephanie O'Malley published her article in the same issue of the Archives and those two articles led to FDA approval of naltrexone for alcoholism in 1994. We have been very helpful in spreading the gospel that appropriately given medications can help treat addiction and that addiction *is* treatable, which many still do not believe. We carried out a number of follow up studies to demonstrate the role of relapse prevention that Kathy Carroll spearheaded. No matter how good a withdrawal technique is or the follow-up medications, it isn't good enough without appropriate

behavioral therapies. Then in 1989, when my research was going very well, I received a call from Bill Bennett's office. The Office of National Drug Control Policy (ONDCP) had just been set up, and Congress had mandated a deputy for demand reduction, who was in charge of treatment, prevention, and research, and a deputy for supply reduction. He wanted to interview me for the demand reduction deputy. By this time, I was divorced, and was seeing a scientist at Johns Hopkins, Marian Fischman, one of the world's cocaine experts. When they first called me, Bill wanted me to go to Washington for the interviews, and I said, "I'm too busy. I'm leaving for Hong Kong in a week". We agreed to meet in New York and spent two or three hours at a hotel lounge, talking quietly with one of his staff present. We both like bourbon it turned out. At the end of that time, he offered me the position.

- AT: But it required Senate confirmation.
- HK: Before Senate confirmation, it required a White House nomination. Bill could not nominate for the job. He could just suggest to the President. The President nominates. The law set up the positions and Presidential appointees, requirie Senate confirmation. Some of the Republican right wing began to contest my nomination. They said I was soft on drugs. Their mode of operation was to take quotes out of context from my work. Take, for example, that first paper I described to you earlier on student use of hallucinogens. In that paper, when I described all these prolonged adverse reactions from the drugs, I also noted, "The good news is that most students who take these don't get bad reactions". And, they said, "In 1965, Dr. Kleber said that LSD was safe, leaving out the title of the article the purpose of the article. In 1983, we wrote an article on cocaine, describing how hard it was to treat and the problems it caused". We said, "The good news is that most of the people who try cocaine don't get addicted". Again they said, "In 1983, Dr. Kleber said cocaine was safe". And so Bill brought me in a room with the leaders of those groups figuring that once they met me, they would be fine and they would withdraw their opposition. It was clear early on that wasn't going to happen. Finally after about half an hour of fruitless discussion, he got up, walked over to where they were sitting, stood over them, and said, "If you're saying to hell with my deputy, I'm saying to hell with your organizations, and I can make it stick". Over the course of the next couple of weeks, some of the organizations were threatened with loss of their funding by the corporations who were giving them money, and they withdrew their opposition. At the same time, a number of scientific organizations began to write letters supporting my nomination, the ACNP, APA, AMA, CPDD, and thousands of school

superintendents among many other groups. In any event, the White House, the President, did nominate me finally. One of my favorite interviews was with the head of White House personnel who said, "Well, why should George Bush appoint you? What have you ever done for him? Have you ever campaigned for him? Have you donated money"? I said, "I'm an academic. I have no money to donate, and we don't have time to campaign". And he said, "So why should he appoint you"? And I responded, "Well, because I'm the best in the country for the job". And he said, "You don't understand the situation. What does that have to do with it"?

AT: Did you believe it?

HK: No, but it was a good line at the time. I couldn't think of what else to say. The original idea behind ONDCP was a very good one and our original policy was a balanced approach. Bill was a very bright, very thoughtful man, willing to fight for what he believed. One of the first things he did was ban the import of AK-47 weapons, which infuriated the NRA. He said, "Look, I am not about to have our police and DEA outgunned by the drug dealers". And he had the power to ban those imported guns. He felt that we needed to keep pressure on the supply side, especially in terms of putting pressure on production of drugs, especially cocaine, the major drug of concern then. Heroin had been guiescent and stable for most of the decade of the 80s; cocaine was going through the ceiling. If you looked at the graph of emergency room visits, deaths, and murders, especially after crack had come along in the mid '80s, cocaine was the drug that everyone was worried about. We knew where it was being produced, in Peru and Bolivia, and so the feeling was you put pressure everywhere. You put pressure on the growers. You put pressure on the countries to do something to help develop alternative crops. You put pressure on our Coast Guard and Customs in terms of dealing with smuggling. You put pressure on all areas of the supply side. It was a total comprehensive approach. And we did the same thing on the demand side. During the two and half years I was there, we doubled the budget for prevention and treatment and we started the community partnership program ending up with over 200 cities having community programs organized around doing something about drugs in their community. We tried to get the Department of Education to mandate that school-based education had to be based on scientific principles. My general idea was that anything that I did, on the demand side, had to be backed up by data. You didn't just plunge ahead. You looked for science, and you tried to figure out what was the best approach. I had a lot of support, fortunately, from a lot of different facets of the scientific and

treatment community. There were a number of important contributions that our Demand Program did that are too numerous to go into now but let me mention a few key ones. We markedly improved the key Federal data sources including the high school survey, "Monitoring the Future," the household survey, and the emergency room data, DAWN. We were instrumental in working with HHS to move NIDA, NIAAA, and NIMH to NIH and creating CSAT & CSAP. The concept of a Central Screening Unit that we had helped pioneer at Yale became a Federal program, and so on.

Let me tell you about my congressional confirmation for a minute, because that was an interesting experience. I had to be confirmed by the Senate Health and Human Services Committee, chaired by, I belive Ted Kennedy, and the Committee was not all that friendly toward Republicans. Still, it went fairly well with some rough questioning. And then near the end, Senator Kennedy said, "Dr. Kleber, how have you managed to keep your optimism up during all of these years of working in the field"? And I thought for a minute, and I said, "Well, what keeps me going is a quote from the Talmud, 'The day is short, the task is difficult. It is impossible to complete, but we are forbidden not to try". That ended the hearing basically. It's hard to ask nasty questions when someone has said that. But the fun part is that about a week later, my Yale staff asked what they could give me as a going away present. And I said, "I would like that quote, framed so I can have it on the wall of my office." My administrator, Roz Liss, called me later and said, "I can't do it". And I said, "Why"? And she said, "Because you misquoted it. You left out a line". I said, "I know I left out a line". I left out the third line. "The day is short, the task is difficult, the workers are lazy". There was no way in hell I was going to put in that third line. So, on the wall of my office across from the White House and in my office at Columbia is that quote, my quote, and it says at the bottom, "The Talmud, as misquoted by Herb Kleber".

- AT: Let's just think quickly about media hyperbole about addiction, especially in the 1980s, when there was an opportunity for government to change people's attitudes about drugs.
- HK: One of the themes of the strategy was "de-normalizing" drug use. You have to put that in context. During the Carter era, drugs had become "normalized". Marijuana reached its highest peak ever in 1980, the last year of the Carter Administration, when 33% of high school 12th graders were smoking marijuana on a regular basis. Peter Bourne, the President's drug advisor, not only advocated decriminalization of marijuana, but he also said that cocaine was "a perfectly harmless drug,

no more dangerous than skiing. Sure, a few people die every year from skiing, but most people who ski are perfectly safe". It was that kind of attitude about drugs, that cocaine is a harmless recreational drug, and marijuana, everyone does it, that led to sharp increases in use. Time magazine had a cover article in the early 1980s which showed a martini glass filled with cocaine, white powder, an olive, and the caption on the side was, "Cocaine," in big letters, "A drug with status," in smaller letters, "and menace". But what was the symbolism? It was the equation of the social use of cocaine with the social use of alcohol. And so we felt that one of the things necessary was de-normalization. Saying these are not safe recreational drugs. These are harmful drugs. Crack had come along which was devastating the inner city. So when you say de-stigmatize the addict or deal with the social problems, we tried to deal with the social problems. We felt that poverty was important, that racism was important, but addiction made everything worse. It is hard to get out of poverty if you are using drugs, and the communities that paid the biggest price for addiction were the communities of color. We would have leaders in there from the black and Hispanic communities who were saying, "You guys aren't doing a good enough job of getting the dealers off the street". They weren't saying, "Be nice to our dealers. They're deprived and they're poor". They were saying, "Get those dealers off the street. They're destroying our community".

- AT: It's interesting what you said about Ted Kennedy before. He conducted a hearing in 1979 on the use of drugs in which he was trying to say, "Look, the problem of addiction isn't just a problem in the cities, it isn't just a problem for persons of color". To what extent do you think there was political pressure to tackle what is seen as threatening to Americans versus the kind of hidden epidemic that was occurring in Manhattan penthouses?
- HK: We tried to address both. Our office pushed, for example, for model state laws that would deal with the middle class addict, the lawyers, business executives, real estate agents, insurance agents, and all of middle class America, encouraging workplace testing. I wrote the policies for drug testing in the executive branch of the government, which was not exactly an inner-city population. So, yes, we were very concerned that this was not simply an inner-city problem. We kept hammering at that again and again. This was a problem of America. This is a problem of the poor. This is a problem of the middle class. This is a problem of the wealthy. It does not spare any particular economic class. Bennett would often say that we should not permit open-air drug

markets in the Bronx or northeast Washington that we would not permit in the Upper East Side or Georgetown.

- AT: Do you feel marijuana is addictive?
- HK: It's not a question of do I feel it's addictive. A number of laboratories, including ours at Columbia, as well as clinical studies, have shown that marijuana does produce physical dependence and tolerance, and there is a clear-cut withdrawal syndrome. If you come to the symposium here at this meeting on the endo-cannabinoid system, there will be some of the leaders worldwide talking about the cannabinoid system in terms of how it may relate to alcohol and cocaine and opiate dependence, as well as how it may be more protective in terms of certain kinds of neuroshock syndromes. Again, you have to go where the science is. Also, the marijuana today is much more potent than it was in the 70's. Kids are much younger when they try it. In the 70's, the average age of kids trying marijuana first was 16 or 17. Now it's around 13. So, they're trying it earlier, they're trying a much more potent variety, and we now have the evidence that it can be physically addictive. I have treated a number of patients who can't stop marijuana use. When we put ads in the paper offering free treatment for marijuana use, we get a large number of phone calls. People will say, "I can't stop. I've been doing it 10 years, 15 years, 20 years. I can't stop". So, we are developing treatments for it. Now, having said that, I also believe there may be useful ingredients in the cannabis plant. In fact, when the Secretary of Health wanted to abolish the compassionate exception for marijuana. our Office refused to let them do it unless they got NIH to agree that they would study potential medicinal uses of marijuana. Unfortunately, they did the first and reneged on the second, and the Head of NIH at that time said that the reason was that none of the NIH institutes were particularly interested in studying it. They didn't feel it was very interesting. I think that's changing, as you will see from the symposium, that there's lots of fascinating research on the whole endo-cannabinoid system. We now have a ligand, we have receptors, and I think endocannabinoid research is going to be one of the growth areas of the next decade. So, I'm basically a scientist, and you go where the data is. And the data today suggests that marijuana can cause dependence. Our group at Columbia is probably the leading one in the country developing medications for treating marijuana dependence.
- AT: Thinking about contexts in which marijuana may be beneficial, in which narcotics can be beneficial, there`are people who feel strongly that marijuana should be legalized. What would be your opinion?

HK: Two very separate issues. As far as the use of opioid analgesics for pain, I come down very strongly on the side that the fear of addiction among people in pain has been greatly exaggerated. It is important to treat pain. It is important to treat terminal patients as well as chronic pain patients. When my late wife died a few years ago from cancer, she was in the hospital for six weeks, and one of the battles I fought with some of her physicians was how much analgesia she was going to get. I wanted to make sure she was not going to be in unnecessary pain. Having said that, it is always a trade-off; if you give too much, you depress respiration. And the issue can be that you hasten dying. So you somehow want to draw that fine line between not hastening dying, but at the same time not having people suffer. As a physician, I don't want people to suffer. But I believe we need better opioids, better long-acting ones, and we need better ways to treat pain that may mitigate some of these side effects. For example, one theory is that perhaps adding small doses of antagonists might delay the onset of tolerance and increase analgesic effects. So, my answer to your question is yes; it is one of the areas of my research. We are now into pain research also at Columbia. As far as cannabis is concerned, I believe there may be useful components of the plant that can be used for medicine. But we have no medicine that is used by the smoking route. It is too hard to adjust dose, and you may take a joint and take a deep breath and I may take a joint and take a short breath, I mean, how do you titrate dosage that way? So I have argued for a number of years that we should be doing a lot more research in developing components of the plant that can be used medically, synthetics or active extracts or whatever, and we should develop non-smoking routes, patches and aerosols, for example. My talk at this meeting is entitled, "The grass makes the other side of the hill look greener". It deals with why it has been so hard to study this class of drugs and look at the forces on both sides. Many of the people pushing medical use of marijuana could care less about medical use of marijuana. They really are using that as a stalking horse to legitimatize recreational marijuana, and in fact, they are not thrilled with the idea that we could come up with synthetics and alternative methods of administering it because that would take away the argument for legitimatising recreational use. On the other hand, you have people on the other side who don't want any research on potential medical uses of the cannabis plant for fear that will make marijuana legitimate and will heighten its allure. The trick is walking that thin line in the middle that makes it possible to do the research and develop it, and I think we're getting there. A number of the talks tomorrow night

are going to be very fascinating in terms of some of the data that is presented.

- AT: You have been a forceful advocate of the benefit of treatment, whereas not everyone has been as enthusiastic about it and instead believe addicts need to exercise proper self-control. And you, as far as I can tell, have argued that addiction can be treated and that position has been incredibly important in developing drugs that clearly treat addiction. Thinking ahead, 50 years from now, what do you think treatment will look like?
- HK: In the late 1990s, I gave a talk at NIDA's 25th Anniversary on the future of addiction treatment. I started with a slide that said, "Within 10 years, we will have antagonists and vaccines to all the major drugs of abuse". On the second slide I had the same quote, but giving the date as 1979. So I said, "Take my predictions for the future with a certain grain of salt".
- AT: That's like Nixon saying he was going to cure cancer.
- HK: That's right, the War on Cancer. It's interesting. People have trouble with the idea of a war on drugs. We tend not to have trouble with a war on poverty, war on cancer, war on racism, etc. But, that's another argument for another day. In the future I see, indeed, better agonists, long-acting blocking agents and vaccines to all of our major drugs of abuse. For example, at Columbia now we are researching an injectable form of naltrexone that will last 30 days. We are about to submit a grant in collaboration with Australian colleagues for an implant of naltrexone that will last up to a year. We have developed a buprenorphine induction and maintenance center, but we are also looking at an implant of buprenorphine, which may last 3 months. We are already in trials with a cocaine vaccine, and I predict we will have much better cocaine vaccines. I also think that we will know a lot more about how stress is related to relapse, especially to cocaine. And one of the things I see happening, even in the next 10 years, is that we would have a pump, here, the same way you have the insulin pumps or the pain pumps, and maybe planted just underneath the skin, with a button on the wrist, and the pump would be filled with a CRF antagonist, and when you feel stressed, when you feel a lot of craving, you push this little button on your wrist and it releases a CRF antagonist, and the craving goes away. I have been trying for three years to get hold of a marijuana antagonist. The company has not been happy about trying it for treatment of substance abuse, because they are studying it for much larger indications, such as obesity and dementia. They figure if marijuana impairs memory, maybe a marijuana antagonist will improve memory. If marijuana leads to the munchies, maybe a marijuana antagonist will

decrease appetite. So they are not terribly interested in using it to treat people who are marijuana dependent. But we want to get hold of it for that, and eventually we will. Likewise, I want like to get hold of a CRF antagonist, to try with our cocaine patients. We've tried, first my group at Yale and now our group at Columbia tried probably tover 25 different medications for cocaine, so far, unsuccessfully. We may even have a successful treatment and not know it. One of the arguments that I've used sometimes is that if Thorazine (chlorpromazine) had come along in the 1850s, it would not have worked to treat schizophrenia. Because what was schizophrenia in the 1850s? It was not just schizophrenia. It was bipolar disorder as well. It was tertiary syphilis, heavy metal poisoning, vitamin deficiencies, and there would have been so much noise. It would have been very hard for anything to show efficacy. And so, a lot of our research now is trying to look at subgroups of cocaine addicts. For example, we are doing work with cocaine addicts with ADHD to see whether that's a subgroup that may be more treatable. We are looking at depressed cocaine addicts, schizophrenic cocaine addicts, to see if some of these subgroups might be treatable with medications that already exist without any new ones. We hope to get into genetic differences. We have begun studies to try and develop subgroups that may be amenable to different medications. But, I guess I am both optimistic and pessimistic about the future, in terms of medications that is. I believe that we will develop much better medications than we have today. I also have a great deal of confidence in my patients and the tendency of human organisms to want to alter their consciousness. So, if we come up with a cocaine vaccine, I am sure some clever street chemist, will come up with a way of modifying the cocaine molecule so that the vaccine will not block it. So we are dealing with a very difficult situation because in many ways we are programmed to enjoy these drugs. I was at the Pontifical Symposium some years back, and I even helped organize it. And I asked Floyd Bloom to address the question of why do people take these drugs. And since it was at the Vatican, Floyd gave an appropriate answer. He said, "Because God, in His wisdom, created in the brain certain kinds of receptors, and, then God, in His wisdom, created in the brain these messengers, these neurotransmitters, that when they act at these receptors, the brain says, 'this is good. Do it again.' And then God, in His wisdom, created in the outside world these plants and these chemicals that mimic the action of these messengers, only more so. And when you take them, the body says, 'that was good. Do it again." So these are very potent agents, and we are wired to enjoy them. We are wired to enjoy having the brain changed like that.

And part of the struggle of treatment is to help people realize there are other ways to enjoy life. When you go down the road of drugs, it is going to lead ultimately to heartbreak and destruction, not just of you, but your family and the larger society. Finally, it is becoming increasingly clear that chronic use of these addicting drugs leads to long-lasting brain changes. Ultimately we need treatments that can improve these brain changes and restore the brain.

- AT: I have a final question and then I'll give you the last few minutes to finish your history lecture. It seems that you've looked at substance abuse chiefly through the lens of narcotics addiction. Is there a danger that we exaggerate the danger of narcotics addiction through privileging its damaging consequences over other forms of substance abuse?
- HK: Well, I'm not sure I agree with your summation. That is, I don't think I've looked through the lens of just narcotic addiction. In fact, much of my time during the last 20 years has been involved with cocaine. In addition to the research work at the Medical School, I spent half time at the Center on Addiction and Substance Abuse at Columbia (CASA), at a policy center with Joe Califano and I started in 1992 which has become one of the leading policy centers for substance abuse in the country. I gave that up in 2000 when my late wife had developed cancer and our program at Columbia Medical School had grown too big for her with my only being there half time. A lot of my energy and grants are involved with trying to develop new treatments for cocaine. But the model we are using is not for any one particular drug. We are surrounded by chemicals that mimic natural neurotransmitters, what one of my colleagues has called "false messengers", and they deceive the brain into believing this is desirable. So it isn't just narcotics. All these drugs, especially narcotics and marijuana, have receptors and endogenous ligands. Cocaine binds to the dopamine transporter and acts primarily through the dopamine system, but also through serotonin and noradrenaline. So it's not any one drug. It's all of these agents, all of these so-called false messengers. I also want to throw in just to make sure it isn't left out, that when I left government in November of '91 instead of going back to Yale; I came to Columbia with my late wife, one of the world's cocaine experts, who was then Professor at Johns Hopkins, Marian Fischman. The Dean, at the time, Herb Pardes, who remains one of my key mentors, recruited us. Marian and I spent nine years together at Columbia, nine wonderful years together, developing what I think is the best substance abuse research unit in the country so recognized many times by US News and World Reports Annual Issue on Medical Schools, and a superb cadre of young researchers.

Our program at Columbia spans everything, from our own animal colonies of baboons and Rhesus monkeys to imaging work with PET. We have seven human behavioral laboratories using non-treatment seeking volunteers to study cocaine, opiates, marijuana, pain, nicotine, methamphetamine, and alcohol, and clinical trials on promising medications. So we span the gamut from animal research to human laboratory studies and clinical trials. We have over 40 projects going, primarily NIDA-funded; and a P-50 Medication Development Center Grant and a T-32 Training Grant which trains the next generation of substance abuse psychiatrist researchers, both finishing their third 5-year renewal. Over these decades I have received many awards including election to membership in the Institute of Medicine, the Nathan Eddy Award for Excellence in Research from the College on Problems of Drug Dependence, the Jellinek Award and Distinguished Alumni Award from Yale, the Brinkley Smithers Distinguished Scientist Award from ASAM, and many others; been named in Best Doctors in New York and in the US; co-editor of the leading textbook on Substance Abuse Treatment. now in its 3rd edition; and influenced policy at the city, state, and national level to improve prevention and treatment of substance abuse in ways that would be beneficial both to the field and to patients. I received two honorary degrees; and serve on nine pro-bono boards including the Partnership for a Drug Free America; NIDA's National Advisory Council twice; etc. etc. All along, I have been fortunate to enjoy immensely what I'm doing. As I tell my young faculty, take your work but not yourself seriously. But I believe my contribution may lie as much in the people that I have mentored over these 35 plus years in the field as my own contributions. I am reminded of the epitaph of Andrew Carnegie that he wanted on his tombstone, "Here lays a man who was fortunate to be surrounded by people who were more talented than he was". And I have been fortunate to have a wonderful group of people, first at Yale, and then at Columbia. The latter include Richard Foltin, Ned Nunes, Francis Levin, Suzette Evans, Sandra Comer, Meg Haney, Adam Bisaga, Carl Hart, and Maria Sullivan, who I have had the honor to work with. Finally, and most important of all, with all the scientific accomplishments, awards, mentoring, in spite of all of the long hours, I have been blessed with three wonderful children, warm, loving, talented, and caring towards each other and their spouses and six delightful grandchildren, and a wonderful new wife, Anne Lawver.

AT: Thank you very much.

GERALD D. KLEE

Interviewed by William T. Carpenter, Jr Baltimore, October 9, 2008

- WC: I'm Dr. William Carpenter. I'm Professor of Psychiatry and Pharmacology at the University Of Maryland School Of Medicine and Director of the Maryland Psychiatric Research Center and I have the honor of interviewing Dr. Gerald Klee* for the Archives of the American College of Neuropsychopharmacology. This interview is taking place at the University Medical Center in Baltimore, MD on October 9. 2008. Gerry, if you'll go ahead and introduce yourself and say a little bit about how you got into medicine and where your career started.
- GK: Our country was in World War II when I completed high school in 1944. I immediately enlisted in the US Army and was sent to Princeton to study engineering. Before long they transferred our unit into the infantry. My military experiences redirected my choice of a career from engineering to medicine. After the war I enrolled as a premed student at McGill, in Montreal, I was admitted to Harvard Medical School in 1948 and graduated in 1952. The GI bill paid my way. By then our country was involved in the Korean War and I enlisted in the US Public Health Service (PHS). I served on active duty for two years and remained in the Regular Corps inactive Reserves until retirement age. My first PHS year was spent in a rotating medical/surgical internship in the Marine Hospital in New York. The next year was spent doing internal medicine at the Medical Center for Federal Prisoners in Springfield, Missouri. The two assignments provided a good medical foundation for me. In 1954 I began a Johns Hopkins Dean's Committee psychiatry residency at Perry Point, Veterans Administration Hospital in Maryland.

In 1954, chlorpromazine (Thorazine) was introduced to psychiatry in this country. At the time I was working on a ward of severely regressed chronic schizophrenic women veterans who had been there for years. In most cases they improved dramatically on Thorazine. Since this was a new form of treatment we didn't know what to expect, but we knew something unusual was going on when patients began communicating better and became accessible to simple psychosocial therapy and other forms of treatment. Many could eventually be discharged.

- WC: Could you say a word about what treatment was available before chlorpromazine?
- GK: Well, we were supposed to conduct psychoanalytically oriented psychotherapy with every patient, regardless of diagnosis. I was attempting to

^{*} Gerald D. Klee was born New York, New York in 1927.

do individual and group psychotherapy with severely regressed schizophrenic patients. My supervisor, Al Dreyfus, MD, was a psychoanalyst who had a private psychoanalytic practice. The psychotherapy wasn't helping my patients, but it helped me get to know them better than if I only saw them on routine ward rounds. It clearly wasn't the best treatment for schizophrenic patients. Once they were on Thorazine however, they became accessible to simple, basic psychotherapy and rehabilitation. Many were able to return home to their families for the first time in years.

- WC: Was there any psychopharmacology available before Thorazine?
- GK: I've read that in both Denmark and New York lithium salts were used to treat mania during the late 19th century. In 1949 the Australian, John Cade rediscovered the use of lithium salts for treating mania. It was years before it became widely used. Other than that, there was little I know of that we would now describe as psychopharmacology. However, there were attempts to treat mental disorders by physical means. For example, before penicillin was discovered many patients admitted to mental hospitals were diagnosed with general paresis. In 1919, Wagner-Jauregg introduced the malaria treatment for paresis, which is said to have helped this condition by inducing hyperthermia. Before chlorpromazine there was Dr. Egaz Moniz, who introduced prefrontal leucotomy, which was often used to treat schizophrenia before being discredited. Both Wagner-Jauregg and Egaz Moniz were awarded the Nobel Prize.

If one could call it psychopharmacology, insulin coma therapy was used with schizophrenics at Perry Point and elsewhere. I had no part in it except to observe it being conducted a few times. As far as I could tell it wasn't helpful. It was abandoned long ago. Carbon dioxide inhalation therapy was promoted to treat neurosis, but it was ineffective and could be dangerous. There are other kinds of "pharmacological" therapies that were sometimes used; Meduna had introduced the stimulant Metrazol as a way of producing convulsions, but ECT was used more often. I never saw any form of shock treatment being used at the Veterans hospital, but some hospitals throughout the country used ECT to treat a wide range of mental disorders. Over the years I saw many patients that suffered brain damage as a result of excessive amounts of ECT. I know it can be done safely, but it wasn't always done that way. As you know, methods of applying ECT have been improved and it is still used occasionally.

WC: So, your experience with chlorpromazine was very shortly after it had been introduced.

- GK: Yes, and it was very exciting. In a way that was a real awakening for me, as well as for the patients. I'll never forget it.
- WC: So, where did you go next in your career?
- GK: As I mentioned earlier, our teaching faculty were all on the Johns Hopkins staff; Jacob E. Finesinger, MD, generally known as "Jake", was the one exception. Jake, was a 1929 graduate of Johns Hopkins School of Medicine. He spent most of his career on the Harvard Medical faculty at Massachusetts General Hospital (MGH) in Boston, with Harvard professor Stanley Cobb, who was Department Chair. In 1950 he came to Maryland to found the University Of Maryland Department Of Psychiatry. John Whitehorn, Chair of Psychiatry at Hopkins and Head of the Dean's committee, who also had a Harvard background, enlisted his old friend Jake to help teach residents at Perry Point Hospital. I had great admiration for Finesinger. He must have liked me too, because he twisted my arm to come and work for him. He was trying to build his research staff at Maryland when he recruited me.
- WC: What year was that?
- GK: It was in 1956, which was two years after the awakening with Thorazine that I described.
- WC: So, you got into other areas of psychopharmacology then after you came to the University of Maryland?
- GK: Finesinger got a research grant from the US Army Chemical Center (ACC) in Edgewood, MD, to support research with psychoactive chemicals. I was paid a small stipend to work on it. Grant money was still pretty scarce in those days and ever since World War II, academic centers relied heavily on military funding for research. That situation changed as NIH funding grew in subsequent years. I didn't know we would be working with the Army until after Finesinger hired me. I needed security clearance before I could be told. The military connection didn't thrill me, but it worked out okay. We did some interesting research and I learned a lot.
- WC: Which psychoactive chemicals were you studying?
- GK: We started with LSD, because that's what the Army was interested in. In those days there was more hoopla than science about LSD. We chose to pursue basic science, which was more constructive than anything else we could have done. Our work with LSD in human volunteers led us to study serotonin among other things. At that time there was a debate about the role of serotonin in mental disorders. The subject was raised by Gaddum in 1953 and ignited by Woolley and Shaw's 1954 report that LSD acts as an antagonist to serotonin on rat uterus in vitro. This led to speculation by Woolley and Shaw, and later by others, that

mental illness, such as schizophrenia, might be somehow related to serotonin and it's receptors in the brain. Some thought this plausible since, like serotonin, LSD and some other "psychotomimetic" drugs contain an indole ring. "No twisted thought without a twisted molecule" was a popular slogan around that time.

Not long after Woolley's report, our group was among the first to publish studies that cast doubt on Woolley's serotonin hypothesis. This is not to suggest that serotonin plays no role in mental health or illness. As is known today, it plays a vital role in a wide range of brain functions, even that far back, there was a lot written about LSD, especially about employing it for psychotherapy. There was a lot of wild psychotherapy, but little good scientific research related to LSD. Over the next three years our group conducted biological, behavioral and cognitive studies related to LSD. Before embarking on LSD studies in our subjects I felt an obligation to volunteer as an LSD "subject" myself, both for ethical reasons and to learn first hand what an LSD reaction is like. I felt it would be unethical for me to administer a possibly dangerous experimental drug that I wouldn't take myself. I also reasoned that it would be useful in designing studies and in knowing how best to create a supportive environment for volunteers during their LSD experience. During the six hours or so that the effects lasted I wrote a detailed account of what I was experiencing. The 50 microgram oral dose I was given was enough to elicit the basic symptoms of LSD without preventing me from recording them. While undergoing this experience I used it as a basis for writing an outline of the kinds of things we should study; such as cognitive and perceptual functions, including immediate memory, abstracting ability, time sense and perceived changes in body image. I subsequently had my handwritten notes transcribed and saved them. They served as a useful guide in designing our studies for the next three years.

Our biological studies were aimed at gaining new evidence about LSD interactions with natural substances in the brain. It had been shown that brain serotonin levels can be raised by intravenous infusion of 5-hydroxytryptophan, or its effects can be blocked by BAS (I-benzyl-2-5-dimethyl serotonin). We demonstrated that, contrary to what happens with rat uterus in vitro, mental reactions to LSD were unaffected by raising brain serotonin or blocking it's effects in the brain. We published most of our results in peer reviewed scientific journals. In 1959 we also conducted and published a small study testing the effects of elevating brain serotonin in volunteer schizophrenic patients in remission. Brain serotonin levels were briefly raised by administering intravenous

5-HTP. The results suggested a possible effect on schizophrenic symptoms, but we discontinued the study because of potential side effects. Although the results were not conclusive, I think the experiment should be mentioned because it is one of the first published studies of its kind in schizophrenic patients.

In addition to other biological and psychological studies, we conducted and published extensive evaluations of the effects of LSD on cognitive functions in normal volunteers. Such information was generally lacking or inaccurate in the "scientific literature" of that time.

- WC: Gerry, say just a word about what kind of reactions, what was it like for the people who were taking LSD?
- GK: That will take more than a few words. LSD reactions vary widely. There are dramatic changes in perception, as well as in affect and in cognitive functions. Alterations occur in most sensory modalities, especially in vision and somesthetic perception. Our focus was on conducting studies of cognitive and perceptual functions, which had not been adequately studied by then. We also observed behavioral changes. A few "normal" subjects developed paranoid delusions while under the effects of LSD. A few other "normals" had hard to control violent impulses while under the effects of LSD. In one case it was necessary to administer I.M. chlorpromazine to calm an LSD subject who became potentially violent. The injection calmed the subject almost immediately. We learned how to identify such men in screening interviews and exclude them from our studies. I won't take the time or space to go into details here because I've published such information and it can be found elsewhere. I will list highlights of what we frequently observed in our subjects: Impulsive laughter often occurs in spurts shortly after the LSD takes effect. This seems "reflexive" and unaccompanied by an elevated mood. Affect tends to be heightened in positive or negative directions. Some subjects find their LSD symptoms entertaining. The social environment plays a significant role. Visual "hallucinations" are accompanied by synesthesia, in which flashes of light are perceived in time to the experimenter's hand clapping. Distortions of visual images and of somesthetic perception occurred in nearly all subjects. Body image distortions, depersonalization and sense of unreality were dramatic. Altered time sense and time distortions were reported, "Time has no meaning," "Time is standing still," "Time passes very slowly," and subjects without a timepiece often estimate the time to be much later than it really is. They may, in fact, express the feeling that days, months, have gone by since they began the experiment. We conducted experiments that confirmed those reactions.

There are frequent distortions of the way in which other persons are perceived. Features of others sometimes seem grotesque and constantly shifting; behavior of others may be seen as amusing or absurd, and sometimes threatening. These phenomena sometimes contribute to the experience of one's being isolated and utterly alone in the world, if indeed one exists, and if there is a world.

Subjects' perceptual distortions of other persons, or even themselves, may assume psychodynamic significance. For example, an experimenter who seems malevolent to the subject may seem to grow horns, or a subject who feels impotent may "see" his genitals shrivel up before his eyes. A subject who is experiencing diffuse boundaries may be unable to clearly differentiate his thoughts and feelings from those of persons about him. To LSD subjects, objects may seem to change shape and distances. Their bodies feel as though they are changing shape. A subject may feel he has no body; even uneducated subjects would say such things as, "I feel like I have no boundaries; I feel like I'm blending with the universe. Tie me up in a sack to give me some boundaries," and so on. We did a systematic study of human figure drawings by subjects during their reactions. Their spontaneous drawings dramatically reflected body image changes.

Symptoms can be magnified when a subject is placed in a dark, sound proof room. Around the time of our studies Canadian neuropsychologist Donald Hebb, known for "the Hebb Neuron", studied the effects of sensory deprivation (SD) on volunteer human subjects. No drugs were involved in those studies. John Lilly also studied SD around the same time. Both Hebb and Lilly described effects in SD subjects that resemble LSD effects.

- WC: Were there any unusual LSD reactions you'd like to mention?
- GK: Yes, we observed some potentially illuminating reactions that couldn't have been predicted. I'll briefly describe one such reaction that opens a window on significant events in the history of neuroscience.

One of our subjects stuttered severely, but since he showed no other psychological irregularities we included him in our studies. To our amazement, his stuttering disappeared while he was under the effects of LSD and returned as soon as the LSD wore off. The study in which he was a subject required a second dose of LSD a week later. Once again, the stuttering disappeared and returned when the LSD wore off. This experience reminded me of Stanley Cobb, MD, one of my psychiatry professors at Harvard. Cobb was accurately described as "A builder of the modern neurosciences", by his biographer, Benjamin White, MD. Unfortunately, Cobb was severely handicapped by his stuttering since the age of four. He made numerous attempts to overcome this problem, but without success. It is tempting to speculate that his choice of careers was influenced by his handicap.

Besides being a neurologist, a neurophysiologist and having the title, Bullard Professor of Neuropathology, Cobb was the founder and Chair of the Psychiatry Department at Massachusetts General Hospital (MGH) at Harvard. I will never forget Cobb's occasional lectures to our class. He would lecture while simultaneously writing on the blackboard with both hands. Because of his speech defect I couldn't understand anything he said, but my mind was occupied with speculations about the neurophysiology underlying this performance. Little was known about this condition at the time.

As I sat in the lecture room I wondered, "What is the connection between ambidexterity and stuttering"? "Is there some physiological conflict between speech and motor centers of the cerebral hemispheres"? While thinking about Dr Cobb and stuttering recently I looked for some answers. As far as I know those questions still haven't been fully answered, but in a 1942 report to the New York Academy of Medicine, Cobb said "stammering (stuttering) is often linked with a left handed or ambidextrous tendency". He indicated that although it has physical causes, associated social anxiety can lead to a "neurosis".

Beginning in his early career, when studying with Dr Adolf Meyer at Johns Hopkins, Cobb frequently sought psychoanalysis to relieve his "neurosis". He believed it helped him, although the stuttering was never conquered. This history may help explain why Cobb had many psychoanalysts on the staff at MGH. In 1951, when I was a senior medical student at Harvard, I had my psychiatry rotation at MGH, which was strongly under the influence of the psychoanalysts. When Cobb retired as department chair he was succeeded by his assistant Eric Lindeman, a psychoanalyst. Years later, I heard that the noted neuroscientist, Seymour Kety, MD, while at Harvard/MGH participated in a coup d'état, in which the psychoanalysts were overthrown and replaced by biologically oriented faculty. Returning to LSD and the underlying causes of stuttering, I always thought that "psychochemicals", such as LSD might be useful chemical probes of brain functions. What could have been learned if there had been LSD and neuroimaging back in Cobb's time? Might Cobb have found the cause and cure of stuttering?

Our contract with the Army Chemical Center lasted for only three years from 1956 to 1959. It was discontinued when Finesinger died in 1959 and I turned to other activities. However, I was recently surprised to learn that after we left, the Army Chemical Center continued a large
program of testing psychoactive compounds in army volunteers well into the 1970s. This program was under the direction of Colonel James S. Ketchum, MD, a Board Certified psychiatrist. I have had no contact with the ACC since our contract ended in 1959 and I had never met or even heard of Dr Ketchum. I only learned about him when I stumbled across online advertisements for his recently self-published book on the subject, called, *Chemical Warfare Secrets Almost Forgotten.*

- WC: You'd also gotten concerned about the adverse effects of LSD and could you say a bit more about the kind of experimental work that was going on in that era with LSD?
- GK: It seemed to me that the most common use of LSD was in attempts to treat mental disorders. I could understand using chlorpromazine to treat psychiatric patients, but LSD didn't seem to be a good candidate. As I mentioned earlier there was a lot of wild psychotherapy going on in the US, Canada and various European countries. Abram Hoffer, MD in Saskatchewan made a well publicized claim that he could cure skid row alcoholics with a single dose of LSD accompanied by a "transcendental experience". This caught on like wildfire across the continent. I never saw any evidence to support that claim. In 1959, Charles Savage, MD reported conducting psychoanalysis in patients to whom he administered LSD. Savage was one of several analysts that claimed analysis works best if the doctor takes LSD along with the patient. In 1961 I visited the Marlborough Psychiatric Day Hospital in London, which was a busy institution under the direction of Joshua Bierer, MD. There were many psychiatrists on the staff and, with Bierer's encouragement, most of them seemed to favor the use of LSD in treating their patients. In witnessing these "treatments" I neither heard nor saw any systematic theory or method of psychotherapy, if there was any. Frequently, patients were given the LSD and with little or no input by the psychiatrist and were watched over by the nurses until the drug wore off. I saw no evidence of systematic psychotherapy of any kind or recording of results.

It was around that time when I was recruited by Jonathan Cole, MD of the NIMH Psychopharmacology Research Center (PRC), also known as the Psychopharmacology Service Center. I was one of the consultants rather than being a full time staff member. Working with teams of psychopharmacologists I helped evaluate grant proposals from coast to coast in the US over a period of seven or eight years. Most of those I evaluated involved the use of LSD in psychotherapy. Under Cole's leadership the scientific standards we required were well above the usual levels of those days, but looking back, the standards were seldom met. I don't remember seeing systematic data from any studies that would

support the use of LSD in psychotherapy. In retrospect I can't help wondering if there was political pressure on NIMH to support this kind of research.

- WC: During that time, there was also interest in the military of experimenting with LSD. Could you say a little bit about what was going on and I know there was some concern on your part, certainly, in the letter you wrote to President Nixon in 1970.
- GK: Before discussing my 1970 letter to President Nixon about LSD I should mention my invited testimony before a United States Senate subcommittee four years earlier. In 1966 I was invited to testify before the United States Senate Subcommittee on Executive Reorganization, of the Committee on Government Operations, Co-Chaired by Senators Robert F. Kennedy and Abraham Ribicoff that was held in Washington, DC. May 25, 1966. As an "expert" witness I was asked about my views on the drug abuse epidemic on college campuses. The senators also wanted to know about scientific research with LSD and similar substances. In addition, the Senators asked whether I favor restrictions in the availability of such chemicals in order to limit recreational use. In my reply I said that neuroscientists can learn a lot about the brain by using such substances as "chemical probes" in the laboratory. I added that I believe the use of such drugs should be restricted to bona fide scientific research. In a direct reply to a guestion from Senator Kennedy, I described the alarming LSD reactions we were seeing in patients admitted to hospital emergency rooms and psychiatric clinics. I expressed the hope that Congress would support measures to limit those problems and to provide treatment for them.

Now I'll get back to my 1970 letter to Nixon about his proposal to ban the use of chemical weapons. In 1970, President Nixon announced that for humanitarian reasons he was proposing to ban the use of chemical weapons by the United States military. I hoped that if this included LSD and other "psychochemicals" it would discourage people from using them for recreation. Why would anyone use a chemical warfare agent for recreation, especially if its military use had been banned for humanitarian reasons? Unfortunately, it turned out that LSD wasn't included on Nixon's list of banned chemical warfare agents. What a missed opportunity. What a shame. Hoping to influence the decision, I wrote to President Nixon almost immediately. I recently gave you a copy of my letter. In my letter I told Nixon that between 1956 and 1959 I had studied the effects of LSD under a contract between the University of Maryland and the Army Chemical Center in Edgewood, MD. I said that for a variety of reasons LSD is believed to have no military value. Nothing would be lost by including LSD and similar "psychochemicals" among those agents that we would ban for humanitarian reasons. I reminded the president that our society is currently experiencing a dangerous epidemic of recreational drug abuse among young people. As a psychiatrist, I was seeing many of them admitted to emergency rooms and hospitals due to effects of LSD and related drugs. The prevalence was high among college students. Perhaps if those patients had known LSD was a chemical warfare agent they wouldn't have used it; especially if they knew military use had been banned for humanitarian reasons. In 1970, when I wrote the letter to Nixon I was a professor at Temple University in Philadelphia. I succeeded in persuading both senators from Pennsylvania, Hugh Scott and Richard Schweiker, to write letters to the president, supporting my appeal. Others supporting my appeal included Leroy Burney, MD, a former surgeon general of the US, many medical NIMH scientists and other psychiatry professors throughout the country; all of them writing the White House. I received a disappointing reply from the President's scientific advisor, Lee DuBridge, PhD, who wrote that it wasn't possible to discontinue work with psychochemicals such as LSD. He gave no explanation but he was polite enough to thank me for my concern. I've heard that research with psychochemicals at Edgewood was discontinued in the 1970s.

- WC: Let me change the subject and ask you to tell us what it was like when the ACNP was first forming.
- GK: The ACNP was founded in 1961. My entrance into the international neuropsychopharmacology community took place in 1958 in Rome, Italy, at the first meeting of the Collegium International Neuropsychopharmacologicum, where I presented a paper about Paranoid Reactions Following Lysergic Acid Diethylamide. The report describes a study in which we were able to correlate the occurrence of paranoid reactions with personality factors in subjects. This enabled us to screen out subjects at risk for pathological reactions. In 1961 I was invited to become a founding member of the ACNP. The organization was not large in the beginning and meetings were small, informal and close to my home in Maryland. As the years went by the ACNP grew and meetings were more often distant from my home, my family responsibilities made it more difficult for me to attend them regularly.
- WC: Would you like to say something about yours research in epidemiology?
- GK: Before Finesinger died, he arranged for me to be the Director of the outpatient Psychiatric Service at Maryland, a regular job rather than grant money. I enjoyed working with patients. There was less opportunity to

engage in psychopharmacology research so I fulfilled a dream I'd had since medical school, of getting into epidemiology. One summer, during medical school, I had an internship in the division of epidemiology in the Department of Health in Massachusetts. I got hooked on epidemiology. My thoughts were, "Wouldn't it be nice if we could put epidemiology and public health together with general medicine and psychiatry; all rolled into one". So, now I had my chance. Right across the street from the UM Psychiatric Institute, where we were, was the headquarters of the Western Health District (WHD) of Baltimore City Health Department. I made a liaison with them, working with the health officer, Dr Wilson Wing, as well as with Chief public Health Nurse, Anna Scholl and her nursing staff, who made regular home visits and knew the families in the WHD. This was in 1959, before Community Mental Health was even off the drawing boards. The Baltimore Health Commissioner agreed with our plans and I got a small NIMH Demonstration Grant for the project. Next, I became a Consultant to the National Institute of Mental Health Office of Biometry and worked with the Director, Dr. Mort Kramer and his associate, Dr. Anita Bahn and other staff in developing the Maryland Psychiatric Case Register. Data derived from this program provided psychiatric statistics that were useful for planning and research. We also collaborated closely with the Maryland Department of Mental Hygiene staff. We were able to report on all episodes of psychiatric care, excluding private outpatient care, but we had data from private hospitals. Identifying information was protected for all patients. We had no access to their names or other personal information. This was as it should have been to protect patient privacy. With those data we were able to make some important correlations and fulfill a dream. The way my mind works, I see public health, psychiatry, neuropsychopharmacology, general medicine, epidemiology etc, linked together in complex ways. There are also links with social and economic factors. I wasn't the first person to think of that, but that approach was rarely put into practice.

The study I'm most proud of is one in which we studied rates of diagnosed mental illness broken down by census tract in Baltimore. In this study, we looked at data for many issues, social, economic, medical, psychiatric etc throughout the city. We found some important correlations. For example, alcoholism and drug addictions are an important part of this picture. Correlations that we found between addictions and the other variables in our study should be of interest to psychopharmacologists. For example, residents of Baltimore's vice headquarters, "The Block" had exceptionally high rates for crime, venereal disease, tuberculosis, mental illness and drug addiction. In our work with the Baltimore Health Department we attempted to develop integrated services for these problems.

- WC: Are there other things that you think we could touch on?
- GK: Today's discussion began with the time when psychiatrists had little more than psychotherapy to offer patients, even the sickest ones. From there we went on to speak of the benefits the psychopharmacology revolution brought to psychiatric treatment. Since then, our field has gone from one extreme to the other. Drugs are in and psychotherapy has lost a lot of ground. Today there are forces operating that increasingly require psychiatrists to prescribe drugs for most patients in 15 minute interviews a few months apart. Under these conditions there is a risk that the psychiatrist will have insufficient time to even get to know the patient or make an accurate diagnosis. If the patient has psychotherapy at all, it tends to be by nonmedical counselors who have little chance to communicate with the prescribing psychiatrist. Psychopharmacology is of immense value, but I don't believe psychiatrists can be effective without spending time listening to their patients. Listening is an essential element of both psychotherapy and clinical psychopharmacology. Outside of psychopharmacology, epidemiology and public health, my other professional interests have primarily been in clinical work and teaching. I continued seeing patients in private practice until my retirement. In my experience with patients, treatment with psychotherapy was augmented by appropriate medication when it was called for. I also continued supervising psychiatric residents and helping them learn how to do psychotherapy. I first taught at the University of Maryland, then at Temple University in Philadelphia and then at Johns Hopkins until I retired. My two major loves have always been my family and my work.
- WC: I've enjoyed doing this interview with you. I think we've covered a lot of material and it might be a good place to end it. Thank you.
- GK: Thank you, Will.

CONAN KORNETSKY

Interviewed by George F. Koob San Juan, Puerto Rico, December 12, 1995

- GK: Hi, I am George Koob. I am at the Scripps Research Institute in La Jolla, California and I am interviewing Conan Kornetsky* who is a professor in psychiatry and pharmacology of the Boston University School of Medicine. Dr. Kornetsky is the former editor of *Psychopharmacology*, the Journal, and he is also a founding fellow of the ACNP and he has worked for many years in both animal and clinical aspects of psychopharmacology. And, so we will begin today with asking Dr. Kornetsky what sort of training did you have to begin in this field and was there any kind of specialized training in this area? And, also how did you become interested in psychopharmacology?
- CK: Well, I think I was interested in science, first, and started my undergraduate work in the College of Engineering at the University of Maine, Oromo. This was interrupted when I went into the Army Air Corp in March, 1944 during WW II. When I was discharged from the service in December 1945 and went back to school at the University of Maine and I decided that I did not want to be an engineer and started my second vear of college as a Psychology major. As a senior thesis I decided to compare social attitudes of members of Phi Beta Kappa with those of the Tau Beta Pi, the national honorary engineering society. Because I had no hope of being elected to an honorary academic society I decided that I would study the members. The findings were interesting in that, as expected, on every test of liberalism the Phi Beta Kappa scored higher; however, I could find no difference between the two groups in religious upbringing, occupation of major bread winner in the family or any major social or economic family difference. From this I concluded that the differences I saw were the result of their respective curriculum. Many years later I heard a symposium lecture by a sociology professor that compared engineering and liberal arts students and came to a similar conclusion. that curriculum counts.

As a senior I decided I wanted to be a clinical psychologist. The only US approved clinical psychology program in New England at that time was at Yale. Considering the fact that I had a very uneven academic record I did not apply to Yale. A young philosophy professor said he had been at a University in Kentucky before coming to Maine and suggested that I see if the University of Kentucky had an approved program. If so he said he would write the type of letter that would get me accepted and

^{*} Conan Kornetsky was born in Portland, Ohio in 1926.

it did. Although I was interested in science my primary ambition was to become a clinical psychologist and work with patients. Although I had the GI Bill when I went to Kentucky I found I needed additional funds so I found a job as a "House Boy" at a sorority house. However, because as an undergraduate at the University of Maine where I took a course in IQ testing that qualified me as a mental tester, about a month later I was offered a job in the Clinical Psychology Department at the US Public Health Service Hospital/Prison for the incarceration and treatment of drug addicts in Lexington.. Because the stipend was "board, room and laundry" it was obvious that I needed to make a career decision. As you probably suspected I decided to give up the sorority house boy job. The hospital job was quite consuming. I administered every afternoon, four to five days a week two to three IQ tests. In the evenings I started to spend time in the day-rooms of the addict patients. The most interesting day room was the one in the Research Department. Harris Isbell, who was the Director of Research, came around almost every evening to check on patients who were subjects in experiments. About this time he was planning an experiment of chronic barbiturate administration in human volunteers to determine if the convulsions and psychosis that had occasionally been reported were due to withdrawal or was it an intoxication phenomenon. Because Isbell did not have a psychologist in the Research Department and luckily for me he believed that a student who was approximately two months into his graduate program was qualified; I was invited to participate. Thus, my entrance into the field of psychopharmacology was based on a number of chance events with the elimination of any single one may have resulted on a different career choice. This experiment was carried out in five post-addict volunteers and I was one of the co-authors of the paper published on it. . It was the first paper in my research bibliography; it was written by Isbell, Altshul, Kornetsky, Eisenman, and Fraser and published in the Archives of .Neurolpgy and Psychatry in 1950. Isbell was pleased enough to suggest that I submit the detailed psychological finding in a separate paper that was ublished in the Archives of Neurology and Psychiatry, written by me alone in 1951. The surprising thing was that in 1948 and '49 when that experiment took place it was not known that there was physical dependence to barbiturates. In someway that clinical experiment probably had more direct impact upon what clinicians do than anything I have ever worked on. This long wordy answer is how I became interested and committed to a research career.

GK: Now, was this part of your graduate work or something prior to your graduate work?

- CK: No, it wasn't actually part of my graduate work; however, it contributed to my graduate education. It was actually carried out while I was a first year graduate student. During that time the research was so time consuming that I actually began to have academic difficulty. However, the Chairman of the Psychology Department at the time, James Calvin, in order that I continue my research began giving me academic credit for my work at the hospital allowing me to not take as many courses as most of the graduate students. He did require that I give a seminar on my research at the weekly department seminars every semester and most important pass the PhD qualifying exam that consisted of seven areas of psychology. In fact, I began to have trouble in graduate school because I found that it was more fun doing the research than to go to class.
- GK: So, what was your dissertation in for graduate school and where, so we have all the details?
- CK: Okay, well, my dissertation was at the University of Kentucky, and although my dissertation advisor of record was the Chairman of the Psychology Department, my de facto thesis mentor was actually Abraham Wikler at the Addiction Center where the work was done. My dissertation was on the effects of anxiety and morphine on the perception of pain in humans. It was part of a whole series of studies done in Lexington, trying to understand the analgesic action of morphine.
- GK: Do you want to, maybe, kind of say some things about your interactions with Abraham Wikler, given that he was probably one of the primary movers in the group that you worked with.
- CK: Well, at that time, Abe was very interested in trying to understand the role of anxiety in the analgesic effect of morphine and how did this contribute to its addiction liability. I think I should mention what my first encounter with Abe was like. The first year I was at the Addiction Center Abe was on sabbatical. In June of that year, 1949, I was on vacation when Abe returned. At my first day back I heard that Abe had returned. Although he was back for only a month he had already started doing experiments in spinal dog preparations. In these experiments he recorded autonomic responses of the animal on smoked loops of paper which were later fixed by shellacking the loops. Prior to fixing them with shellac he had them hanging on pegs just outside of his door. In my eagerness to meet him I brushed against some of the unshellacked loops. I then heard the first words that Abe ever said, or I should say, yelled at me. It went something like, "Who the hell is this stupid ass"? After this he became my mentor and great friend. Also, we were interested in what Abe was always interested in, what was the

driving force resulting in addiction and why people liked morphine and heroin, you have to remember at that time the major belief was that drugs were reinforcing because they normalized pathology. And, most of the clinical work at the hospital at that time and a lot of the research was directed to understanding the psychopathology that made individuals vulnerable. Wikler believed that an important component of opiate action was its anxiolytic effects. Because of this we developed a very simple experimental model for the study of anxiety. Of interest was the directness of Wikler and his willingness to reevaluate his position. Most mornings at 8:00, Abe, Harris Hill and I would meet in the cafeteria for coffee. Harris Hill was a recent PhD in experimental psychology from Indiana University. Although a new PhD, Harris did not attend graduate school until he was, if I remember correctly, in his late 30s. During these meetings of the three of us which were more mini-seminars Abe would conduct discussions about current research, future research and the field in general, and at one of these mini-seminars, I suggested a method to experimentally study the effects of morphine on anxiety. It was a simple reaction time experiment in which the subject would release a telegraph key at the onset of either of two lights. The only difference was that with one light it indicated that the subject would receive an electric shock to his hand at the completion of the response. The criterion of receiving the shock was based on the subject's medium reaction time on a previous series of unpunished reaction times. If the subject's reaction time shortened in order to avoid the electric shock, the criterion to escape the shock was increased in the next series and so on. When I first presented this model Abe's first response was something like, "that is the most stupid idea I have ever heard". However, a few days latter at our morning meeting he said that he has been thinking about the experiment and if we made certain changes he thought it might work. With Abe's suggestions the experiment did work. In a control situation the subject's reaction at first became faster but as the criterion was raised, the reaction time precipitously became disorganized and markedly slowed. Morphine normally caused an increase in reaction time and under these conditions the fastest reaction time was when the experiment was carried out under the influence of morphine. Of interest was that we ran a few non addict volunteers. They were psychiatric residents at the hospital. There were two sessions for each subject, one control and one with morphine. If the first session was a control, if I remember correctly, none of the residents returned for the second sessions. Also, we reactivated an ulcer of one of the non addict subjects.

- GK: Now, after you finished your PhD at the University of Kentucky, did you do a postdoc like people do today?
- CK: No, I believe post doc appointments, if any, were rare in 1952. The strange part of the story was that when I was a graduate student I also held a commission in the US Army reserves. Although I had served in the Army during WWII when I was an undergraduate student and I was under the GI Bill, which was enough for tuition and books, I had to supplement this by working in food service. Also, I found I could pick up additional funds by taking ROTC. So, when I received my BA degree I also received a commission in the US Army, never thinking that we would soon be in another war, the Korean War. Thus, while I was in graduate school and working at the USPHS hospital I was called to active duty in the Army. Because the USPHS, a commission corps, was still part of the armed forces, a hold-over from WWII, Dr. Isbell was able to have me transferred from the Army to the commission corps of the USPHS while I was still a graduate student doing research at the USPHS Hospital and completing my PhD thesis. Being in the Commission Corps of the USPHS meant that they could send me for duty anywhere which in my post-doctoral year. However, that did not take place until I finished my thesis and I was assigned to work at the Lexington Hospital.

During my last year as a graduate student, in 1952 to '53, in addition to working on my thesis on the *Effects of anxiety and morphine on the anticipation and perception of painful radiant thermal stimuli*, that was to be published in *Comparative and Physiological Psychology*, in 1954 I was assigned to work on a clinical study of juvenile drug addiction, a rapidly developing problem at that time, with a psychiatrist, Donald Gerard who was fulfilling his military commitment in the USPHS. Also, during this period the Research Department at the hospital became part of NIMH. In June 1952 Gerard and I were transferred to NY City to continue the study of juvenile drug addiction. During this period it was not expected that one do a post-doc. The actual awarding of my PhD was at the August graduation at the University of Kentucky.

The juvenile addiction study was unique in that our control group was non drug users who were friends of heroin addicts. Because of good contact we had with juvenile addicts we were able to find a group of adolescents who were friends of addicts but were not addicts. We originally tried to recruit juveniles who had never used heroin. We found none that had never used heroin that matched our heroin addict group. We thus changed our criterion to not currently using and who never became dependent; however, they had to be friends of juvenile heroin

addicts and who lived in areas of NY with high prevalence rates of heroin addiction. This was a very difficult group of subjects to find. It took us a year to to collect 22 subjects that met our criterion. We found some interesting difference between the control and the addict group. Gerard and I were also given another role in NY and that was to help a research group at NYU get started on a social/psychological study of juvenile drug addiction. This group, under the direction of Isidor Chein did the most complete study of juvenile drug addiction in an urban setting that was published in a book, The Road to H. Gerard went to work with Isidor Chein and was one of the co-authors of that book. At the completion of our study I was assigned to work with Murray Jarvik at Mt Sinai Hospital and at the Long Island Biological Laboratory, in the academic year of 1953-54 on the psychological effects of LSD. I coauthored a number of papers on the effects of LSD in humans and one on the effects of LSD on Betta Splendensa Siamese Fighting Fish. Our paper was published in Science in 1956.

- GK: I didn't even know about that one!
- CK: Not many people know about that one.
- GK: That one, I missed; go on.
- CK: So, I spent some time studying LSD and I became very much aware that people taking LSD all say that their perception is improved and you wonder. Well, I looked at LSD in terms of perception and they are always impaired, so how is it improved? I think what is improved is that actually they are seeing the world more realistically, but they are losing perceptual constancies. So, when we sit in a corner of a room, we see it as a cube; however what we are actually seeing is a trapezoidal room. Under the influence of LSD subjects often report that the sides of the room are leaning because they have lost the perceptual constancies that allow us to function in a visually trapezoidal room. It is sort of like going up in an airplane the first time and you look down and everything looks like toys and then after you fly for a while it no longer looks like toys. So, I think that is one of the effects of LSD, it breaks down these perceptual constancies that are necessary for functioning. At the end of that year NIMH assigned me to the laboratory of Clinical Science at Bethesda, directed by Seymour Kety.
- GK: Was this where you did your schizophrenia work?
- CK: Yes, although I continued some of that work when I went to BU in 1959. At NIMH I did a number of psychopharmacology studies with many of them directed toward the study of schizophrenic patients. I also collaborated with Kety and Louis Sokoloff on cerebral metabolism studies in normal aged volunteers. In my participation I measured and

recorded galvanic skin responses of the subjects. I worked closely with Allan Mirsky during this period. Our experiments suggested that the primary behavioral deficit in the schizophrenic was one of inability to focus attention. This led to our proposing a hyperarousal theory of schizophrenia.

- GK: Now this theory, as you well know, is persistent today and can be found in some of the presentations, even at these meetings associated with inhibitions of pre-pulse.
- CK: Yes.
- GK: The blocking of pre-pulse inhibition. But what was the date that led you to this early insighting factor; it was one of the first, if not the first, insights that there was a breakdown in the intentional processes in schizophrenia. What exactly cued you and Mirsky into this idea?
- CK: Allan Mirsky arrived at NIMH Bethesda at about the same time as I did in 1954. Although we were in different laboratories we became close personal friends and research colleagues. The findings and the development of a hyperarousal theory of the schizophrenic was prior to my leaving Bethesda in June, 1959. Allan had been researching the attention problems of petit mal epilepsy patients using a very simple but sensitive test of attention, the Continuous Performance Test (CPT). We then thought it might be interesting to see if schizophrenic patients would show a deficit on this test. The deficit seemed specific when compared to some simple test of cognitive function that did not require continuous attention. We also found that chlorpromazine in normal subjects' impaired attention; however, in schizophrenics it improved attention. The question was why it has different effects in normals and schizophrenics? Our hypothesis was simple. We postulated that attention performance, as a function of arousal, was an inverted U, that is, as arousal increased performance improved however, at some higher level of arousal, performance began to deteriorate. Thus we hypothesized that for chlorpromazine to improve the performance of a schizophrenic patient, the patient must be on the descending limb of the inverted U, i.e., hyperaroused. In a later experiment done in rats when I was at Boston University, we published an animal model of the hyperarousal theory in which we caused increased arousal in a rat by low level stimulation of the mesencephalic reticular formation. This resulted in performance impairment in an animal adaptation of the CPT. Under these conditions chlorpromazine improved performance of the rat while under basal levels, i.e., no stimulation, chlorpromazine impaired performance. Unfortunately I do not believe that we impressed the Schizophrenia research community.

- GK: When did you go to Boston? Was that after that period at NIH?
- CK: I left NIH in June of 1959 to take a position of Associate Professor of Pharmacology at Boston University of Medicine. Although I was happy at NIH my acceptance of the offer at BU had much to do with personal reasons. My wife, Marcia who came from Boston wished very much to return because of the illness of her father. At BU I was required to be responsible for all the lectures on centrally acting drugs. It was a great learning experience for me. When the Chairman of the Department assigned me to give the lecture on anti-epileptic drugs and I told him that I didn't understand anything about anti-epileptic drugs, he said, "You have all summer to learn". So, I prepared one of these lectures. You may have been in the same situation, when you prepare a lecture in a field that is new to you, in that one hour lecture you tell the students absolutely everything you know about a subject and that you are afraid that you are going to get a question.
- GK: Didn't you start animal experimens at BU?
- CK: Yes, I set up two laboratories in Boston, a rat laboratory at BU and laboratory for human experiments at Medfield State Hospital. However, I should regress at this point. While at NIH I started working with Joseph Cochin who was in the Cancer Institute. He was doing pain studies in rats as well as clinical analgesia studies in cancer patients. When I was at Lexington my pain and analgesia studies in humans involved the measurement of autonomic responses. When I met Joe Cochin who was doing clinical work in the Cancer Institute I mentioned that I thought I might be able to develop a non-verbal measure of pain in patients using autonomic responses. Although, I spent a year in this effort it turned not to be a reliable measure. However, my year of contact with cancer patients was an important learning experience for me. One of the things I learned was that the clinical environment is almost as important as the analgesic drugs in keeping a patient comfortable. At the Cancer Institute at NIH there were two clinical wards. They were mirror images of each other and the same physicians serviced both wards. Assignment of patients to either ward was random. In the course of my studies I became aware that in one of the wards a lot more morphine was used than the other ward. The only difference between the wards was that one had a stable nursing service and other one did not.
- GK: So, the patients with the stable nursing staff used less morphine?
- CK: Yes, that's right. It gave clinical support to my PhD dissertation findings in which I found I could manipulate the experimental pain threshold by changing my relationship with the subjects.
- GK: Interesting.

- CK: Yes. This carries over in animal experimentation. If you are gentle you will get a different result then if you are not gentle. So, in Boston I set up an animal laboratory.
- GK: Now, this would have been about the time you published that famous paper, or did the work on that famous paper with Joe Cochin that tolerance to a single dose of morphine can last for many months, right?
- CK: Yes. That's right. We started working together when we were both at NIH. Joe's main dependent variable was the "hot plate" pain procedure. I added a simple behavioral method to the experiments. I measured swimming time to a goal in what you would call a "single alley maze". An aside is that many people thought that a critical thing was that the alley had to be 13 feet. The reason for 13 feet was that I had a counter that was thirteen feet long with the last foot hanging over a sink that allowed ease of draining. The importance of these experiments with Joe Cochin was that there was tolerance to a second dose of morphine administered months later. Also, the tolerance to the analgesic effect was more lasting than the effect on swimming. We tried to determine why there was such a long term effect. Among the things that we entertained was that tolerance may be a type of an immune phenomenon. Actually this hypothesis was suggested in the 19th century. We tried some passive transfer experiments and some worked and some did not. The thing was that it probably was a real phenomenon; however, it was never stable enough that would allow you to go on to the next step. It was sort of like, you have a finding and you want to investigate it, but you always have to go back to make sure that you have the phenomenon every time you do it. So, you always have to start at zero; you never can advance very far beyond that, because you will always have to demonstrate each time that you still have the phenomenon.
- GK: But, in a sense in some of your latest work you are more or less, pursuing the same question, namely what is the basis for these long term effects of morphine.
- CK: Yes.
- GK: I mean, you have some new work with brain imaging of brain activity if I remember correctly. Do you want to tell us a little bit about that?
- CK: I did collaborate with Dr. Linda Porrino who at that time was a member of the Laboratory of Cerebral Metabolism at NIMH and demonstrated that the brain does change with continued use of a drug. The long term effects of addicting drugs really started with my work with Joseph Cochin. These experiments that I have already described certainly suggested that there must be some long term effects that may contribute to continued drug use. The story of a different long term effect appears

in a number of our experiments, many not related to tolerance. The big leap on long term or residual changes in the organism started with an interesting phenomenon having to do with brain stimulation reward that was not discovered by us. There is an old observation of brain stimulation of reward that if rewarding brain stimulation is left on, rats will press levers to turn it off. The question that we asked was why the rat turns it off? Does it turn off the stimulus because it is the onset that is rewarding and the rat learns that if it turns it off the experimenter will turn it back on? So, we thought we would see what morphine did in this model. If morphine raises the threshold to the onset of the stimulus it would suggest that the stimulus became nociceptive, however, if the threshold was lowered it would suggest that the animal was turning the stimulus off so the experimenter would turn it on and it was the rewarding effect that was driving the behavior. This seemed like a nice simple experiment that answered an old question. However, something else was happening. We were using large doses of morphine, 10 mg/kg and about the third time, the first animal we studied received this dose of morphine my student who was carrying out the experiment came running into my office and said that he did something bad to the rat. He said the rat appeared to be having some kind of seizure. Well, the animal wasn't having a seizure; what it was doing every time it got morphine, not at first, even when the stimulating current was not on, the animal would bite and chew. It was displaying a stereotypical biting behavior. Well, this is sort of interesting and many people that worked with morphine realized that you don't really need the electrical stimulus. If you do repeated high doses of morphine in the rat, you will see stereotypic behavior. So, we got interested in finding what would block this effect. We found that dopamine D, antagonists would block this behavior. We also found in the literature that MK-801 would also block the behavior. When we found that rats receiving three 10 mg/kg doses, 24 hours apart when challenged even months after the original three doses of morphine would bit and chew after a low dose of morphine, you have to think that somehow that the brain has changed. There is no magic in the system; the brain has changed but how has it changed. So, we thought of one way of looking at it was to use the 2-D-oxyglucose method of measuring metabolic activity in the brain. We had previously instituted the method in my laboratory in collaborative experiments carried out with Linda Porrino from the NIMH Laboratory of Cerebral Metabolism. And, so, what we did was sensitize these animals with four 10 mg/kg doses of morphine in thirty six hours. Six days later, to our surprise, we found that these animals showed a remarkable increase in metabolic

excitation throughout the brain, in the limbic areas, and especially in the frontal cortical areas.

Because of the possibility that the effect was due to conditioned cues, we eliminated these cues, and the metabolic experiment was done in a different environment. Then, we repeated the experiment in which in one group of rats, the metabolic experiment was carried out in the presence of all the possible cues and in another group of rats without the cuse and we found that although both groups of animals showed changes in metabolic rates at six days, the extent of the effect was significantly greater in the presence of cues. Thus, these results strongly suggest that just drug alone will cause long lasting brain changes; however, the presence of conditioned cues will enhance these protracted effects. We were excited by these results because they clearly indicated that there could be long term changes in the brain and these changes could be enhanced by conditioned cues. I believe experiments by the O'Brien group at Penn have shown that conditioned cues do activate areas of the brain that are altered by the abused drugs themselves. We have got some preliminary data that indicates that two weeks after the original drug treatment we still have the changes in the brains of a rat. Now, we do not know if these effects are going to be there in six months. Also, this effect in some ways related to the long term tolerance effects I found with Joseph Cochin.

- GK: Well, it does parallel the increase in biting behavior, correct?
- CK: Yes, yes. We know that an animal model is not necessarily completely homologous to the natural situation. But, the data has other implications and has implications that are surprising because we find that dopamine D₁ antagonists will block the effect.
- GK: How are you coming throughout your career to be able to balance your clinical work with the animal work? Did you do clinical work for awhile and, then, animal work or did you sometimes do both together?
- CK: I have done a great deal of clinical research. Most of my research was clinical in nature when I was at Lexington and it continued to be clinical research while I was in NY and when I was in Bethesda. However, while in Bethesda I did some animal research with Joseph Cochin. When I came to Boston in 1959 I set up an animal laboratory as well as a laboratory for research in schizophrenics at Medfield State Hospital and later at Boston State Hospital. However, once the deinstitutionalization movement took hold I no longer could carry out my research in schizophrenics. Although my PhD was in clinical psychology, the only time I did clinical work was when I was a graduate student at Lexington. Some of my pharmacology graduate students at BU liked to dig up

some of my early research papers in which I used the Rorschach and kid me about them. I strongly believe that my early experience with patients both at Lexington and later at NIMH was significant in shaping my research and how I looked at a research problem. It made me think more about the relevance of my experimental work. I believe, for example, that the research of the molecular biologist working on some aspect of schizophrenia would be enriched if he/she had some experience with schizophrenic patients.

I would like to see that drug dependence researchers spend time in a drug treatment clinic. I don't think people are aware of the severity of withdrawal with things like alcohol and the severity of withdrawal from drugs like barbiturates or even withdrawal from opiates. Although cocaine does not seem to produce physical dependence, e.g., somatic withdrawal signs, knowledge of what that user is going through, I believe, add a positive aspect to the research. At least for me, I have always thought about the possible relevance of my experiments to the clinical situation. Thus, I believe I was lucky to have had that clinical training.

- GK: Who do you think would have been the most influential on your career, and directing you toward psychopharmacology? Was it Abe Wikler or was it Harris Isbell, or a combination of both?
- CK: It was both, although initially it was Isbell. He taught me a lot about doing clinical research. One of the important things I learned by being on his research team was his sensitivity and appreciation of what the subjects were going through. If he were a different sort of person I do not believe that the experiment would have been completed. Even though the severity of the barbiturate addiction and withdrawal was much more severe than had been expected, the subjects did not want to quit even though they could at any time. Except for the first year when I worked on the chronic barbiturate experiment, I mainly worked with Wikler, although during my last year at the hospital I also was involved in a clinical study of juvenile drug users with Donald Gerard. What I learned from Wikler is to be critical of one's own work. Challenge your experimental design. Think out of the box. Wikler made one think through the relevance of an experimental model to the clinical situation. Isbell did not need models for he actually studied the disease.
- GK: Now, this is a tough question, and my short career I would have trouble answering this question, but what is your favorite study? I mean, what is the study that you think made the biggest contribution? Let's start with that and which one do you think will perhaps have the longest or

the most impact; I'd say not the longest, because who knows where we will be down the line but, so far?

- CK: Well, I think, in terms of impact or long term impact, I played a major role in understanding how the reward system with opiate drugs and cocaine drugs, brain stimulation works. And, I brought something to that field and there was a study, a first study by Richard Marcus, a graduate student, and then Ralph Esposito, in which we decided to do classic psychophysics with brain stimulation. There really was not one specific study but the series of studies that demonstrated that the driving force of drug use was the positive or rewarding effects. This was during the period when the opiate model with its severe physical dependence shaped the thinking. I remember the first time I formally presented my findings and the argument that the driving force for drug use was the positive rewarding effects. They made you, at least at first, feel good. This was at a CPDD meeting. Wikler was sitting in the front row. I could see him fidgeting as I was presenting my hypothesis that the driving force for drug use was the pleasurable effect resulting from activation of the brain reward system. As soon as I finished Abe jumped up and argued that continued use of opiates or any drug was its restorative effect.
- GK: I think that was really a conceptual breakthrough. I know for myself that your studies were the framework for understanding that drugs really act on the reward systems of the brain and have that threshold changing effect. Obviously, this came from your pain work, but much like the effects of drug on pain to raise the pain threshold in the case of reward the threshold was lowered.
- CK: It seemed obvious to me if one did psychophysics to obtain a threshold for pain that the same psychophysics should be applied to determine the reward threshold. Olds and Milner were first to report in 1954 that stimulation of certain sites in the brain were rewarding. Psychologists in studying rewarding brain stimulation found that the operant methods of Skinner could easily be adapted for the study of the rewarding effects of drugs. Although it was fairly easy to train rats in the operant procedure where the dependent variable was rate of response, I believed drug effects on reward using operant procedures could be confounded with motor effects. Thus, I decided to use a classic psychophysical model that I had used approximately ten years earlier in the study of pain and analgesia in human subjects. A graduate student, Judy Nelsen was assigned the problem. She was to put two electrodes in each animal, one in a reward site and one in a pain pathway. Thus we believed we could in the same animal study the effects of morphine on two different

neuronal systems. We had no difficulty in placing the electrodes but we had difficulty in training the same animal on a multiple schedule using the two procedures. At that time my colleague from my days at NIMH, Allan Mirsky, came on the faculty at BU and he was doing EEG studies in primates. We borrowed his EEG set-up and simultaneously recorded from our implanted electrodes, one in a reward site and one in a pain site with and without morphine. We quantified the EEG recordings and found that in simultaneous reco4rdings of EEG from both pain and reward sites opposite effects were happening. In the pain pathway, morphine resulted in an increase in high amplitude waves and lower frequency. In the reward pathway it was just the opposite. Thus, morphine was simultaneously exciting one area of the brain and depressing another.

- GK: That's great!
- CK: Although we were excited about our findings, we still had not demonstrated the difference in behavior. My next graduate student, Richard Marcus demonstrated the difference that morphine at a certain dose raises the threshold for nociception, brain stimulation, and at the same dose lowers the threshold for rewarding brain stimulation. Unfortunately, the positive and negative stimulation were carried out in different animals. Most investigators using intracranial rewarding stimulation adopted the Skinner model in which rate of response was the dependent variable. Our group adopted as the threshold at which the "half-maximal" response rate intensity was obtained. Although my psychophysical method and the half-maximal response rate gives somewhat similar effects there is a problem in that the maximal response rate of many drugs is not identical to that of saline. Thus, for example the maximum rate of response with cocaine is usually greater than that of saline. Depressant drugs, e.g., neuroleptics often have a maximum response rate lower than that of saline. Surprisingly this is often interpreted as a motor effect.
- GK: How did you react when you first heard about the Old's study? What were your first thoughts when you heard about it, did you hear about it through the grapevine or did you see it presented or did you actually see the paper appear in press?
- CK: I think I first heard about it at an American Psychological Meeting in which I also had given a paper. My first thought, I believe, was, "Where was the drive reduction"? However, I thought it was a most exciting finding. I must admit that I did not fully see the implication of Old's experiment. Remember, the drive reduction hypothesis was quite prevalent at that time. I still believed that drug use was maintained because

of drive reduction, what ever the drive was. People only used the drug, because acutely the first time they used it, provded a kind of self treatment. Almost, every drug addict in Lexington was diagnosed as a character disorder or depressed. Now, there are people that certainly use drugs for these reasons, but I no longer believe that the majority of drug dependent drug individuals do so to normalize themselves. . Do I believe that there are no drug users who use drugs to normalize themselves? Of course not! I believe that if we, psycholgists, do not have an obvious drive, we invent one. It has been suggested that a priming stimulus creates a drive to press the lever again that creates a drive to press again.

- GK: Conan, how did you stay in the field? I mean, you have a prodigious history of publications in both the clinical and in the basic science area. What kept you from being tempted from going into advertising or clinical psychology where certainly you probably could have made a better salary? What kept you in this field and how did you manage to do it?
- CK: I think the major reason was that I enjoyed the research and never found it boring. Although I would have liked more income I really cannot complain. I have had an NIH Research Scientist Award or its forerunner since 1959 when I came to BU. Another thing that has kept me motivated is that I love mentoring students. They keep you on the ball and they are exciting to work with, but sometimes they are a pain in the ass, but they are exciting. In fact, just before I came here I was thinking of how many people have come through my lab
- GK: Well, that was going to be my next question.
- CK: OK.
- GK: You, probably of all the people I know in this college have trained more students than anyone I know.
- CK: Now I believe there were 22 PhDs, plus two who unfortunately could not get it.
- GK: Stephanie?
- CK: Stephanie Raznick was one of these students and she did her dissertation in your laboratory; although, her degree is from Boston University. The other student was Ellen Weinberger who did her dissertation in the laboratory of Eva Killam, at the University of California, Davis. Both of these students had two mentors. Weinberger's defense of her thesis was unique. It was held in a hotel room at a FASEB meeting in Chicago. She had people from three universities examining her. In addition to PhD students I also mentored a number of MA of Medical Science Students as well as honor undergraduate students who did a research project in my laboratory. Most of these went on to graduate school or

medical school. I believe a few of these students may have ended up in your laboratory. If I include all of these students including post-docs, I probably have had close to 35 to 40 students.

- GK: I think one of the most remarkable things that I think about your career, is that you obviously have a form of excitement that you generate that has been catching to the student This is a very important part of the College and I don't know how we would do that, but I think, you know, the Kornetsky ability to attract people to psychopharmacology. And, well, I think that probably more than anyone I know, you have attracted people to the behavioral end of psychopharmacology.
- CK: Well, one of the things I try to do is I tell them you are working on an experiment. It does not matter how simple that experiment is, you are doing something that you don't know the answer to and hopefully something that, no one else has done yet. It is something entirely new. You have to get them excited about the research.I do not believe that most people realize that when you have trained an animal you have developed a common language with that animal. When you fail to train an animal it means you have failed to communicate with that animal. Also, I occasionally ask them some "crazy" questions. I try to make them think. I want them to be excited about their research. Often the work itself may be tedious but the excitement is in the search. If I do not become excited by what they do I cannot expect them to become excited.
- GK: Are you happy with the way things have turned out for your career or would you have been rather a jet fighter pilot?
- CK: I wanted to be a fighter pilot in World War II. I enlisted and entered the Army Air Corps, as it was called then, in March 1944. Once in the Air Corps I was required to take a full week of tests, both performance and IQ. If I passed I would end up as a pilot, navigator or bombardier. I passed for all three and my highest score was for navigator. It was interesting the scores given were standard scores with a mean of 5 and a standard deviation of 1. I believe I had an 8 for navigator and 7 for both pilot and bombardier. This meant I probably would be sent to navigator school. I was disappointed. It was toward the end of the war and a score of 8 was needed for any of the three flight trainings. I was disappointed because at 18 years of age I wanted to become a fighter pilot and not a navigator in a large bomber. While I was waiting to be sent to navigator school I was given a two week crash course on being an airplane mechanic and later a flight engineer on B24 bombers that were being used to train copilots and gunnery students. I was responsible that my plane was in flying condition every day and as the engineer I

would fly with a pilot and co-pilot and a gunnery instructor and about 6 or 7 gunnery students. Luckily for me, I never got trained as a navigator because I found that I had a tendency for air sickness if in rough weather I could not see the horizon. Navigators sat in a small darkened area which in rough weather was a prescription for air sickness. Luckily for me the war ended in the summer of 1945 before I could be trained. I still worked as a mechanic and engineer until discharged in December, 1945. The Army gave me the choice of going through training or receiving an early discharge. I took the early discharge for if I chose the training I would have to serve three years after that. That was a long answer to a simple question about being a jet pilot. I returned to the University of Maine, Oromo in January, 1946. I had completed my first year in college as an engineering student prior to going into the service. If I had not gone into the Army I probably would have finished my undergraduate career with a degree in mechanical engineering. However, upon returning to the University I decided I did not want to be an engineer and enrolled in the College of Arts and Science. Engineering students had to work too hard!! Actually, my first choice of a major was history. And there were a lot of reasons I didn't go into history. One of them was that there was a small history department and the Chairman in that department and I didn't see eye-to-eye on political issues. He believed that Roosevelt was a communist. I did not believe that I could survive in a small department with the Chair who believed that. So, I took a psychology course and that seemed to be a field that would fill my interest in science and that seemed interesting. By my senior year I began to think that I could earn a living as a clinical psychologist. I found that the University of Kentucky in, Lexington had an approved program in clinical psychology. I applied and was accepted. I fairly quickly found that doing the psych testing was interesting but sitting with a patient doing therapy was not my forte. After the first session I found it repetitious and boring. The only type of patient I really enjoyed being with was schizophrenics. With feelings of grandeur I believed that I could cure a schizophrenic. I had read a book about that time I believe by John Rosen on treatment of schizophrenia. At the Lexington USPHS was a ward for patients with severe mental illness. Most were schizophrenic. I started spending time on the ward and with the confidence of the ignorant I believed I could cure a schizophrenic patient. I asked the ward director if I could work with a schizophrenic patient. He was most happy to give me free rein. They gave me a patient. However they did not tell me that he was a feces thrower! As you might expect I did not cure this patient. I would spend approximately 30 minutes with him

almost every day. Although he was mute when I first started to see him after probably about a month he started talking to me. He did not make sense but he would speak. He also stopped throwing feces.

- GK: So, that was some success.
- CK: I certainly did not cure his schizophrenia but he would go to the dinning room to eat. I would do some of his crazy behavior with him. For example, the floor of the ward was cement with wide expansion crevices and he would spend considerable time trying to clean them with his finger nails. I found he liked if I did it with him. It seemed to me at that time that schizophrenia was a neurological disease. I read Kraepelin and I thought, maybe he had it right. Dementia Praecox seemed like a more appropriate name for the disease to me
- GK: Where do you see our field is going? Obviously you have a game plan for your own research. Obviously, schizophrenia research is starting to return to the origins that you saw back when you were training, both from a dementia hypothesis and the neurological hypothesis, which are both very much at the forefront of the field right now. But, where do you think schizophrenia research is going to go, if it's really going to help people? And, where do you see drug abuse research is going, given that we still obviously have a major drug abuse and drug dependence problem in the United States and in the world, for that matter?
- CK: It's hard to tell!
- GK: Let's start with schizophrenia.
- CK: OK, Unfortunately I lack the training to really investigate the molecular relationships to behavior. Certainly people with schizophrenia have changes in the brain but I would not know where to start without extensive additional training. So, I think we have got to learn about what are the differences and who are the vulnerable people, and I have been very pleased with some of our research on attention and CPT research, suggesting we may be able to pick up those most vulnerable. And, not all schizophrenic, for example, have these deficits, so we are dealig probably with more than one disease so we may be able to separate out which ones have deficits and which ones do not. However, we have to be very careful when we define deficits for a disease. What we may be looking at may just be an epiphenomenon. Although we may be able to model in the rat some aspect of the schizophrenic process I do not believe we can make a rat schizophrenic.
- GK: I think that is another one of your conceptual contributions that has been picked up by a number of individuals and that has to do with formulating animal models, how animal models can be validated and what they can mean. I know Mark Dyer, for example, has written and spoken

on it, and a number of other investigators, about the fact that one cannot mimic the whole syndrome but can at least model in a predictive way one symptom of the disease.

- CK: The major difficulty is that it is difficult to overcome dogma. An example: I did some experiments at NIH that seemed to suggest that schizophrenic patients have an attenuated response to amphetamine. This of course was completely counter to the belief that amphetamine exacerbates schizophrenia.
- GK: Yes, right, I remember that.
- CK: We didn't know what to do with it; we never published the work at that time. Then, in the late 1960's when I was at BU and had a laboratory at Medfield State Hospital, the dopamine hypothesis was popular. A major support for the hypothesis was that schizophrenia symptoms were exacerbated when the patients were administered amphetamine. And, there I was sitting on data, suggesting the opposite. In fact, Allan Mirsky and I thought that if schizophrenics have an attention deficit disorder, amphetamine may have a positive effect. I proposed such an experiment to the hospitals review committee, the equivalent of an IRB. They would not approve the experiment. They said I could do a brief pilot experiment. In this pilot experiment we gave 20 mg of d-amphetamine or placebo each night at 8.00 to a group of chronic schizophrenics and by observation rated them as asleep or awake. This was done by nurses who were blind as to the treatment. Of the 9 patients the following effect was obtained: with d-amphetamine compared to placebo, 3 slept slightly more, 3 slept slightly less and 3 showed no change. Twenty milligrams of amphetamines, which is not a minor dose, given at eight o'clock at night would probably have significant effects in nonschizophrenics. I never did anything further because of the difficulty to do research in a mental hospital because of deinstitutionalization. Also I was focusing more on drug abuse at that time because of the difficulty of doing research with mental patients. I did not publish that finding until late in the 1977s in the Archives of General Psychiatry. Danny Freedman was editor at that time. I did not follow up on these findings, mainly because no one paid attention to anything that questioned the dopamine hypothesis. Advancement in any research area depends greatly on having an open mind. Researchers need not to be afraid to pursue a problem or an idea that is contrary to current thinking. The risk may be great but you might find something that is not just more of the same. The same holds for drug abuse research. The best example I can think of is the experiment by Wikler, published in 1952 in the Psychiatric Quarterly, in which the subject is allowed to have any drug

in the formulary; he allowed an addict to self regulate morphine use. The subject had been a long term user who had been "cured" of his addiction many times. The main problem with drug addiction is that it is a complex behavior. It is a social, psychological and economic problem. In the inner city population of Boston, eighteen to twenty percent of youngsters are out of work. How do they get their kicks besides killing each other? A lot of people try drugs and don't continue into addiction. In my study of teen age drug abuse I did with Donald Gerard in NY City in 1952 and '53, we went looking for teen agers that were friends of addicts and had never used heroin. It was a hopeless task. We found many teen agers that were not or had never been addicted to heroin but all, at some time had tried heroin. We quickly changed the criterion for our control group from never tried to was not a user and never had been a regular user of heroin. Other people, like me for example, has been a subject of an experiment. Frank Frazier at the Lexington Hospital was doing an experiment in which he compared post addicts to a control group and I was one of his control subjects. We were administered 20 mg of intramuscular injected morphine. That is a pretty large dose. Although I found it pleasant and enjoyed the whole day, I never wanted to repeat the experience. Why didn't I want to repeat the experience? I didn't like the loss of control and, more important, I get my kicks other ways. The main thing about drug abuse is that it becomes biological when people take the drug, but there are people that are more vulnerable, but the vulnerability may not be a biological vulnerability. An interesting thing about research in drug abuse is that it has become a vehicle of undersanding of brain function and behavior. I think that we would not have the understanding of the brain reward system and the role it plays in normal behavior if we did not have the model that drug addiction and drug effects on the brain give to us. The system is not just there so that we can have pleasurable effects from the addicting drugs but it has to do with all positive feelings and its absence may have an important role in understanding many pathological states.

- GK: And, this will probably have major impact, I would just guess, for affective disorders and for other mental disorders the College is much interested in.
- CK: Well, people have to have their mind open and a number of years ago I organized a workshop at the College with a former student of yours, Neal Swerdlow, on the role of dopamine in depression. I am trying to think of who the other person was. I believe he was from Vancouver.
- GK: Fibiger?

- CK: Yes, Chris Fibiger. We felt that dopamine is certainly involved in pleasure, because if you don't have dopamine then maybe you don't have much pleasure. And, there were a couple of drugs out there that were dopamine agonists that we used and historically people use amphetamine for depressed patients and, in fact, they still do.
- GK: They still use methylphenidate.
- CK: Yes, It is of interest that many people briefly looked into the session. However, the audience was very small and most was hostile to the idea.
- GK: Why?
- CK: Because it went to the contrary to what was the "thinking". Now, we could have been completely wrong, but that's beside the point. I think that drug abuse research will have relevance for depression and mania. If you take cocaine and gradually increase the dose you will have a model for a manic patient.
- GK: Absolutely.
- CK: A slightly manic person is a lot of fun; somebody with a little cocaine is fun and somebody with a lot of cocaine is not and somebody that is very manic is not much fun at all.
- GK: Right, I think that is a very good point. Well, my last question for you would be, what about the College? Where do you see this College of Neuropsychopharmacology going? What do you think they should be doing, perhaps, that they are not doing? Obviously, you and I share concerns about training and the need for the continuation of influx of fresh young people into the College and that is, of course, one of the goals of the College over the last few years. But, what else would you see as an important issue that the college should be addressing?
- CK: Well, the College should never lose sight of the fact that it is a major multi-disciplinary organization. And, if it becomes and moves too much in one direction or the other, it will be in trouble. A lot of the basic science in the field has become very molecular. Now, as people say, you can't even have a thought without molecules changing in the brain. There's no magic up there. And, so, we can't become overboard one way or the other. We have to keep a balance in this organization and that includes more integrated types of panels. By integrated, I mean, not all the molecular here, and then all the clinical there, we have got to get the clinical people going to the molecular people and the molecular people have to explain the non molecular scientist that they can understand the significance of their findings. I am sometimes on a PhD student's graduate committee whose thesis is very molecular. If I do not understand much of the thesis, I try to get them to explain it so I understand its implications, etc. If after a few questions they still

don't explain the significance in a way I can understand the problem I think there is a problem. I have, always felt that any discipline needs to be able to talk to the reductionist at least one step below it and to the expansionist at least one step above it. I think it is important that we maintain the original intent of the organizing committee of ACNP that we maintain ourselves as a multi-discipline organization and not an organization of multi-disciplines.

- GK: Thank you, Conan, I think that was really...
- CK: I enjoyed talking, as I always do.
- GK: Enjoyable discussion.

MARY JEANNE KREEK

Interviewed by Lisa Gold Boca Raton, Florida, December 10, 2007

- LG: Good afternoon. I am Lisa Gold and I am here interviewing Mary Jeanne Kreek.* We are in Boca Raton, Florida, attending the 46th Annual Meeting of the ACNP and today is December 10, 2007. Mary Jeanne, I'm going to ask you some questions to hear about the very interesting, productive and significant contributions that you've made throughout your research career. I'll start with some simple ones. Where and when were you born and please tell us something about your education and your early interests?
- MK: OK, Lisa, it's a pleasure to be interviewed by you. I have known you since you were a CPDD Travel Awardee and then won our Young Investigator Award at CPDD, so it's really a pleasure. I was born in Washington, DC and I grew up in Washington, in Richmond, Virginia and back in Washington, again. I went to public schools. I had a wonderful education in those different public schools in two cities. You might ask where I first got the idea of science or medicine or medical science. No one in the family really knows, but apparently by age two, I was already chattering that I was going to be a doctor. We think, my mother thinks, it was because I had an aunt, a distant aunt, who was a physician in Washington, whom she had taken me to meet, and, obviously, this lady impressed me positively. Both my father and then much later, of course, my brother went to MIT, so they were both scientifically trained, although they both went on to law school and got involved in intellectual property law for their entire careers. My decision was made quite early. I enjoyed, from really the earliest times, asking questions about science and so when I had an option of either becoming a professional classical ballet dancer or pursuing science and medicine, at age 14, I chose to stick to science and medicine. The only time I deviated from plans for a biomedical research career was roughly ages 12 to 14 when I became very impressed by theoretical physics and I became temporarily determined to go in that direction. However, I realized that my mathematic skills at the theoretical level probably would not be great enough, so I went back to a plan of biomedical work.
- LG: Great, and so what did you major in college and what did you study and where did you get your degrees?
- MK: Well, I was very lucky in that I had won science awards for a couple of years and had been in the "top forty" and then the top three of the

^{*} Mary Jeanne Kreek was born in Washington, DC in 1937.

Westinghouse Science Talent Search, so I was able to get scholarships at a lot of different places. But, of course, there were certain schools we couldn't go to then, because we were women. I went to Wellesley, like a lot of other people have done, and at Wellesley I majored in chemistry, but I took a second major in biology and, in fact, I obviously loved the lab so much that they let me do an honors thesis beginning at the end of my junior year going through senior year. I had my own laboratory space and I worked on my own project. I was given a project of trying to find out what made the very newly developed yellow carnations, which had been created by a professor of horticulture at the University of Connecticut, what makes them yellow. This involved chemistry, genetics and botany (about which I knew nothing), but I was able to find out, by the end of the year that it was a chalcone, a multi-hydroxylated chalcone, which yielded the yellow color. I wrote my thesis on this and from that time, henceforth, I've loved yellow carnations. I was the only college senior that received, every week, a bouquet of thirteen yellow carnations, of which I studied one and had twelve in my room, so it was quite a perk!

- LG: And, after you got your undergraduate degree?
- MK: I went to Columbia College of Physicians and Surgeons. I looked at and was accepted by many medical schools, but, for unclear reasons, I have a feeling in large part due to my long-lived love of New York City, I came to New York and studied at 168th Street. I had worked at the NIH many summers and winters. I'd worked at the Bureau of Standards before that. I enjoyed research work very much. I was very bored during the first year of med school, so I recall going to the Dean, after about two months, telling him how bored I was with all the memorization. He assured me that it was going to be guite tough and it was important that I do well, so he could not let me go to a research lab, but he would allow me to affiliate with the endocrine group and go to their Journal Club and participate in their rounds. That was just enough to make me happy enough to persist in med school. By third year, I'd started doing my own research in the Department of Medicine. I did research work on the peripheral biotransformation of steroids. I was able to define, for the first time that a less active steroid was transformed to a more potent one in the intestinal wall. That led to my first paper and my first presentation at a national meeting. Utterly panicked, I presented at the Endocrine Society in my senior year of med school. It was at the plenary session and I immediately followed the famous stress physiologist, Hans Selye. I was already interested in stress and stress responsivity, but I've often wondered if that imprinted on my future focus on stress

and stress responsivity and their role in depression and in addictions. I felt the stress that day. I listened to Selye. I got up and gave my own talk, which was very well received, and that was the beginning for me.

- LG: What was the year of your first publication?
- MK: My first publication was in 1963.
- LG: 1963, and, so, here we are two hundred and sixty-five plus publications later in 2007, so that's quite an accomplished career.
- MK: Thank you very much.
- LG: So, that was sort of the beginning, it sounds like, of your getting involved in neuropsychopharmacology.
- MK: It very much was. It was from my work in endocrinology, neuroendocrinology. I'd worked at the NIH with the late Frederic Bartter of "Bartter's Syndrome". I had helped count the juxtaglomerular apparatus granules and with Fred I also had been introduced to a lot of techniques with animal modeling, as well as basic clinical research. Neuroendocrinology, actually, is a close cousin of neuropharmacology and I think it was just natural that I gravitated in that direction. I should point out, there were seven women in a class of one hundred twenty at med school, and I learned that many of the most prestigious university hospitals did not take women on their house staff. I went to one that did in New York City, an outstanding place, Cornell University Medical College-New York Hospital then, now called the New York Presbyterian Hospital, Weill-Cornell Campus. I started what we now call PGY-1 in Internal Medicine, and planned a three-year course in Internal Medicine to be followed by Endocrinology. During that very first year, I was approached by the Head of Gastroenterology and Hepatology, Marvin Schlesinger, and his number two, Graham Jeffries, who said that I really ought to study the brain-gut axis, because the brain-gut axis is very important for integrative endocrinology. Besides, GI and liver would give me a broader base to understand neuroendocrine work. I said I'd be interested in doing that, but that I wanted to be able to have enough time to do research. They suggested that either group could put me on their training grants, but why didn't I apply for a special NIH postdoctoral fellowship, which I did, and I got it. Thus, I was able to train dually, but still have ample research time. However, the real shift in my career came during my first year of residency, before I started the GI/liver/endocrine training. At the beginning of our first year residency in mid-1963, Professor Vincent Dole, Jr., a Professor from the nearby Rockefeller University, directly across the street from us, with beautiful gardens but surrounded by a very high and formidable iron gate, came over to Cornell and said he would like to have two first year residents, PGY-2s, to join him, in

the beginning of 1964, in a new research venture. His laboratory had studied lipid metabolism, hypertension and related topics which he was going to phase out over the next year. He had served on a public health committee of the Health Research Council of the City of New York and, along with the late Lewis Thomas, had identified the number one underaddressed health problem in the city and state to be heroin addiction. So Dole decided to change his lab to study addictions, specifically heroin addiction, and to attempt to develop a new approach to treatment for this problem. The Chair of Medicine said that he could send one person, not two, yet all of the PGY-2s wanted to be interviewed. I don't think any of us precisely understood what the topic of research was going to be, if I'm very honest. But we all wanted to go to Rockefeller and do research, so we all were interviewed. Two were chosen by Dole, and then I was selected from the two by the Chair of Medicine. It was a case of reverse discrimination. I was the only female on the entire medical House Staff and he therefore knew that I would not be drafted in the next year or two; thus I could serve as a link between Rockefeller and Cornell for some time to come, since this was the very first time any Cornell House Officer had been allowed to go to Rockefeller to do research. He was very wise, because from that time, henceforth, I have been a link and have had adjunct appointments across the street at Cornell.

Vince also recruited another person; he looked around for somebody that knew something about addiction. He certainly knew nothing, I absolutely knew nothing, but he found a woman, Marie Nyswander, who has long since been deceased, a psychiatrist who had worked in New York City, in the streets of our city, as well as in the hospitals at Lexington, Kentucky, in a facility for addicted criminals. She was convinced that addictions needed to be addressed with a pharmacotherapeutic approach and not just with behavioral treatment. She had seen the numerous failures in behavioral treatments. Our team of three coalesced in the beginning of '64 and that was the beginning of our research on addiction.

- LG: So, I was going to ask you about some of your mentors in the field and the scientists who've have had the most impact, so it sounds like we've heard about, at least, a few, and I'm sure there's many more.
- MK: Well, there was Dr. Frederic Bartter at NIH and Dr. Don Tapley at Columbia P&S; Drs. Marvin Schlesinger, Ralph Peterson and Graham Jeffries at Cornell and, then, Dr. Vince Dole at Rockefeller. Those were my mentors. I think it was Bartter, though, that taught me laboratory techniques and how to ask a specific question and to initiate research;

none of my other mentors had to teach me how to formulate a question, or how to design an experiment. That was a wonderful head start, to have been able to do that from teenage years onward.

- LG: Yes, so in this very long and productive career, would you say that there was a central theme of your research?
- MK: Well, my very first work, in studies of treatment of addiction, really set the theme. Instead of going into neuroendocrinology or brain-gut axis research primarily, I became involved in research on addictions with Vince and Marie. In 1964, the three of us worked on developing the first pharmacotherapy for an addiction and, in that work, we had to do several things. We had to learn about the persons, or patients, as we still insist on calling them instead of "clients", and especially we had to learn about how they got to their disease problem. Then we had to identify a potential pharmacotherapeutic agent that would affect the central components of the problem. We wanted to use an orally-effective, longacting morphine-like compound. Marie and Vince didn't think we'd find one, but I found that the early work of Beecher and Hood in pain had shown that a synthetic compound, methadone, from Bayer Industries in Germany, which had been brought to the US by our military at the end of World War II, and which had never been studied there beyond pre-clinical level, was orally effective, and possibly long-acting. Both Beecher and Hood had found that it was a good medication for pain management. However, both groups had shown that when repeated doses of methadone were given to opiate-naïve persons, respiratory depression ensued, which suggested that methadone was long-acting in humans.

It's hard for anyone now to appreciate the fact that in 1964 we had no sensitive analytical techniques. We had to look at patients, listen to patients, and talk with them to understand what was happening pharmacodynamically. We decided to use methadone as an orally-effective "opiate-like" medication, which we assumed was targeted at the same site of action as morphine, the major metabolite of heroin. Within a few years, with the delineation of the opiate receptors, we found this was true. We wanted to be sure we had a medication that was long acting, and it took about seven years before I could develop a gas chromographic method to measure plasma levels of methadone. In the first six months, we interviewed numerous heroin addicts and we brought several of them into the Hospital at the Rockefeller University. We induced them slowly, starting with a low-dose, 20 to 40 mg a day, of methadone, the same as we recommend today, and slowly raised the dose up to what we estimated, and then showed, would be a full treatment

dose of 80 to 120 mg a day. Then we conducted two sets of four-week studies, in which we superimposed one time a day a short acting narcotic, such as heroin, morphine, hydromorphone, methadone itself, or saline, against the background of daily oral treatment with methadone. We found that subjects felt nothing, no euphoria, no "high", no somnolence. Then we increased the doses of the superimposed medications; we did a single blind study where we administered ascending doses of heroin against the background of 80 to 120 mg of daily oral methadone. We found that it took over 200 mg of pure heroin administered intravenously to exceed the level of tolerance and cross-tolerance which had been developed. We had assured ourselves of two things; first, that people who would be treated with methadone would not accidentally kill themselves when they would try to use heroin on the street, which was very important. But we also confirmed our hypothesized mechanism, that methadone was acting through the mechanism of providing tolerance, as well as cross-tolerance, to any superimposed shortacting opiates, blocking their effect while also preventing the signs and symptoms of opiate withdrawal. And, we, therefore, entitled our first paper Narcotic Blockade That paper was actually held back for two years from our original research in 1964, until mid-1966, because Vince wanted to present the findings at the prestigious "Old Turks" scientific meeting, the Association of American Physicians, and the data had not been fully analyzed prior to the abstract deadline for that meeting in 1965. Therefore, in the second piece of work we moved from the wonderful, beautiful, but protected environment of the Rockefeller Institute for Medical Research out into an absolutely terrible environment of a challenging community based, fee-for-service detoxification unit in a proprietary hospital. Of course, it was shown that methadone was equally effective down there. That second piece of work, plus a one year follow up of our first patients in our original studies was actually published in mid-1965, before the first basic clinical research work was published in 1966. I think the most important thing that we were trying to communicate in the "Narcotic Blockade" paper was that we were documenting that addiction is a disease, and looking back on it, I think the most important contribution of our early work possibly was just that. Addiction was thought to be a criminal behavior or the result of a weak personality. Even with the very interesting and elegantly conducted pharmacology work at Lexington, primarily in prisoners, who were heroin addicts, or in some volunteer medical personnel patients, the underlying research concept and goal was never that they were looking for treatment of a disease or that there was even a disease to be treated. The addicts were perceived as "criminals" or "weak-willed persons" to be used in research. Lexington was trying to test compounds that might be non-addicting drugs for pain. So we created a paradigm shift. Although it took many years, I think, right now, there is really almost nobody that will deny that addictions are diseases. Recently, we were talking with a group of participants at the NIDA/ CTN "Blending" meeting in Seattle and the diverse participants they had no trouble understanding this concept. They had seen enough, heard enough in their own families;, they still had questions about all the mechanisms of these diseases.

The rest of my career, I would say, splits into four domains of research focus. The first decade from 1964 to 1975 was devoted to my work in defining the safety and effectiveness of methadone maintenance treatment; to elucidating the physiological effects of long acting and short acting opiates, and to developing pharmacokinetic techniques, including the gas-liquid chromatogaphy methods, so we could measure plasma and urine for levels of methadone and other opioids. What we learned was that methadone has a half-life of twenty-four hours and, using stable isotope techniques with chemical ionization mass spectrometry with selected ion monitoring techniques, we learned that the active, s or d enantiomer of racemic methadone has a half-life of fortyeight hours in humans. But in rats we found that methadone has a halflife of ninety minutes and in mice, sixty minutes; if you want to mimic the human situation, you have to put methadone in by pump. Also, in that early work, our now colleague, Chuck Inturrisi at Cornell, found that heroin has a half-life of three minutes, that 6-acetyl-morphine, its first active metabolite, has a half-life of about thirty minutes; that morphine's half-life is around four hours and its active 6-glucoronide metabolite has a half-life of six hours. The "short-acting vs. long-acting" concept we have incorporated into many of our animal and molecular models. We coined the phrase "on/off vs. the steady state", and the "jack-hammer effects of a drug of abuse", which characterizes the mode that gives rapid and repeated delivery to brain, such as intermittent administration of intravenous heroin, binge alcohol, and binge freebase cocaine. Such a delivery will impact upon every receptor or other site of action, signal transduction and downstream events in a way that begins to change the brain through the mechanisms of neuroplasicity, including synaptogenesis.

The second decade or so of my work, from 1976 to 1986, was focused on the endogenous opioid system and how it interacts with the exogenous opioid system. Also, I got more deeply into an early

hypothesis on the role of altered stress responsivity in development of an addiction, which is something I pursued from '64 onward in our prospective studies. Those prospective studies from 1964 to '73 led to the new drug application (NDA) for methadone. There was no corporate sponsor for methadone. However, one company was willing, pro bono, to put together all of our studies for the NDA, all investigator-initiated work with investigator-conducted studies. Methadone was approved by the FDA in 1973 for long-term use in the maintenance treatment of opiate addiction. At that time, I was able to turn more to the physiological studies on the role of the endogenous versus exogenous opioids, i.e., pharmacodynamics. By the mid 1980s, it became clear to me that drugs of abuse were changing the brain at the molecular level. We embraced all the techniques, as they were developing, of quantitative molecular biology for gene expression studies; studies of proteomics but of course we didn't call it that then, we referred to "resultant peptides"; asynaptogenesis, we called "connectivity," as well as overall neural plasticity, and related behaviors were all a focus of our studies. By the late 1980s, I was determined to create some new animal models that would emulate the human patterns of drug abuse, but especially excessive alcohol, opiates, and cocaine. In the late '80s, I coined the term, "bi-directional translational research", not just translational, but working in the clinic, talking to patients, then creating animal models back at the bench, with measurements made at the molecular level and then discovering new things, which we could take forward again. And, that's been the theme of my lab. In the third decade, from 1987 to 1997, we developed a research center. By the late '80s, we already had a large team of molecular biologists, neurochemists, behavioral scientists, using animal modeling and clinical research staff. Psychologists, psychiatrists, internists, nurse practitioners, and research nurses are also on my team of my NIH/NIDA Center. The Center, originally a P50 Center, has been for some time a P60 Center, that uses an integrated transdisciplinary approach to focus on specific questions.

- LG: So, let's talk about how you got from that, that very energetic and enthusiastic PGY-2, to actually having a faculty position at the Rockefeller. Maybe you can tell us about that.
- MK: Now, this is a good question, I have a feeling you have a bit of an insight on this one, but it's probably very good for the Archives to bring this out. It is unclear whether there had been 2 or 3 female Members at the Rockefeller Institute before it became a University in 1965. There was Florence Sabin, who was a Member in the '20's. She came from Hopkins, already a full professor at Hopkins, and the first woman ever

to be elected to the National Academy of Sciences. She didn't stay at Rockefeller long. No one seems to know why, but she stayed two or three years and moved on. Then, in the early '60s, two women became Members. One was Rebecca Lancefield. I had learned in med school the "Lancefield classification" of streptococci. I assumed "he" was dead. I met her at Rockefeller when I came in 1964; she was made a Member when it was known that she would need to leave in a short time because her husband was on a university faculty where they did not allow Professors beyond a certain age to stay and they were going to be moving elsewhere. The third woman, who also may or may not have become a Member, was the late Gertrude Perlmann, who was given some kind of an additional appointment when it was found that she had a metastatic disease; this was not a good track record for women. There was then a twenty-five year hiatus, during which time the Institute became a University in 1965, and when Torsten Weisel, Nobel Laureate, a wonderful Swedish scientist, became our President in late 1991. He visited my lab within a couple of weeks and said, "there's something strange here, Mary Yeanne," as he would always call me. In early '92, he was to propose the appointment or promotion of two people for full professor. One was Mary Beth Hatten, who had worked with him up at Harvard years earlier and by now was a full professor at Columbia, and myself, an intramural candidate. So, at the end of 1993, beginning of '94, Mary Beth and I both became full professors and we were the first two women to become full Professors at the University. There are now, in 2007, six of us, so six out of the forty-five full professors are women, Lisa.

- LG: Great; that sounds like progress, hopefully the number of female faculty will be increasing in the future.
- MK: However, I had an independent laboratory from 1975 onward, which was atypical. Now we have had non-tenured Heads of Lab for over fifteen years, but at that time we had no such thing. In 1973, towards the end of the year, Vince Dole had recognized that the resistance against accepting treatment for heroin addiction was so great that he very seriously contemplated, over the next two years, closing his lab, leaving the university, and fighting the social battles of stigma. He did not want my research work, which was then going full tilt with pharmacological and physiological studies to be halted, so he went to the President F. Seitz and asked if I could have my own laboratory; President Seitz said, "Well, you know, there is no precedent for that at Rockefeller". So, Vince said, "Well, if she gets all of her own funds, could you at least give her space for a while, because I'm going to have to move my space
from the Founders to the Tower building, and I may leave; she needs to have independent space". So Seitz said, "If she can raise all of her own funding within the next twelve months, both for her salary and everything else, then, I will find space for her". So, I got to work and got two NIH grants and won a Health Research Council Career Award within twelve months. I got also some funding from New York State. Dr. Seitz held to his word; hegot me space and the space was the space of the late Lyman Craig, who had developed the techniques of countercurrent distribution, the precursor of all kidney dialysis work and the precursor of all high performance liquid chromatography work. Craig had passed away; he had a small lab at the end of a floor in Flexner Hall, one of the two floors occupied by Stein and Moore, the Nobel Laureates. Professor Moore interviewed me for an hour and, at the end of the hour, this incredibly formal and marvelous man looked at me and said, "I would like to have a physiologist, who thinks in integrative terms, on my floor." So, I got an independent lab at the end of the fifth floor and, in fact, I now have the entire Stein-Moore space, a floor and a half, as you know.

- LG: Yes. So, tell us a little bit about this. You're trained as a clinician. Is there a portion of your time that you spend, actually seeing patients? And, tell us a bit about some of your teaching responsibilities and of your students, residents and supervising post-doctoral Fellows.
- MK: I am fully trained as a physician, an internist, endocrinologist, gastroenterologist and hepatologist. You certainly wouldn't want me to do it now, but I actually have endoscoped many people and have performed many liver biopsies. However, I also had, from teenage on, been trained in bench laboratory research work, so I always saw biomedical science and clinical research as logically combined together. I taught house staff, obviously, while I was finishing my medical training at Cornell. After the first six months at Rockefeller, I had to return to complete my training. I had done some prospective studies of the medical safety and physiological effects of long-term methadone maintenance treatment. It went on across 68th Street, because I could run back and forth with ease. Then, after I had finished all my training, I returned to the, by then, Rockefeller University, full time, in 1967 and have never left. And once I returned full time to Rockefeller, my teaching of medical students really dropped way down. For the first three to four years, I would still do some voluntary clinical work one month a year, which I enjoyed enormously. However, after that first three to five years, it was too much of a time drain. The teaching that I do now includes primarily special lectures. I do those not only across the street, but all

around the nation and world, and give special lectures for physicians in general, for psychiatrists, for internists interested in our area, as well as, more usually now, for pre-clinical departments. I have a lot of students come to the lab for training, however. We're very proud of them. We've trained over three hundred people. And we have some special programs to train minority candidates as well as other groups. We also have students who come to us because they have heard about us. We cannot take most of those, but we take a few. We have, of course, the Rockefeller pre-doctoral students coming in the laboratory and working with us to do all or part of their work for their degree. And we have a lot of medical students from Cornell, but also from uptown at Columbia, who come to do research electives in the lab. We have postgraduate training and it's mostly post-doctorals, mostly PhDs but some MDs who have completed their postgraduate clinical training. Occasionally we get a resident in psychiatry or in internal medicine who is allowed to do a research module with us during their postgraduate clinical training. So, we do a great deal of training.

- LG: Are there any particular people that you've taught or trained or supervised that you want to call up?
- MK: Well, I have so many that I'm extremely proud of, but one of them, a close personal friend now, and, in fact, I credit him with having taught me much of what I learned early on, at least, about molecular biology, is my student Jeff Friedman, who later discovered leptin. Jeff came to the lab in 1981, having been referred by a colleague in Albany. He wanted to do one or two years of research before going on for his GI and liver training. Within two months, I said to Jeff, "you want to do science; you don't want to do only clinical work". Further, I said, "you need to take a PhD if you wish to do pure molecular biology. In '81, you cannot become, and be accepted as a molecular biologist without having PhD training in this field," and he looked at me and said, "I don't think that's correct". I said, "Yes, it is correct". He didn't believe me, but he went and spoke with three different people that I recommended and whom I knew well. One was Jim Darnell at our institution, and one was David Baltimore, then up at MIT, and one was Bert O'Malley down in Houston, Texas and they all said, "Mary Jeanne is right; you have to take a PhD". So, he did it at Rockefeller with Jim Darnell. He worked on one of Jim's very highly focused questions involving the liver. But Jeff, before he left me that first year, said, "I want to work on something like what you're working on, but I don't want it to be identical; what should I work on"? And, we talked about it a lot and I said, "well, we could call the addictive diseases a parallel to the greater domain of appetitive

disorders; why don't you take on obesity, a major appetitive disorder"? So throughout his PhD training we would meet for lunch about once a month. He would teach me the latest things about gene expression and new molecular biological techniques, and I would talk to him about continuing with this appetitive behavior and related obesity research. And, then, he began to tell me about his conceptualizations for reserch, building on his early work while in my lab after he completed his PhD and became head of an independent laboratory. The rest really is history. He went on to use reverse genetics to discover leptin, which was the first major gene and gene product involved in feeding disorders and obesity. So, Jeff is one I am very proud of.

I'm very proud of many others, several of whom, like Ellen Unterwald, are absolutely marvelous neuroscientists. She came to me after having trained in pharmacy, pharmacology, and neuroscience, but really wanted to get into something different. It was suggested to her that possibly the addictive disease area would be exciting, so she spent several years with me, training in cellular, molecular and behavioral neurobiology and research related to the addictive diseases. Now, of course, she's a full professor at Temple University and doing absolutely outstanding work, both scientifically and in administration and teaching. Then, one of my more recent trainees, John Mantsch, came to the lab and was introduced to our concepts of addiction. We also introduced him to molecular biology and the question that, maybe we would find different brain changes and resultant behaviors if animals had longaccess versus short-access to drugs; he's gone on to show that, initially in my lab and then subsequently. Now he leads a wonderful group at Marquette University, where he elected to go and open up a whole new department of neuroscience, as a young scientist.

We also have trained an early career physician-scientist, sent to us by the government of Israel, in both laboratory and clinical research, and also in pharmacological treatment of heroin addiction using methadone maintenance treatment. That physician, Dr. Miriam Ochshorn-Adelson, has gone on to create and run two highly successful research and treatment clinics, in Tel Aviv and also in Las Vegas, Nevada. Miriam Ochshorn-Adelson remains an adjunct member of our Laboratory and actively collaborates with us on many clinical and genetic research projects. These are four out of dozens and dozens of fantastic people.

- LG: Outstanding; quite a legacy. So, going back to your scientific research, what do you believe was your most important contribution to the field?
- MK: Well, I think there are maybe, four different important contributions. The first was developing a hypothesis that addictions are diseases of the

brain with behavioral manifestations, which led immediately to the logical conclusion of the need for pharmacotherapies, leading to our contributions in the development of methadone maintenance treatment. Developing methadone maintenance treatment was a major achievement. Now, 43 years later, it is still being used to treat over one million persons worldwide. Its use is growing rapidly in China, in Iran and throughout Europe, Our research in pharmacotherapy led to the development of LAAM and buprenorphine, that is preferably combined with naloxone, which are also very effective agonist or partial agonist treatments for opiate addiction. The concept, that pharmacotherapy is not just for relapse prevention but also for normalizing the brain is also our contribution. The physiological work we did, coupled with the pharmacological work taught us that brain normalization occurs.

The second domain that has been important in my research is that atypical stress responsivity, either existing before drug exposure on a genetic or environmental basis, or caused by drugs of abuse, may alter the progression to addiction, and may also enhance the likelihood of developing addiction, and relapse after one is rendered drug free. We have modeled that at the bench, and documented it in our clinical studies. Many people are doing elegant work on this topic. My wonderful collaborator, Rajita Sinha, has done great work at the clinical level; many people who are working at the bench level have contributed to this concept as well. I think nobody doubts now that stress plays a role, and thus stressors of diverse types play a role, along with drug exposure itself and drug-related cues, in developing and perpetuating addictions. Stress is one of the three things that consistently causes relapse to self-administration in animal models of addiction. I think our early and continuing work on stress responsivity has resulted in many insights into the addictive diseases, especially once we got into the molecular biological studies which showed that drugs of abuse, in fact, alter the very genes involved in stress responsivity.

The third area of contributions was our early hypothesis that we would see drug-induced changes in the brain as molecular events after chronic exposure. I have to tell you, in 1985, when we started doing that research, most did not think gene expression would be changed by a drug of abuse, but now everyone knows that is so. It is no longer a question. In 1985, people were very skeptical that drugs of abuse would really cause these major changes on the molecular level resulting in synaptic plasticity.

I think the fourth domain and focus, most recently added to our wide research portfolio, has been human molecular genetics and, now,

molecular genetics studies with a little bit of epigenetics. We have made some incredibly exciting findings; I think the single most exciting finding was the one Lei Yu and I made, early on, by the end of the '90s, that the µ-opioid receptor has a common variant, or SNP, in the coding region, resulting in an amino acid change from asparagine to aspartic acid in the N-terminus of the receptor. We showed in molecularcellular constructs, increases in both binding of the longest endorphin, β -endorphin, and increases in signal transduction when that neuropeptide is bound to the receptor. Further, we had for years shown that the mu opioid receptor plays a major role in modulating stress responsivity in humans and experimental animals. In humans, our lab has shown that with one or two copies of this 118G allele in a healthy human, one may have greater binding and greater signal transduction, but from our laboratory-based data, fewer mu opioid receptors, so the one is normal until a stressor comes. Two groups "beat us to the punch" by showing that if you objectively measured stress by putting in repeated doses of a mu-opioid receptor antagonist, healthy persons with one copy or two of the A118G variant would be hyperresponsive to that stress challenge. We've gone on to show that healthy humans with one or two copies have modestly higher basal levels of the stress hormone cortisol. I think we know now that this SNP is incredibly important for physiology and we coined a term, "physiogenetics", meaning change of response to one's own hormones, or neurotransmitters, because of a gene variant such as a single nucleotide polymorphism, or SNP, in a receptor or ligand difference. This concept is in parallel to a very old term of "pharmacogenetics," meaning some people respond differently to a medication on a genetic basis, a term coined long before there were genetic techniques to define those changes. We have been able to show that this A118G variant is associated with both opiate addiction, where one has atypical stress response as a contributing cause for the addiction, and also with alcoholism which is also associated with atypical stress responsivity, but in the opposite direction from opiate addiction. So these functional molecular genetics findings have been very exciting and a lot of our other molecular genetics research is turning out quite excitingly, as are the current and upcoming epigenetic findings.

- LG: We talked a little bit about some of your first publications. Would you like to comment on any other specific publications and, maybe, say something about your last publication?
- MK: Well, I'm going to admit to whoever is reading these Archives that this lady, Dr. Gold, taught one of the persons in my lab, Roberto Picetti, how to do self-administration studies in mice and he then taught that

technique to Yong Zhang in our lab. Both of them are now working very productively in my group doing self-administration studies in mice and rats. I think one of the very exciting pieces of work we completed, in the not too distance past, was in collaboration with Paul Greengard. In this research we were able to study mice with each of the four major phosphorylation sites deleted using mutant strains that Paul and his group had developed. In these mutants he had changed two sites of phosphorylation, serine or threonine, to the neutral alanine, so one amino acid only was changed, molecularly. We found that changes at two of the sites of phosphorylation led to greater self-administration when a high dose of cocaine was reduced down to a lower dose. Those same two strains had lower dopaminergic tone when challenged with cocaine. These extremely exciting findings were corroborating some of the findings of Nora Volkow, suggesting that altered basal dopaminergic status, or lower dopamine levels after drug challenge, may contribute to the acquisition of self-administration or addiction, but also showing how very important a single amino acid change can be!

Also, I've told you about the 1998 PNAS paper reporting the discovery and elucidation of a functional variant of the mu opioid receptor gene. We have a paper that was just accepted to days ago where we have done a whole-genome scan (GWAS) with a limited (10K) covering of the genome and found the m opioid receptor coming out with pointwise significance in a group of culturally admixed, though ethnically solely Caucasian, subjects who have heroin addiction as their disorder. That's extremely exciting in a whole-genome wide scan! Also, we have some exciting early data about stress responsivity and the µ opioid receptor ligand system. And what we have been able to do is go on and show, using more advanced techniques that in steady dose, longterm methadone maintenance treatment, the atypical stress responsivity that has developed in the severe heroin addict becomes normalized. Further, we also have been able to show that in cocaine addicts, there is persistent hyperactivity of stress responsivity as objectively measured in humans. One of our goals now, of course, is to develop, not just a pharmacotherapy for cocaine addiction, but a pharmacotherapy that can help normalize the brain, even while cocaine is still being intermittently used; our data suggest possible usefulness of both mu and kappa opioid ligands. Our wide experience with the development of methadone maintenance treatment has taught us that no medication is magic. You're not going to get immediate cessation of use of the drug of abuse or cessation in all persons. What you have to hope and look for is a medication that will allow or promote the brain to go toward normalization.

- LG: So, aside from submitting publications, have you published or edited any books or been involved in editing journals in the field?
- MK: I have done a lot of journal editing as associate editor or frequent reviewer, for just about every addiction journal at one time or another and two or three GI journals. However, I have avoided writing a book or editing a book. I am constantly approached by publishers, as well as by writers, and I am frequently told that I really must write a book or two. I do see this as a mandate, but, Lisa, I have a lab of thirty-five scientists in my Laboratory of the Biology of Addictive Diseases, the NIH-NIDA Center with many more scientists elsewhere and we have other grants beyond the Center. The research is just so thrilling and I insist on getting personally involved in each new technology or approach that we put into the lab, and with all experimental designs and data! Therefore, I actually have not found time; and we have not even mentioned my family.
- LG: We'll get to that.
- MK: And, I had to really laugh at some of the types of queries that were suggested for this interview; everything was in the past tense! I have to say we have just been very successful in getting funded again within the last two months for a five year competitive renewal of our P60 Center, so we are not looking at past tense. We are looking at future tense.
- LG: Great, that's great. We all look forward to that. So, I know that you've received numerous honors awards and distinctions for your work and, maybe, you could highlight a few that are most special to you.
- MK: Well, I will. AMERSA, which is an organization devoted to medical and scientific education about drug abuse and drug addiction, a wonderful and important organization, gave me the Betty Ford Award for outstanding outreach teaching and in education through science. ASAM, the largest society of professionals involved in treatment of addiction, gave me the Brinkley Smithers Award for outstanding bench research, but also clinical research and then translational work to persons in need. I received two marvelous awards from the College on Problems of Drug Dependence! I received the Marian Fischman Award. The late Marian Fischman was herself, a fantastic investigator, and, after her untimely death, her husband Herbert Kleber, created an award to be given annually for a woman who has had outstanding contributions in science related to addiction. I also received the most coveted Nathan B. Eddy Award of CPDD in 1999, which is for lifetime achievements in research related to addictions. Another award given to me was from the

Columbia College of Physicians and Surgeons, the annual Gold Medal for Distinguished Achievement in Academic Medicine. It was given to me in 2004. And then two universities, University of Uppsala in Sweden and the University of Tel Aviv in Israel, have given me honorary doctorate degrees in 2000 and 2007 respectively. Both of those events were extremely moving. Possibly the most moving was the doctorate I received in Tel Aviv in this past May of 2007, when in front of an audience of over two thousand persons, most not known by me, the President, Itamar Rabinovich, said, "for your lifetime of science, your contributions to genetics, molecular biology, as well as clinical research," and also "for developing the first effective treatment for an addiction that continues to save millions of lives". I got a standing ovation and I was extraordinarily moved at that, just extraordinarily moved.

- LG: So, we're here, actually, conducting this interview for the ACNP International Archives of Neuropsychopharmacology, which are part of the American College of Neuropsychopharmacology and, so, we'd be very interested to hear a little bit about your ACNP career. So, when did you actually become a member of the ACNP? And, tell us a little bit about serving on some of the committees of the college.
- MK: Sure. Having served twice on the Credentials Committee, I'm almost embarrassed to sav into the recording machine, but I'll sav it. Before I was a member, I did not know how formidable and difficult it was to become a member, but I was nominated by some very strong people. I became a member in 1985, at time of first application, and I became a Fellow in 1993. I'm completing my second and elected turn on Council. The first time I served for one-year tour, filling in for someone. I also have been on the Credentials Committee twice and on the Committee on Relationships with Advocacy Groups. I'm happy to let everyone know that I'm now on the Human Research Committee, so I've been very active. One major task to which I was appointed, as Chairman, was the ad hoc Task Force on Ethical and Legal Issues concerning clinical research. A special Presidential Commission had been appointed in Washington, the deliberations of which threatened the ability to do Clinical Research in mental health or chemical dependency, drug abuse and addiction. The Presidential Commission had recommended that anyone with a DSM III-R diagnosis was incompetent to sign any informed consent for research, and would need a special surrogate/ advocate to sign any consent for participating in any research. Further, aides of the appropriate legislative committees of Congress were drafting legislation to put this concept into effect, by law. Our committee took a very aggressive, but scholarly, approach to addressing this issue,

culminating in having an evening workshop to which we had staffers of key congressmen come and speak. During the dialogue of that session, it was pointed out that many of the staff and many in Congress had a current or past history of some DSM III-R diagnosis, especially a diagnosis of unipolar depression or an anxiety disorder, and yet certainly were competent to make major decisions, such as signing an informed consent for research. This was pivotal in that it resulted in having all plans and drafts for proposed legislation, which had been built on the Presidential Commission suggestions, withdrawn!

I think ACNP is just an incredibly important organization with very exciting science and proper concepts of sharing, but like CPDD, they also, I think, perceive the need, and we constantly need to remember this, to nurture young scientists, both bench and clinical, and those organizations do both.

- LG: Right, so, what other professional organizations have you been intimately involved with?
- MK: Well, I've just finished a four-year tour of duty as President of INRC. INRC is the International Narcotics Research Conference, an international think tank of three hundred to four hundred scientists, primarily bench scientists, all working directly or indirectly on the endogenous opioid system, so very basic science with some applications to physiology and very little clinical emphasis, but a wonderful organization. I still am serving on the Council, the Executive Committee, as Past-President, with Lakshmi Devi, who is now the President. Then the College on Problems of Drug Dependence, CPDD, is possibly the longest and dearest organization in my overall career. In 1976, I had been at the Rockefeller University part-time since 1964 and full-time since 1967 and, then, for two years, 1974-1976, I had been working, essentially, all alone. Even when in the Dole lab, it was not a lab where the Professor was a member of or attended any meetings of neuroscientists or groups related to drug abuse and addiction like CPDD, except one time to receive an award, so it was in 1976, a project officer from NIDA told me I really needed to go to two scientific meetings, and one was INRC and one was CPDD. I went to both CPDD and INRC. By 1983, I was elected to serve on the then "Committee" on Problems of Drug Dependence, and, then, I served as Chairman/President of that from 1985 to '87. The thing that I'm most happy about CPDD, though, that I accomplished while Chairman and still see the results every year, is the Travel Awards program that has blossomed. I established it in '86, and the track record of young scientists who have received those Travel Awards is outstanding; they go into various fields of science

and very frequently neuroscience. It has an extraordinarily higher yield than any of the career awards from the government or foundations, so I'm extremely proud of that program and insist on coming to the annual event, be it a tea or a luncheon or whatever, to celebrate the new awardees.

- LG: Great! I know that as much as you like to talk about your science, you also like to talk about your family.
- MK: Oh, yes.
- LG: So, tell us a little bit about your family and how you actually managed to sort of reconcile your family life with your professional career.
- MK: Well, I have a wonderful husband, number one. You know Bob Schaefer. He is an academic gastroenterologist, full time, and Head of the Training Program for GI and Liver at, what they now call Weill Cornell affiliated with New York Presbyterian Hospital. In his earlier days, he did clinical research, but in more recent years he teaches, runs the Fellowship program and does the high specialty referral patient care. He is superb at that and enjoys it enormously. We have two children, both of whom are marvelous. My son, Robert, Jr., went to Yale and Boston University Law School and is a litigator. He decided by age three not to go to science or medicine. Almost two years ago now, he married a wonderful woman who is a publisher, Heather Fain. They live in Manhattan, Robert is a litigator at a medium size firm, enjoys going in and out of the courtroom. My daughter, Esperance, who's a good bit younger than my son, had to go to NIH with me to argue for a grant at age two weeks, which probably served as imprinting (epigenetics!), and she has been determined since age five to go into science and medicine. She went to Yale, majored in Molecular Neurobiology, but became somewhat incensed about the erosion of healthcare in the U.S., so decided not to do the MD/PhD, rather did the MD and MPH. She won a Macy Fellowship Foundation Award to do the public health degree (MPH) at Mailman School of Public Health at Columbia in the middle of medical school. But, she took advantage during that public health year to study lots and lots of statistics courses and advanced ones! She got excited about clinical research and she had spent many summers working in clinical research, especially with John Rotrosen and Paul Casadonte at NYU. She spent a seminal summer internship at age sixteen working in Paul Greengard's lab at Rockefeller. She is now a PGY-2 second year trainee, which we used to call first year resident, in Internal Medicine at Harvard University at the Massachusetts General Hospital and she loves it up there. And she's made a decision very recently to go into academic gastroenterology and liver disease and to combine

laboratory-based and clinical research. She also demanded, and they gave her, bench research experience during both her internship year and first residency year which introduced her to working with transgenic mice; she learned how to work with small adolescent mice and do all the things one needs to do to dissect mesenteric lymph nodes and analyze what kinds of subsets of lymphocytes are there, as well as to determine and measure the cytokines and chemokines in the different mutant animals. She now is almost programmed to go into GI-liver related immunology and wants to go into hepatitis C progression fibrosis and transplantation hepatology/immunology. She'll be back working with our patients, since most of the hepatic transplants are for those patients who were exposed to hepatitis C by exposure to drug abuse, if not addiction, or chronic alcohol addiction. She knows she's going to be working at the interface of addiction, with patients who are doing well in treatment who now need to be treated for their end stage liver disease. She's very excited about the future. She has to go through another match and she'll be probably be at some place on the East Coast, possibly right there at Mass General, or possibly back in New York.

- LG: So, it sounds like the acorn didn't fall very far from the tree.
- MK: I've had three friends in the last forty-eight hours talk about her as a "first clone". She makes me seem shy, though.
- LG: Maybe we could finish up by hearing your thoughts a little bit about the future. So, what do you see developing in the next five to ten years in your area of research? What would you like to see happen in this area?
- MK: First, in the research area, I think looking at what the drugs of abuse do to everything from receptors to channels to signal transduction pathways and then looking at those specific genes of affected peptides to see if they have potentially functional variants, either in the coding region, which might, or might not, alter the peptide itself or change levels of gene expression, and thus the amount of peptide, or in a promoter or other region to increase or decrease in mRNA to effect changes in the productions of messages. To be able to relate back and forth what we find at the bench with what we may be able to discern at the human genetics level and at any physiological level is extremely important, i.e., bidirectional translational research. Although I think genome-wide scans are fantastic, nevertheless, any array probably does not have every base marker you want and certainly not everything is there for discovery. Though, with much refinement from the earlier days, the arrays help in further identifying diverse regions of the genome to look at. I

like going both ways; the whole genome-wide scans, but then intense studies possibly using deep sequencing as well as more conventional techniques, of specific genes for which we have a hypothesis, based on findings at the bench or the clinic.

Once we find a gene variant, which either is, or may be, functional, what we're now starting to do is relate it to our basic clinical research studies. For instance, when we administer dynorphin to a human, we have been able to document that the tuberoinfundibular dopamine is lowered, just as the striatal dopamine is lowered when one puts dynorphin directly into specific regions of the rodent brain. Well, now we would like to know if the magnitude of changes in the dopamine levels, as we can read out indirectly by peripheral serum prolactin levels, is altered, dependent upon the presence of a K-opioid receptor variant or possibly some dopamine receptor variant or some variant in a gene downstream of the receptor. Studies of the relationship, both for physiology as well as pathology, of the role of any functional gene variant is very exciting, as we have demonstrated with our discovery of the functional differences of the A118G variant of the mu opioid receptor. I think, going into other domains, in the future we have to think about individual personalized approaches to pharmacotherapy. The lay public and pharmaceutical industry will have to get used to higher cost for each drug, but fewer medications needed per individual and ones that are tailored using pharmacogenetic and pharmacodynamic findings, either to avoid adverse effects, or to magnify positive effects. First, as we predicted, the A118G variant predicts an improved and positive outcome in the treatment of alcoholism with a primarily mu opioid receptor-directed antagonist. We predicted that in our review article of 2000. The first paper; written by Oslin, O'Brien and Kranzler showed it to be true and now another large NIAAA study led by Goldman and Anton has shown it again. To me, this is going to be a future. For addiction, I think that by going back and forth in this bi-directional translational way we will discern critical involved pathways with ability to be able to develop, or refine, a pharmacotherapy to use, coupled with behavioral treatment, which will always be necessary. I think this is feasible. I think we were extremely lucky when we chose methadone for study. It turns out to be a full µ agonist. It has a tiny amount of NMDA antagonist activity, which is probably helpful in retarding development of tolerance. And methadone, unlike morphine, internalizes once it binds to the opiate receptor, just as an endorphin does. Our choice of methadone was based on predicated, and later proven long-acting properties of the substance in humans.

Not in the scientific domain, but in the policy domain, the number one issue we have for the next decade is to stop the stigma against addictions. I'm urging my colleagues now developing DSM-V to "bite the bullet," to stop pretending that addiction is "dependence" because "dependence" develops with use of too many unrelated medications. Dependence is not addiction. Addiction is the compulsive, relentless drug seeking driven by "drug hunger" or craving, and resultant drug selfadministration, despite knowledge of consequences that are negative to self and others. In addiction, a chemical such as alcohol, cocaine, or heroin alters the brain, and alters the brain in measurable ways at the bench level more easily detectable than at the human level. I think we will need to use imaging technology, both PET, and fMRI to relate to our genetics work and to relate to our diagnostic and pharmacotherapeutic intervention work. But unless we get rid of stigma, we're not going to get acceptance of treatment of addictions. Unless we get rid of stigma we're not going to get major pharmaceutical companies to want to put in huge efforts and costs involved to develop new medications and get them out there for treatment of specific addictions. And, we have to stop pretending! Addictions are the number one cause, directly or indirectly, of hospital admissions in the US. They are the number one financial burden for health care and social services and indirectly prisons, in the U.S. It is just amazing to me that medical schools, nursing schools, graduate schools and all kinds of other schools are avoiding teaching about drug abuse and addiction, with some wonderful rare exceptions, despite the fact that the problem is continuing to grow. Young people are now binge drinking, not two nights a week, but four nights a week, and despite the fact that we're seeing many other drugs of abuse appear, especially with increased use of prescription opiates, and we do not see cocaine and heroin going away. Other drugs of abuse come and go, but heroin, especially, stays an absolute constant and has for many years, so we must bite the bullet. Addiction is a disease and is a treatable disease. We have to prevent addictions when we can. Genetics will help us do that. Nicotine is a killer. Alcoholism is a killer. Cocaine and amphetamine addictions are killers, and heroin addiction is a killer, not only directly, but through the common association with AIDS and Hepatitis C.

- LG: Mary Jeanne, it's been an honor and a pleasure to be able to conduct this interview with you for the Archives and I just wanted to give you an opportunity for any last comments, then, before we close.
- MK: Well, I just would like to thank the College for creating an Archive. I think one of the most wonderful things was when I was asked who

could interview me; I could think of about fifty names that are ACNP members that would be excellent choices! Lisa Gold is somebody that I have watched grow up in science be recognized, win awards and mature, and then become a mentor for some now in my lab. This has been a great honor for me.

LG: Thank you. Thanks, Mary Jeanne.

ROGER E. MEYER

Interviewed by Thomas R. Kosten San Juan, Puerto Rico, December 12, 1996

- TK: Hi. I'm Dr. Thomas Kosten. I'm a Professor of Psychiatry at Yale and a member of the ACNP and I'm here this afternoon interviewing Roger Meyer,* the Past President of the ACNP in 1993. Roger, perhaps you could give more of an introduction of yourself.
- RM: I am Dr. Roger Meyer. Over a 30-year span, I have been an addiction research psychiatrist interested in looking at both experimental and clinical aspects of alcohol and drugs dependence. I served as department chair, Executive Dean and as Vice President for Medical Affairs.
- TK: How did you get prepared for such a career? What's your training been?
- RM: As a medical student at Harvard between 1958 and 1962, I was torn between internal medicine and psychiatry. We had some great lectures in psychiatry and pharmacology, and some wonderful psychiatry clerkship experiences that gave one a "hands-on" feel that was unavailable in other specialties. Internal medicine felt like the more "legitimate" choice of specialty. I resolved my ambivalence by choosing a rigorous straight medical internship under Dr. Robert Petersdorf in Seattle. before entering psychiatric training. Like many psychiatrists of my generation, I sought psychiatric training at a very psychodynamically oriented institution. I was a resident at the Massachusetts Mental Health Center (Mass Mental or MMHC) during it's so called, "Golden Years" when Elvin Semrad, our Psychiatrist in Chief, anchored a belief system that downplayed developments in psychopharmacology. I, on the other hand, hoped that psychiatry was about to change and take off in new directions because of emerging developments in psychopharmacology. The latter not only offered new treatments for seriously disabling conditions, it also seemed to offer a better understanding of the pathophysiology of those disorders. I was fortunate, because one of the first people that I encountered at the Mass Mental was Gerry Klerman. Gerry had returned to MMHC following two years at the Psychopharmacology Service Center at NIMH with Jonathan Cole and an extraordinary group of research psychologists. Gerry was in psychoanalytic training during his years at MMHC, but his enthusiasm about psychopharmacology was infectious; and his encyclopedic knowledge of the history of psychiatry, and of current developments in the field, was a stimulus to creative thinking. Gerry Klerman's vision brought resolution to my

^{*} Roger E. Meyer was born in New York, New York in 1938.

own ambivalence about psychiatry at MMHC. Just as I was starting to think about doing research with Gerry later in my residency, he went off to Yale to head the Connecticut Mental Health Center. Before leaving MMHC, Gerry recommended that I contact Jonathan Cole to see if I could spend two years with his group at NIMH, following my residency. I was delighted when Jon offered me a position to start in July 1966.

When Gerry Klerman left MMHC for Yale, I went on work with Alberto DiMascio in his clinical psychopharmacology research program on a part-time basis at the hospital. Indeed, it was Al DiMascio who invited me to my first ACNP meeting in Washington in December 1964. I was overwhelmed with the content and quality of the meeting, so very different from the environment at MMHC. Al invited me back in 1965, but I felt that a trip to Puerto Rico, even for the science, was too luxurious for a resident, so I opted not to go. By the time that the ACNP Annual Meeting rolled around again in December 1966, I was at NIMH and from that meeting to the present I have attended every meeting except one in 1989, when I had the flu. I regard my early and on-going ACNP involvement as a major pillar in my career development.

- TK: To come all those times is nearly perfect and possibly unmatched attendance record. To move forward in our interview, how did you get interested in substance abuse?
- RM: It was very, very fortuitous. In addition to my research on the effects of imipramine and stimulants in normal subjects with Al DiMascio, I had spent my last year of residency in a special program with Gerald Caplan. The Laboratory of Community Psychiatry, which had its origins at the Harvard School of Public Health, offered a one year didactic and field experience built around a revolutionary public health perspective. In addition to learning about the emerging community mental health movement, I gained important didactic information and some facility in the language and methods of epidemiology, social psychology, and biostatistics. As my time to go to NIMH approached, I contacted Jon Cole about my expected responsibilities and was distressed to learn that he had given my position away to someone who was already at NIMH, but who had been disenchanted with his previous assignment. As Jon and I discussed options, he was intrigued by my work with Gerald Caplan, and suggested that I might be interested in working with him in a new area that was about to fall under his Branch at NIMH: drug abuse. He noted that drug abuse seemed like a great match for my interests in psychopharmacology and public health. Though I had no experience with addiction during my psychiatric training, I was intrigued and agreed to take the new position. My friends at the MMHC thought

that I was making a huge mistake choosing to go so far out of the mainstream of psychiatry.

I arrived at the Psychopharmacology Research Branch in July 1966. Mitch Balter had been given a lot of responsibility for developing the program, and Mitch was one of the greatest mentors that a young psychiatrist could have. He was generous with his boundless knowledge and advice. Without guestion, my six months with Mitch constituted my essential orientation to the field. It turned out to be critical because, by January 1967, there was "another" reorganization at NIMH, and I found myself in a new Center for Studies of Narcotics and Drug Abuse. The man that I was working for at NIMH also held a senior position in the same content area at FDA. Because he was trying to do two jobs, and he had a history of two heart attacks, he died within three months. At the tender age of 29, I found myself with responsibility for identifying and funding the first community based treatment programs for heroin addiction, developing a system for the oversight and distribution of hallucinogenic drugs in psychiatric research, and establishing the foundation for a program to study cannabis, including cthe creation of the government's own marihuana plantation in Mississippi and for synthesizing δ -9 tetrahydrocannabinol. I was also responsible for managing an interdisciplinary grant review committee that would consider the broadest array of biological and psychosocial studies on addiction. At one point, I was tasked with trying to fathom the nature of the epidemic of drug use in Height Ashbury and among American service personnel in Vietnam, in order to advise Congress and the administration about prevention and intervention strategies. It was really an extraordinary experience, learning about a field from the top down. . We funded Avram Goldstein's original work on the opiate receptor. We set up the initial community based treatment programs in New Haven, Chicago, and four other cities, and we resisted the efforts of senior NIMH leadership to use the community mental health centers as the principal vehicle for dealing with the growing drug problem. By July 1967, I was officially made Acting Director of the Center that brought me into an official capacity in testifying before Congress and in meetings at the Pentagon. It was a heady experience, but I had never even treated a heroin addict I decided that the honest thing to do wold be to go back and learn the field from the grond up. I looked at different positions and was recruited by Boston University's Department of Psychiatry (BU) to a position called Assistant Director of Research Training in their Post-Residency Fellowship program. They promised me the opportunity to do research. I worked in Seymour Fisher's laboratory where I designed

and conducted a study of marijuana use in heavy and asual smokers. We fond significant differences in self-reorted experiences, and most importantly in our laboratory-based obsrevatios on the effects of cannabis n these two different cohorts. Securing permission, to conduct te study from federal and local officials, and securing the supply of marihuana for research purposes, presentes important logistical chalanges. Early on, I engaged some residents in my research, notably including Steve Martin who was a first year resident at BU. The resreach experinec brought Steve to addiction research an drepresentes the beginning of his distinguished academic career. Following his residency and service at the Pentagon, I later recruited Steve t join my research team att McLean from 1973 to 1977. At BU, I also got involved in setting up a community based heroin addiction treatment program and began my NIMH, later NIDA, funded research in drug self administration in rodents in Joseph Cochin's pharmacology laboratory. Joe was tremendously generous with resources, graduate students, facilities, supplies and research assistants, and his own time; and Joe and Conan Kornetsky taught me the elements of opiate pharmacology and of behavioral pharmacology that I later applied to my clinical research with heroin addicts. The combination of clinical and basic research at BU was wonderful. but the political challenges related to the development of an addiction treatment program in the inner city proved daunting and ultimately unsatisfying in a city that was at the time more racially polarized than at any time in its history.

Jack Mendelson offered me the chance to join him at Boston City Hospital, then, still a Harvard service in psychiatry. Jack and I followed up on the acute cannabis studies that Steve Mirin and I had conducted at BU. We studied chronic marihuana smoking in heavy and casual smokers over a four-week period in a paradigm that Jack had earlier developed with Nancy Mello in studies of alcohol self-administration. Our study, which was conducted with support from a relatively small grant from the National Marijuana Commission, clearly highlighted the extent of use among self-described marijuana smokers, and the effects of acute and chronic use on neuroendocrine function, behavior, motivation and cognitive function. In addition to our report to the Commission, we put our findings together in a book. The project also introduced me to Tom Babor, who was then a post-doc with Jack. Tom and another post doc manned the research unit in 12-hour shifts for 60 consecutive days.

TK: In spite of doing those 60 days of 12-hour shifts, he still wanted to work with you?

RM: Still wanted to work with me-and did at Boston City, McLean Hospital and later at the University of Connecticut where he is currently Chairman of the Department of Community Medicine. Most importantly, the chronic marihuana study with Jack shaped a Center grant proposal that I submitted to NIDA for clinical and biobehavioral studies of opiate addiction. Cyclazocine and naloxone had been available as experimental treatments for opiate addiction for several years, but each drug had serious limitations. Naltrexone was just coming on to the horizon. It had the narcotic blocking effects and benign side effect profile of naloxone, and a duration of action that made it practical for outpatient treatment. The vision that had fueled my original interest in psychiatry, that psychopharmacology might help us to understand the pathophysiology of addictive disorders, suddenly seemed achievable. A drug that blocked the effects of injected heroin might help us to understand the biological and behavioral dimensions of relapse. A drug that could be studied in a clinical research setting and in the animal behavioral laboratory, and that could then be administered to patients in a real world setting, might enable us to link experimental data to efficacy in the real world. In brief, the Center grant that I submitted brought together Joe Cochin and Conan Kornetsky from BU, Joe Schildkraut at Mass Mental Health Center, Jack Mendelson, Tom Babor and me in a multidisciplinary proposal to study opiate self-administration in rodents and in heroin addicts under blocked by naltrexone and unblocked placebo conditions. Our clinical research studies examined behavioral, mood, and biochemical measures, as well as neuroendocrine measures in plasma and MHPG in 24 hour urine, in these two conditions, i.e., blocked and unblocked heroin administration. After one year, Steve Mirin joined me as Clinical Chief of the unit. The work that I did under this Center grant was probably the single project, over the course of my career, of which I am most proud. The animal model studies took place at BU. The clinical studies took place at McLean Hospital because our original plan to conduct the study at Boston City Hospital was de-railed when Harvard was forced to end its affiliation at that hospital just as we were getting funded.

McLean was very supportive of the work. They moved quickly to establish a four-bed research unit. The IRB at McLean strongly recommended that the hospital attorney secure informed consent from each subject, after ascertaining that each subject was fully aware of the details of the study and was not "coerced" into participation. The extra procedures were very important in establishing our transparency and accountability in case of any controversies. Since this was the first chronic, 10 day, heroin self-administration study performed with volunteers rather than prisoner addicts, it was imperative that the study be done well with full attention to the rights of the volunteers. The FDA and the DEA had to sign off on our procedures for securing the heroin supply, which came from NIDA. In a curious side light NIDA was unwilling to ship the heroin directly to the hospital, so it could only be shipped to the local Belmont Post Office where I was the only authorized recipient. I was concerned that some day one of our former subjects would figure out how we obtained the heroin supply, so I carefully planned each trip to avoid repeating patterns from previous trips to the Post Office.

Our research participants came from a broad swath of territory in the Boston area, presenting us with some interesting logistical challenges related to recruitment and follow-up. Since we were interested in studying naltrexone in outpatients after their participation in studies on the unit, and since we were reluctant to dispense more than a oneday's supply of the drug, we identified the local pharmacist for each subject-and the local pharmacist administered the drug each day to the patient. When early in our study, it became clear that most of our subjects did not show up for their first dose of naltrexone at the pharmacy, we applied the same principles of behavioral reinforcement that we learned in the management of the inpatient unit: in this case we paid them \$1/day at the pharmacy. Our retention over the first 1 to 3 months dramatically improved. In recent years, it has been fun to see Dr. Nancy Petry and others apply these principles to demonstrate that rewarding abstinence can be an important part of addiction treatment.

In undertaking our studies, we felt that a research program involving heroin self-administration by addicts should include access to treatment. In more recent years, the field has focused on "non-treatment seeking" volunteers, but we felt that treatment was our responsibility to the subjects. In running the inpatient unit, we tied monetary reinforcement to therapeutically relevant behavior, such as participating in counseling, studying for the GED (the high school equivalency test), studying for a driver's license, preparing a resume, going for job interviews, as well as research relevant tasks, such as 24 hour urine collection. With regard to the latter, Joe Schildkraut noted that our subjects performed far better than depressed patients in terms of their urine collection reliability. In terms of our efforts at treatment in the inpatient setting and in aftercare, the Governor's Advisory Committee on Addictions who visited the unit and met with patients and staff cited us as an "exemplary" treatment program.

- TK: What did you learn from the clinical research studies of heroin self administration in humans and in animals?
- RM: During the ten-day period of heroin availability, subjects were not required to take it; but no subject refused the first dose and all subjects on placebo naltrexone continued to take unblocked heroin over this period. It is important to recognize that our work was based on models of addiction that had been developed at the Addiction Research Center at Lexington by Bill Martin, Harris Isbell, and particularly Abe Wikler. Following Abe's model of conditioned abstinence, we expected that subjects would self-administer heroin in the context of withdrawal signs and symptoms, which would emerge most clearly among addicts experiencing blocked heroin. We did not find evidence of conditioned abstinence in these subjects. In fact, many subjects on naltrexone stopped taking heroin after a very few doses. Those who continued to self-administer under these conditions seemed to experience conditioned drug effects. What we did find was that self-reported craving correlated highly with actual drug self-administration behavior, under blocked or unblocked conditions. Indeed, for our subjects, craving seemed to be related to the perception of heroin availability-and the craving experience itself was reinforcing. In recent years, it has been interesting to read the reports of Friedbert Weiss and of Bill Shoemaker. who have employed different methods to establish that in drug/alcohol self-administering rats, dopamine release in the nucleus accumbens precedes the self-administration behavior, a finding fully consistent with what we observed in our addicts. At some level, the reinforcing potency of "craving" may account for the tendency of addicts to return repeatedly to settings in which they have previously used drugs-despite the advice of their treatment programs to avoid such settings. I think we learned a lot about the stimulus issues with regard to heroin that has turned out to be quite interesting. In 1984, Stewart, de Wit and Eichelbaum cited our work in their classic paper on the conditioned incentive properties of drugs, arguing that "craving" was an appetitive response rather than an attempt to avoid negative symptoms. I think that other experimental work in the animal laboratory has also been consistent with our clinical research findings. We felt so strongly about this issue that we actually entitled our book summarizing the findings: The Heroin Stimulus, where the heroin stimulus was a signal of drug availability based on expectancies and/or prior experiences acquiring heroin in the community.

In my view, the only way that you can validate self-reports of craving is to examine it in the context of drug self-administration. Our studies of

heroin self-administration on the four-bed unit also convinced me that laboratory based studies of "craving" should include the opportunity to consume the drug, or alcohol. The drug related stimulus minus the opportunity to consume is not the same as the drug related stimulus linked to actual consumption. In our double-blind studies of four housed subjects at a time, the randomization procedures might result in three subjects getting high on heroin while one subject was receiving naltrexone and getting no pharmacological effects from the opiate. Rather than the overwhelming stimulus of three intoxicated subjects driving craving and heroin self-administration behavior in the lone naltrexone treated subject, self-administration behavior stopped and craving fell over the ten days of heroin availability under this condition. Across all double blind studies, most subjects did not challenge narcotic blockade after the first few doses. Indeed, heroin self-administration under blocked conditions only persisted as long as subjects were getting some conditioned effects from the injection as evidenced by subjective reports and papillary constriction. In our animal behavioral studies, rats who had been through multiple periods of drug self-administration and withdrawal were more likely to relapse to saline injections and to persist in saline self-administration behavior than rats who had been through a few cycles of opiate self-administration. These animal studies highlighted the power of conditioned reinforcement following prolonged cycles of drug self-administration.

Our inpatient studies also provided possible insights on the relationship between street pricing and crime. In our study, subjects "purchased" heroin by exchanging points accumulated on a hand counter. This methodology for assessing the motivational value of anticipated drug reinforcement was built on the work of Jack Mendelson and Nancy Mello in their studies of chronic alcoholics. The hand counters were designed to be tamper proof, and worked perfectly when the response costs were moderate. When the "price" was increased to determine if excessive response costs could modify drug-seeking behavior, the subjects figured out a way to "break into" the hand counters to advance their available "currency", unbeknownst to the staff. At the end of their stay, they revealed their strategy to the staff, and the devices were modified. The next group of subjects, faced with the same response costs, figured a new way to "beat" the revised system, and revealed their strategy at the end of the study. For the rest of the study, the response costs were returned to the original level and the "criminal behavior" did not recur.

- TK: If you increase the price of the heroin, you increase criminality rather than decrease drug use?
- RM: Apparently so.
- TK: You also looked at a number of biological measures associated with drug-seeking behavior.
- RM: Yes. Joe Schildkraut looked at 24 hour urinary MHPG which was the most accessible putative marker of CNS catecholamine activity at that time. While the findings were of interest, we were very cautious in our interpretation of the data that suggested a possible relationship between mood elevation with heroin consumption and increased MHPG excretion. Recall that at the time, the predominant theory of drug reinforcement was noradrenergic rather than dopaminergic, so we were looking for links between mood and distal evidence of noradrenergic activity. The neuroendocrine findings that were analyzed by Jack Mendelson and Jim Ellingboe were also very preliminary, but were followed up over the years in rigorous studies by Jack and Nancy Mello and their colleagues. I have come to believe that some of the elegant clinical research paradigms that were applied to behavioral studies in addiction in the period prior to 1980 should be brought back now that we have the technology to assess more direct measures of brain function.
- TK: Who were some of your early career mentors who helped to shape your career?
- RM: Well, I have already referred to the work of Bill Martin, Harris Isbell and Abe Wikler. In my view, Abe stands as one of the most creative psychiatrists of 20th century America whose work at Lexington influenced a number of people including Arnold Ludwig, Jerry Jaffe, Don Klein, Chuck O'Brien, Herb Kleber and me. Regrettably, Abe's influence was not much felt in mainstream American psychiatry which was dominated at the time by psychoanalysis. Jerry Jaffe, Jack Mendelson, and Dan Freedman were my early role models-and each helped me in different ways to harness my research vision and career direction. The research psychologists at BU especially Conan Kornetsky and Alan Mirsky opened my eyes to powerful linkages between clinical and animal model studies-and the unique possibilities for such linkages represented by the addiction field. In my view, this is still true!
- TK: Your career took a turn at some point where you moved away from heroin and moved towards alcohol.
- RM: When I was at NIMH, I came to feel that alcoholism was a greater public health problem than illegal drug abuse, and I tried to get myself reassigned to work with Jack Mendelson and Nancy Mello in their intramural research program at St. Elizabeths'. Because we were short-staffed

in the Center, I was promoted to be Acting Chief and I missed the chance to work with Jack at that time. At Boston City Hospital and at McLean I had a great opportunity to interact with Jack and we talked a lot about issues of alcohol and drugs. Tom Babor, who came with us after his post doc, was an encyclopedia of alcoholism. So, while my research focus at McLean was opiate addiction, I found myself also reading and talking a lot about alcoholism.

While McLean was a great setting for my research, I also felt that our group was never going to impact on medical student or resident education in an institution that was still very psychoanalytic in orientation, and where my research was not really of great interest to my clinical colleagues. To bring what I had learned into the mainstream, I really felt that I needed to seek a leadership position, to become a Chair. Through Danny Freedman and others, I made it known that I would be interested in looking at Chairs. I wanted to be able to find a setting in which I could continue my scholarly interest in addiction, preferably alcoholism, while also being in a position to influence the future direction of psychiatry and the image of psychiatry within the community of academic medicine. I increasingly felt that the addiction field, as poorly understood as it was among our psychiatric colleagues, was well positioned to progress because of developments in neuroscience and genetics, and especially because of the guality of our animal models and the strength of our clinical research. I had looked at several Chairs, and was offered two of these positions before I was approached by the University of Connecticut (UConn). The position at Connecticut attracted me because, it looked reasonably well funded, and the university hospital was suffering from a paucity of medical and surgical patients which enabled psychiatry to develop a second inpatient unit devoted to alcoholism treatment. While there was no federally funded research in the department, I thought that the alcohol unit was a potential gem that could anchor a major clinical research program on alcoholism. I secured a commitment from the Dean that we would always have at least a ten-bed presence on this 20+ -bed unit, and I accepted the position. In January 1977, I started at UConn 2 days per week, while I wound down my program at McLean. I also put the elements together for a Center grant application to NIAAA. I discovered a number of resources in the Hartford area, including Bernard Glueck, who had been on my study section at NIMH, and was at the Institute of Living doing studies with computerized EEG and with autonomic arousal. Tom Babor could easily commute from Boston to the Hartford area and help me put this proposal together. James O'Brien was an internist in the

Department of Psychiatry who had obtained a Career Teacher Award from NIAAA, and was interested in the medical consequences of alcoholism, Jim Stabenau, the former Chair who had stepped down several years earlier, had been a distinguished schizophrenia researcher in the intramural program at NIMH with a strong interest in genetics. Jim proposed a family history study of patients admitted to our alcohol treatment unit. Our initial Center grant application was approved but not funded, and we were strongly encouraged to immediately reapply. NIAAA had funded five centers in the first go-round, and indicated that they might fund as many as four centers in the second round. When we were approved for funding, our budget was immediately reduced from \$500,000/year to \$200,000/year including indirect costs. We were expected to conduct our studies on typologies of alcoholism within our treatment system, conditioned responses to alcohol-related stimuli in alcoholics, and the family history study. Being Chair of the department enabled me to cobble together additional resources from a variety of locations in order to stabilize funding for the Center. We were able to recruit Jerome Jaffe, Dominic Ciraulo, Alexander Nies, and Ovide Pomerleau to the affiliated Newington VA Hospital and to link our VA resources to build the Center. By 1982, when the Center grant came up for renewal, we were the only one of the four centers that had been approved in our cohort to be renewed. Our research had been able to proceed in spite of the huge budget cut, and our new faculty was able to drive exciting new initiatives that we proposed in the renewal application. Being Chairman of the department had enabled me to garner additional resources for the Center, and thereby strengthen both the research program and the qualitative direction of the department across its mission of teaching, research, patient care and service to the community.

While I view the Alcohol Research Center at UConn as the core of my legacy at that medical school, we were very nearly wiped off the map shortly after our grant renewal in 1982. A new Chair of Internal Medicine had come on board and covetously eyed our alcohol unit beds. Our new Vice President for Health Affairs thought that psychiatry should not be part of the campus but should be somehow placed elsewhere. Thus, by 1983, I was involved in a protracted struggle to keep the alcohol unit, while the powers that be in the University were trying to have it converted to the use of the Department of Medicine. It was a very tense time, and it was only fortuitous that the federal government, at that moment, imposed the DRG system which shortened the lengths of stay of patients in internal medicine and surgery, and, thereby abruptly eliminated the urgency to change the configuration of the alcohol unit. But the protracted battle to preserve the Center, and a contemporaneous set of problems at the Newington VA Hospital, led to the departure of my closest colleagues: Jerry Jaffe and Ovide Pomerleau. Somehow, during this time, I was able to recruit Tom Babor to UConn, and we were able to link some research to Herb Kleber's group at Yale, re-creating a critical mass of researchers in alcoholism and addictive disorders within our Center. As you know, Herb is one of the most generous and wonderful people in psychiatry, and I owe him a great debt of gratitude for making this linkage possible.

By 1984, I felt secure enough to take a mini-sabbatical in London with Griffith Edwards, and to think through where I wanted the Center to go next. Using Edwards' alcohol dependence syndrome as our model for defining aspects of alcoholism in patients and in animal models, we proposed some studies with animal models, the expansion of our clinical studies of conditioning factors, craving and drinking behavior, and we proposed to build on our typology study data to launch a program of pharmacotherapy studies in alcoholic patients. The studies of autonomic reactivity and subjective effects of craving and conditioned stimulus effects of placebo and alcohol in alcoholics had mirrored my earlier findings on the effects of the heroin stimulus and of blocked heroin injections in heroin addicts. Our linkage with Yale brought in Bruce Rounsaville, Stephanie O'Malley and Bob Innis. The departure of Jerry and Ovide actually opened opportunities for younger faculty at UConn like Hank Kranzler, Ned Cooney, Lance Bauer and others. Our research on typologies has helped to differentiate patients with better and worse prognosis entering clinical trials. While it has not yet produced a valid treatment matching strategy, it has highlighted the importance of sociopathy, alcohol dependence severity and family history as very important factors affecting outcome. The family history studies led to major collaboration in the Collaborative Study on the Genetics of Alcoholism, in which Victor Hesselbrock at UConn has played a major role. Victor, Hank and their colleagues have greatly expanded the genetic studies on alcoholism at UConn and Yale with Joel Gelertner. Hank Kranzler and Stephanie O'Malley have conducted some elegant clinical trials on the drug and behavioral treatment of alcoholism starting with their studies of buspirone led by Hank and naltrexone, led by Stephanie. Based on their work in the Center, Tom Babor. Ron Kadden, Ned Cooney and Mark Litt played a major leadership role in Project MATCH, the largest comparative psychotherapy study ever supported by the federal government. By the time I left UConn in 1993, our NIH-support on a per capita basis was the highest in the school, and our department was one of the stronger research departments of psychiatry on a national basis, one of the few small departments to be in the top quartile of NIH support. Our department had also been key to UConn's successful GCRC submission, especially because of the contributions of Victor Hesselbrock and Hank Kranzler.

After my efforts to save the Center had succeeded. I realized that the existence of the Center itself and of a successful department would not guarantee survival. So when our new Dean asked me to come into his office part time in 1987 to re-organize the faculty practice plan, and in 1989 to become Executive Dean to help him to manage multiple aspects of our clinical care and research programs, including our relationship with the hospital, strategic planning, and the GCRC application process, I felt that I needed to take on more administrative responsibilities in order to avoid unexpected adverse decisions coming down from the administration. It also pulled me toward higher academic administration and away from day to day involvement in research and teaching. By 1992, I was ready for a sabbatical from my three roles, Department Chair, Center Director and Executive Dean to decide the future direction of my career. Our youngest daughter was off to college and my wife and I went to the Center for Advanced Study in the Behavioral Science at Stanford for the year. During that year the appointment of new leadership at the UConn Health Center convinced me that it was time to move on to become a Dean or VP Health Affairs at another institution, and to give my younger faculty a chance at leadership in the department and the Center. Mostly, I did not want to try to educate a new group of leaders on the importance of our programs. By becoming VP Health Affairs and medical center CEO at George Washington University, I also recognized that my time as an active researcher was coming to a close.

I have been privileged to be part of a great research renaissance in the addiction field and alcoholism. I have been pleased to watch the impact of our field on ACNP over the past four decades. From very small numbers, in the late 1960s, ACNP now includes many distinguished behavioral and neuroscientists and clinical investigators who receive their primary funding from NIAAA or NIDA. Several ACNP Presidents and a number of ACNP Council members have had very distinguished research careers in the addiction field. I've also been pleased to see the evolution of CPDD into a membership society, now the College on Problems of Drug Dependence, and to be part of the Research Society on Alcoholism as it has taken off as a multidisciplinary research society in the alcohol field. As I said in my Post-Presidential address at the

1994 meeting of ACNP, I think the addictions field, including alcoholism, is in many ways much better positioned than other areas of psychiatry to begin to take advantage of molecular biology and to apply imaging technology to understand pathophysiology. Because of developments in science and technology, the addictions field can test some of the theories of addictive behavior that emerged from clinical and basic science research dating back more than 50 years. Concepts such as "protracted abstinence", "neuroadaptation", "conditioned abstinence", and "opponent process conditioning" can be examined in the context of changes in gene expression following chronic exposure to drugs of abuse. There is already a revised consensus that while the reinforcing properties of drugs are a critical piece of the risk of addiction, they are an insufficient explanation of risk which resides in the genetic makeup and developmental histories of individuals, and the impact of culture and the peer group. We have become much more concerned about what accounts for the power of the memories in the relapse process, and what makes for the power of the compelling emotional memories that shape the anticipatory state.

Finally, while the addiction field seems to be at an extraordinary time in terms of science, and the growing interest in the development of new pharmacotherapies to treat alcoholism, tobacco addiction and stimulant dependence, the field has been substantially diminished in terms of the impact of managed care on the treatment system and cutbacks in public funding at the State level. Sadly, just as we could be on the verge of some really interesting and therapeutically relevant breakthroughs, the clinical care system that could receive these innovations is not promising. It is dominated by addiction counselors who are not well-prepared or disposed to recommending pharmacotherapy. To advance the clinical care of addicted patients, we need a therapeutically and scientifically sophisticated workforce that can incorporate validated new treatments. Unless there is a treatment system in place that can incorporate these scientifically driven developments, the promise of the science will not be achieved.

TK: We've covered a broad range of achievements in your life. It's hard to think of a question that we might not have hit on. What else can you say about how drug abuse as an illness might be treated during the next five to ten years? We have talked through many potential developments in the field. Are there any developments that you would particularly target as becoming the most critical development in the next five or ten years? RM: I think it's going to be terribly important to interest industry in developing drugs to treat addictive disorders. Virtually all drug development in this field outside of heroin addiction and recently nicotine addiction has come from studies of off-label use of drugs originally developed for other disorders in psychiatry and neurology. If the impact of managed care discourages young psychiatrists from entering the addiction field, and the treatment environment thus remains dominated by addiction counselors unreceptive to new drugs, it is going to be a huge task for ACNP and for others to stimulate industry interest in developing drugs to treat addictive disorders based on the exciting developments in science. With new drugs and new targets, we will be in an excellent position to stimulate a new generation of translational research. We have already learned a great deal about requirements for clinical trials in this field, including the importance of monitoring patient adherence. Importantly, the latter is one of the best predictors of patient outcome in placebo-controlled studies in the addiction field.

In the alcohol field, The Collaborative Study on the Genetics of Alcoholism (COGA), now linked to the Human-Genome Project, is going to tell us a great deal about those aspects of alcoholism that are inherited, which may end up telling us a great deal more about the environmental factors that lead to the expression of the phenotype. With the genetic basis of risk better understood, the environmental risk factors will become clearer than ever in the past-and this will open real opportunities for prevention research.

Finally, I am constantly perplexed about how so many of our colleagues in psychiatry seem not to understand drug addiction or alcohol related disorders. In my view, it is one part of psychiatry that connects most easily to the rest of medicine. I continued to do histories and physicals on our heroin addict research subjects right through the end of my time in Massachusetts, and I think that was terribly important to my identity as a physician and as a clinical department Chair in Connecticut. I continued to see patients until I came down to Washington as VP Medical Affairs. Patient care was an important reminder that the best research ideas did not necessarily translate into successful therapeutics. Patient care is a complex mixture of art and science, and in psychiatry it continues to be overwhelmingly art informed by experience. In the addiction field, we should be able to shift the balance of art and science to be closer to the rest of medicine.

- TK: That's great. Our interview feels pretty comprehensive to me.
- RM: Fine. Thanks very much.
- TK: Thank you. That was great to spend this time with you.

ERNEST P. NOBLE

Interviewed by Edythe D. London Boca Raton, Florida, December 12, 2007

- EL: We are at the annual meeting of the American College of Neuropsychopharmacology in Boca Raton in 2007. I am Edythe London and it is my pleasure to conduct an interview today with Doctor Ernest Noble* for ACNP's International Archives of Neuropsychopharmacology. Doctor Noble is the Distinguished Professor of Psychiatry and Biobehavioral Sciences at the University of California, Los Angeles. Doctor Noble, could you begin by telling us a little bit about where you were born and some of your early on training?
- EN: I was born in Baghdad, Irag of Armenian parents. My mother was a housewife and my father was a physician who, after receiving his MD degree, was accepted by Madame Curie in Paris, France to be a Resident in radiology. Following three years under her tutelage, where my father learned how x-rays can be used in clinical practice, he came to Bachdad and brought with him radiological instruments. He was the first in that country to use x-rays for diagnostic purposes and to treat cancer. When I was eleven years old my family decided to immigrate to the United States, because of the unstable political situation in Iraq. We boarded a ship in Basra and while we were on our way to the US, Japan joined Germany in a war against the US. Because of the dangerous situation on the high seas, the captain of our ship decided to disembark all passengers next to the closest land, which happened to be India. After staying a short while in Mumbai (Bombay), the family decided to leave that city and moved to Poona, where we stayed for five years. There, I attended Bishops High School, a private school manned by British teachers, where discipline was strict and education excellent.

When World War II ended, we left India for the US and settled in Hasbrouck Heights, New Jersey. After completing the senior year of high school, I attended Rutgers University for two years. My family decided to move to Berkeley, California. There I attended the University of California, Berkeley where I majored in Chemistry. After completing my undergraduate education, I received a pre-doctoral fellowship from the Biochemistry Department at Oregon State University in Corvallis, Oregon. Under the supervision of Professor Chih Wang, I studied carbohydrate metabolism in a mold, Penicillium Digitatum. Soon after obtaining my PhD degree in 1955, I was awarded a Fulbright scholarship to conduct post-graduate research at Sorbonne in Paris, France.

^{*} Ernest P. Noble was born in Baghdad, Iraq in 1929.

Under the mentorship of Professor Claude Fromageot, I purified an egg protein, ovomucoide, and determined its structure.

While I was in Paris, two fortunate situations occurred. In the laboratory where I worked was Professor Warwick Sakami, who was on leave-of-absence from the Department of Biochemistry at Case Western University, in Cleveland, Ohio. Professor Sakami was a renowned scientist in the field of carbohydrate metabolism. He invited me to join him back home to conduct research under an NIH-sponsored post-doctoral research fellowship. This, I gladly accepted. I also met a Swedish woman, Birgitta Kilströmer, while we were having lunch at the student cafeteria in the Sorbonne. We liked each other very much and decided to marry. That we did in her hometown of Göteborg. We have now been married for over 50 years and are the proud parents of three children. In the Department of Biochemistry at Case Western University, I continued my research on carbohydrate metabolism but turned my attention to mammalian cells, specifically leukocytes. In collaboration with Rune Stjernholm, a pre-doctoral fellow in that department, we carried out and published a number of studies on the metabolic pathways in normal leukocytes. After completing my post-doctoral fellowship year in the Department of Biochemistry, Professor Austin Weisberger, Head of the Division of Hematology in the Department of Medicine at Case Western University, because of my interest in blood elements, offered me a position as Senior Instructor in his Department, as well as laboratory space and a technician to conduct research. Together with Professor Weisberger, we studied carbohydrate metabolic pathways in lymphocytic leukemia and isolated a protein in normal serum that inhibited the growth of cancer cells. In addition we conducted genetic research by isolating DNA from sickle cells and incubated it with normal human megaloblasts. We were successful in showing that these normal megaloblasts now expressed the sickle cell hemoglobin. Noting my interest in medical problems, Professor Weisberger asked, "Ernie, why don't you attend medical school? You already have a grant from the American Cancer Society, a laboratory and a technician; you can continue your research and at the same time attend medical school". I discussed this with my wife and she said "why not?" So, I started medical school and graduated with an MD degree in 1962. Following graduation from medical school, I was accepted as an intern in the Department of Medicine at Stanford University. The program at that time required an intern to treat medical patients for the first nine months and psychiatric patients for the last three months. Working with psychiatric patients for me was a fascinating experience, as I had to deal with depressives who

hardly moved or interacted; schizophrenics with their delusions and hallucinations; the "John Does" with their faulty memories; and alcoholics with their withdrawal reactions and seizures. Sadly, the treatment of these disorders at that time was guite ineffective. Treatment was based primarily on Freudian theory, with few pharmacological treatments available at that time. The experience with psychiatric patients was an epiphany for me. So, I decided to go into Psychiatry, rather than Medicine as was my original intent. I approached Professor David Hamburg, Chairman of the Department of Psychiatry and expressed my interest in Psychiatry. Following my interview, Professor Hamburg indicated that he would accept me for the three years of residency training. Moreover, he stated that he would appoint me as an Assistant Professor in my second year as a Resident, and provide laboratory space and a technician to conduct research. This, I wholeheartedly and gratefully accepted. During the end of my residency training, I began again to actively conduct research. This research was stimulated by Dr. Ryoko Kakihana who joined my laboratory as a research associate. Dr. Kakihana had brought along with her two strains of mice that either preferred or avoided consuming alcohol. We studied a number of factors in these animals, including their differential endocrine response to alcohol and stress: the the loss of alcohol preference in animals when certain brain areas were ablated, and other studies. Based on the results of these studies, I was successful in obtaining a Career Development Award from the NIMH. This award provided the financial resources to continue my alcohol research. Noting the successes I was achieving in beginning to understand some of the biological/genetic basis of alcohol consumption, Dr Hamburg stated, "Ernie your findings tell me that it is directly within the brain that your answers may lie. You need a better understanding of brain function. Why don't you call my friend, Dr. Julius Axelrod, and see if he would accept you in his laboratory for a year of study?" So, I called Dr. Axelrod and he asked me to come to his laboratory at the NIH for an interview. Following the interview, Julie said "you are on board". I should indicate at this time that Julie was the best mentor I ever had and the year spent in his laboratory was the most fascinating and rewarding experience of my career.

- EL: With respect to the mentorship that you received from Doctor Axelrod, what were the most important lessons there?
- EN: There were many lessons that his mentees learned from Julie. These were learned mostly through observing his actions and behavior, rather than through his direct utterances. Julie had scientific courage. He was not afraid of publishing studies that went against conventional wisdom.

His openness in divulging the results of his preliminary studies and even the experiments he was planning to scientists who visited his laboratory was a beguiling trait. When NIH scientists expressed concern that this information may be "stolen", Julie's response was that he learned more about his research from the comments and critiques of these visitors than if he secreted this information. Julie was a kind, modest and generous man. He never spoke ill about his scientific competitors. With respect to his research accomplishments, he did not brag about them. When presenting his research at scientific meetings, he always gave credit to his co-workers. When asked what factors accounted for his seminal discoveries, his typical response was "I guess I was lucky". Time limitations prevent me from delineating the many other valuable lessons I learned from Julie. However, it is well established that those scientists who conducted research in his laboratory and came in daily contact with him, ended up with distinghished careers of their own in such fields as pharmacology, neuroscience, neurology, psychiatry, and nutrition.

- EL: And, who were some of your best students?
- EN: Four individuals who obtained their PhD under my supervision: One was Elizabeth Parker who studied the effects of alcohol on memory and learning: she is currently Professor at the University of California. Irvine. Another was Ronald Alkana, who studied ethanol-induced depression and its reversal in humans, and who is currently Dean of the School of Pharmacy at the University of Southern California. A third was Peter Syapin, who studied ethanol's effects on neural cells grown in culture, and is currently Professor at Texas Tech University. And the fourth was Bradley Conner, who studied factors leading to the development of risk-taking behavior in humans, and is currently an Assistant Professor of Psychology at Temple University. I was also fortunate to have had outstanding post-doctoral fellows like Sujata Tewari, who studied the effects of chronic alcohol administration on protein and RNA synthesis in rodent brains. She became Professor of Psychiatry at UC Irvine. Another one was Ross Young, who studied genes involved in posttraumatic stress disorder. Currently, he is Chairman of the Australia Institute of Health and Biomedical Innovation in Brisbane, Australia. I also had Charles Raison, who studied the DRD2 gene in borderline personality disorder, who is currently Chairman, Department of Psychiatry and Behavioral Sciences, Emory University. I should also mention Jamie Feusner; he studied the GABA gene and psychiatric morbidity in post-traumatic stress disorder. He is currently Assistant Professor in the Department of Psychiatry and Biobehavioral Sciences at UCLA.

- EL: Can you tell us something about the thrust of your research and how you got into the field of pharmacogenomics and where you think it's going from here on?
- EN: When I started alcoholism research at Stanford University, the prevailing zeitgeist was that alcoholism was caused by moral weakness. Studying inbred strains of mice, with different proclivities for alcohol consumption, led me to believe otherwise, and that was that genetic factors may be an underlying cause for developing this disorder. When I became Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), my research had to be discontinued because that position, with its myriad activities and responsibilities, required my full attention. After three years at the NIAAA, I decided to leave to restart my academic career.

In 1981, I accepted the Pike Professorship, an endowed chair, on alcohol studies in the Department of Psychiatry & Biobehavioral Sciences at UCLA. I resumed my studies on the effects of alcohol on neural cells grown in culture and began studies to determine whether there were differences in brain function between young children of alcoholics and non-alcoholics, using an electrophysiological approach. I also started collecting brains of deceased alcoholics and non-alcoholics to determine whether there were any differences in their various neurochemical systems. It was about that time that molecular genetic techniques were becoming available to identify genes in human behavioral afflictions. Having brains of alcoholics and non-alcoholics, we isolated their DNA, and with probes for nine different genes we determined whether polymorphisms of any of these genes would associate with alcoholism. The results showed the only gene that associated with alcoholism was the D2 dopamine receptor (DRD2) gene. Specifically, the A1 (minor) allele of the DRD2 was found to be strongly associated with alcoholism. This study was published in the April 18th issue of the Journal of the American Medical Association in 1990.

The next question we raised was whether the DRD2 was an alcoholism gene per se, or if it was involved in other psychiatric disorders.. To begin to answer that question we determined, in a pharmacological study, the number of D2 dopamine receptors in the caudate nucleus of brains of our alcoholics and non-alcoholics. We found that subjects with the DRD2 A1 allele, regardless of whether they were alcoholic or non-alcoholic, had reduced number of D2 dopamine receptors compared to subjects without this allele. This study was published in July 1991 in the *Archives of General Psychiatry*.
Since it is known that the dopaminergic system is involved in brain reward mechanisms, we hypothesized the reduced D2 dopamine receptors in A1 allele subjects renders them "reward deficient". To compensate for this state, AI allele subjects use excessive amounts of alcohol or other drugs which, by enhancing dopamine release and activating their fewer dopamine receptors, obviates their "reward deficient" state. This hypothesis suggested to us that the DRD2 gene should also be involved in other drug addictions. Indeed, subsequent studies in our laboratory showed the DRD2 gene to be also involved in nicotine, opioid, and cocaine addictions and obesity.

- EL: And, what do you think about the availability of new technologies to facilitate this work going forward?
- The Human Genome Project (HGP), which was activated a decade and EN: a half ago, has provided data .and tools which have dramatically accelarated the fine mapping of disease genes. The HGP has identified over 10 million SNP markers in the human genome. With the availability of these high density SNPs, it is now possible to use more effectively genome-wide linkage analysis to identify chromosomal loci that harbor alcoholism genes. However, to conduct such a study it is necessary to have methods that genotype these very large numbers of SNPs. Several strategies have been developed for high throughput chip-based genotyping. One strategy relies on the SNP decreasing the hybridization efficiency under specific conditions. Using this approach, it is now possible to genotype approximately 100,000 SNPs individually. Another strategy pools many DNA samples from ill individuals and estimates the allele frequencies based on differentiatial signal for the SNP variant. Over 1.7 million SNPs can be read in this fashion. The common element among all genomic studies is the vast amount of data generated. The management of such data became a formidable challenge in itself. Completely new statistical approaches have been developed in order to understand such large amounts of data. This challenge has spawned the new and rapidly expanding field of bio-informatics.
- EL: What do you think about the treatment of alcohol dependence, per se, and how that is going to change on the basis of new knowledge?
- EN: That's a good question. It is well known that alcoholism is a heterogeneous disorder with essentially two types: a "genetic" and an "environmental" type. Despite the existence of different types of alcoholics, treatment of alcoholics with pharmacological agents, rarely take into consideration alcoholic types. Treating alcoholics as a homogeneous group may be one reason why mixed findings and high recidivism rates are commonly found in the treatment of alcoholics. The question we

raised was what if the treatment approach took into consideration alcoholic types. I will provide one example where using a pharmacological agent resulted in a differential outcome in the two types of alcoholics. In a double-blind study, bromocriptine, a D2 dopamine agonist or a placebo was administered, over a 6 months period, to alcoholics carrying the DRD2 A1 allele, i.e., "genetic type," or the A2 allele i.e., "environmental type". Four treatment groups were generated: bromocriptine - A1 allele; bromocriptine - A2 allele, placebo - A1 allele; placebo - A2 allele. Changes in the anxiety, craving and retention rates were assessed throughout the course of treatment. The results showed that in the four groups studied, the greatest improvement in craving and anxiety and the best retention rate was found in the bromocriptinetreated A1 alcoholics. These findings suggest that treatment of alcoholics with the A1 allele patients who known to develop the most severe form of alcoholism, benefitted the most when treated with a pharmacological agent. This study, conducted with Australian colleagues, was published in the April 4, 1995 issue of Nature Medicine.

- EL: Was becoming a neuropharmacologist the only path or the right path that was open to you and what made it the right path?
- EN: I also had a strong interest in music. When I was five years old, I started taking piano lessons. When I became a teenager and as my voice changed to a baritone, I became aware that I could sing. The choir master of our church in India, recognizing that I could sing, asked me to join the choir and be the soloist for the Sunday services. When we came to the US, I began to take voice lessons under the tutelage of Professor Richards, in Carnegie Hall, New York. After he felt that I had learned the proper techniques of singing, he allowed me to sing classical songs, including arias from the various operas. It was about that time that auditions were being held to select up-and-coming singers who could perform as soloists at Carnegie Hall. The judges selected a coloratura, a tenor and me. Jointly, we gave several concerts to Carnegie Hall audiences, with apparent success.

At the UC in Berkeley, I joined the University's Glee Club and was a soloist at its annual concert. I performed as a member of the chorus in the Messiah with the San Francisco Philharmonic Orchestra under the direction of maestro Pierre Monteaux. On Sundays, I was choir master for our church in Berkeley. At Oregon State University, I joined its Glee Club and performed as soloist at its annual concert. On my sabbatical leave to Strasbourg, France, I was hired to sing the lead baritone roles in Carmen and Aida at the Strasbourg Opera House.

Whereas my career in music and science followed parallel paths, it was not a matter of whether one path was the right one or the other was the wrong one for me. What happened in reality was when I became Director of the NIAAA, the all-encompassing activities and time requirements of that position necessitated that I forego a career in music and concentrate on developing a career in science.

- EL: Was it the right decision for your family? Was your decision of being a physician researcher good for your family? How did that work?
- EN: To have a personal physician within the family, I believe, can be a good thing. It allowed me the opportunity to observe first-hand whether a developing illness was a serious problem or whether the issue was a normal developing event that required medical attention. If a serious illness I referred any family member to the best specialists I knew at our medical center. If it was a normal event, such as a pregnancy, referral was made to the most competent obstetrician-gynecologist that I knew. To be a researcher especially as a professor in an academic setting, can bring several advantages to the family. The income I obtained from the various universities where I was employed allowed my spouse to be a housewife and devote her full attention to the upbringing of our three children. Another advantage was it broadened the academic and cultural horizons of my children. When I took a sabbatical leave to Strasbourg, France I took our children along and placed them in three different schools, two in Switzerland and one in France. There, they had to learn and speak French in class. They befriended students from different countries where they learned their habits and customs. In addition, they engaged in new sporting activities such as mountain climbing, downhill skiing and canoeing. This broadening experience also occurred when I took another sabbatical leave-of-absence, this time to the Max Planck Institute in Munich, Germany. The children were placed in German schools and learned not only to speak German fluently, but also became knowledgeable about the German culture. These unique experiences left a lasting impression on our children.
- EL: Right. Now, at this point in your career, how are you spending your time? What are your major activities right now?
- EN: While I am now Professor Emeritus at UCLA, I still work full time. I meet with my research colleagues three times a week where we analyze data and prepare articles for publication. I attend the annual ACNP meeting and other conferences where I and my colleagues present the most recent findings from our laboratory. I review articles for publication submitted to me by various scientific journals, including *Science*,

Archives of General Psychiatry, and Drug and Alcohol Dependence. I am also involved with the alcoholism constituency. As a member of an organizing committee, under the aegis of the Christopher D. Smithers Foundation, we are planning to hold a national conference next year on a subject entitled "Consequences of Drinking by Youth".

Noting that I continue to be still academically active, my wife asks, "Ernie, we still have your retirement income, that comes whether you work or not. Why then do you still have to work so hard"? I indicate to her that I still passionately enjoy mining new data and the excitement of discovery. I like working with younger colleagues and find it stimulating to listen to their points of view in interpreting the meaning of new data. I enjoy the new research that I have recently started on the genetics of creativity, diabetes, and post-traumatic stress disorder. All of these activities have been exciting and challenging. If these activities are abandoned I asked my wife, "What would we do the rest of our lives, just take boat cruises"?

- EL: Are you happy about the way things have turned out in your professional life? Would you have done it any differently?
- EN: Life can only make sense looking backwards. My parents impressed upon us that getting a good education as early as posssible in our lives was an important building block towards achieving professional success. This early education was followed by a series of events, seemingly occurring by chance, that propelled my career forward. This included meeting Professor Sakami in Paris and joining him in Cleveland, followed by conducting research with Professor Weisberger and getting into medical school, followed by further medical training at Stanford. It was at Stanford that a clearer definition of my academic future emerged. That included going into psychiatry, beginning alcoholism research and being chosen to take a lead role in the Federal alcoholism effort. Coming to UCLA and assuming an endowed chair in alcoholism further reinforced my role in dealing with alcohol problems.

Looking forward, then, the events that transpired appeared to be disjointed and seemingly occurring by chance. However, looking backwards, the events that followed one another appeared to have a degree of connectivity eventuating into a career that dealt with the problems of alcoholism. Now, to answer your question "Are you happy how things turned out in your professional life?" the answer is yes. To the question "Would you have done it differently?" the answer is no.

- EL: Well, that's your own progression. What do you feel about the progression of the field as a whole since you have entered it? Do you think the progress has been great and what were the major limiting factors?
- EN: Since the establishment of the NIAAA in 1971, funds have become available to support research on alcoholism. Today, approximately 90% of all alcoholism research in the US is funded by the NIAAA. There are several types of studies which are supported by this organization. However, because of time limitations, I will deal with only two of them. The first type is to identify specific genes that associate with alcoholism. The second type is to seek drugs for the treatment of this disorder.

With respect to this first type, various approaches have been utilized to identify genes in alcoholism. These include association, linkage and genomewide studies. Of these three, at this time, association studies have been the most productive. About five genes, DRD2, DRD4, DAT, COMT and GABA have been found to associate with alcoholism. Replication of these studies has been inconsistent, leading some to dismiss the positive association studies. However, it is known that these genes have small effect sizes in the complex disorder of alcoholism. Thus, to resolve the issue of whether an association is true or not would require large sample sizes. Meta-analysis may provide the answer. Unfortunately, with the exception of the DRD2, a limited number of studies area available to conduct such an analysis. With respect to the DRD2, a large number of studies are available permitting a number of independent meta-analyses. The results of these metaanalyses have consistently shown the DRD2 gene to be associated with alcoholism.

In sum: progression in finding genes in alcoholism has been slow and contentious. However, with the new data and tools provided by the Human Genome Project, I am optimistic that soon we will definitely identify several genes in the complex disorder of alcoholism.

Regarding the second type of studies, essentially three medications are available in the treatment of alcoholism: disulfiram (Antabuse) and acomprosate (Campral) developed in Europe, and naltrexone (Revia) developed in the US. Use of disulfiram has been steadily declining due to poor compliance. This may be due, in part, to the fact that when alcohol is consumed, the increase in acetaldehyde levels produces physical discomfort. Naltrexone, which is the current mainstay of treatment, blocks the pleasurable effect of alcohol on brain reward, opioid, circuits. However, the use of this drug alone to treat alcoholics is not recommended because it induces unpleasant behavioral states even when alcohol is not consumed. To diminish the high recidivism rate and achieve better compliance, it is recommended that the use of naltrexone treatment be accompanied by behavioral therapy. Finally, the use of acomprosate, an anti-craving medication which works on glutaminergic circuits in the brain, has recently begun in the US. However, no consensus has been reached about the efficacy of this drug in the treatment of alcoholism.

The sum progression in developing drug for treating alcoholics has not been noteworthy. In fact, it pales in comparison to the availability of a large array of drugs in the treatment of other psychiatric disorders such as depression, schizophrenia, and anxiety. Still, with the intense ongoing effort to find new medications, based on roots in neuroscience research, there is hope that soon more effective drugs will be found in the treatment of alcoholism.

- EL: Were there specific areas where funding is particularly needed and are there new strategies that you think that could be useful for our funding agencies to adopt?
- EN: When I was at Stanford in the 1960s, many of our psychiatry residents were chosen because they had a strong interest in research. The Department of Psychiatry gave them an opportunity to conduct research in collaboration with senior faculty members. After completing their residency training, a significant number of these residents chose careers in academia. That situation has now changed. Few of the psychiatry residents currently express interest in research and even fewer conduct research during their residency. After completing their residenty training, a majority of them go into private practice.

Given the need to recruit and maintain psychiatrists in academia, it is necessary that they be provided the financial resources to conduct research early in their careers. One strategy is for department heads to submit competetive grants to the NIH or private foundations to allow funds for research training for psychiatrists after their residency training. The research training will be done under the supervision of an experienced faculty researcher. A more direct source for funding is to have chairmen of psychiatry departments dedicate some of the endowments they receive from private sources for the research training of their residents.

Another strategy is to provide funds for research to faculty members early in their careers. In this respect, the NIH can play a major role. However, some adjustments need to be made. Currently, grants submitted by both beginning and established investigators are judged by the same Study Section. This frequently results in the beginning investigators to lose out in the competition, with some taking flight into private practice. I believe there should be separate study sections for these two types of investigators. This may make it easier for beginning investigators to obtain funds in Study Sections of their own peers rather than when they are thrown in with more established.investigators.

- EL: Have you written some seminal books about alcohol research and the genetics of addiction?
- EN: I have with Dr. Edward Majchowicz co-edited two volumes of a book entitled *Biochemistry and Pharmacology of Ethanol,* and with Dr. Kenneth Blum as co-editor published the *Handbook of Psychiatric Genetics*. Most of my published studies, however, are articles of original research that I have conducted with colleagues. I have also authored a number of review articles in the area of genetics of alcoholism and other drug use disorders.
- EL: What about the special honors recognizing the work that you have done?
- EN: Early in my academic career, the NIMH selected me as a Research Career Development Awardee. I was chosen a Fulbright and Guggenheim scholar to conduct research in Europe. The International Committee for the Prevention of Alcoholism (ICPA) bestowed upon me their Personality Award on behalf of my efforts in preventing alcohol problems. I was the recipient of the Sidney Cohen Award in Drug Abuse Medicine. The UCLA Academic Senate and Chancellor honored me with the Inventors Award. I was the recipient of the R. Brinkley Smithers Award for Excellence in the Genetic Studies of Alcoholism and Other Drug Dependencies. I have received numerous awards and recognitions by various segments of the alcoholism constituency for my efforts as Director of the NIAAA.
- EL: In terms of impact on the field, do you feel that you, yourself, had more influence as a basic researcher or as the director of an institute?
- EN: As Director of the NIAAA, I believe my efforts had a greater impact on the field than as a basic researcher. Let me give you some examples. As Director of the NIAAA, I had to appear before the US Congress to seek funds to support alcoholism researchers. The NIAAA Director is the Federal spokesperson to bring to the public's attention important developments in the field. One such situation occurred when scientists found that when alcohol is consumed during pregnancy, irreparable harm is caused to the unborn baby. That information was conveyed by me to the public through the print media and the airwaves. That resulted in a Federal law requiring labels be placed on alcohol beverage containers warning about the problems associated with drinking during pregnancy and similar signs posted in drinking establishments. The

Director of the NIAAA is also mandated by the US Congress to establish Federal policy about minimizing the problems associated with drinking. When I became NIAAA Director, per capita alcohol consumption and the problems associated with drinking had reached the highest level in our land. To deal with this issue, I gathered some of the most prominent experts from the US and abroad and asked for their recommendation as to how to minimize these problems. Their recommendation was to use the public health model. That model included three vectors: the host, increase treatment of the alcoholic; the agent, minimize the use of alcohol; the enviroment, reduce alcohol outlets, establish laws to increase drinking age of youth, and make penalties more severe for drinking drivers. I presented this model for minimizing alcohol-related problems to alcohol constituency groups and they accepted it as a new national prevention policy. The only group that objected was the alcohol liquor industry, especially to the vector that dealt with reducing alcohol use.

Now, as a basic researcher, the finding of the first gene, DRD2 that associated with alcoholism had, I believe, a significant impact both in the US and abroad. It drew attention of researchers not only to replicate this finding but also to explore this gene's involvement in other psychiatric and medical disorders and its phenotypic expression. A search on the Internet reveals several thousands of articles have been published on the DRD2 since our findings in 1990. Thus, while as a researcher the impact of our findings was primarily on researchers, the impact of our actions at the NIAAA was much larger as it impacted society as a whole.

- EL: Do you see this kind of global approach to translational research going from basic research to the clinic and to the community is being extended as much in the area of alcohol research as it could be?
- EN: Well, there is a lot of talk of that it is being extended, but, frankly, I don't see much of that happening. Since the NIAAA was established in the early 1970s, considerable information has been obtained as to how alcohol affects brain function and how brain function differs in genetic strains of rodents. However, little of that knowledge has been translated from bench to bed. Why that situation prevails is not clear. Could it be that there are much fewer clinicians than basic scientists who are currently conducting alcoholism research, or that those clinicians who are available, choose "safe" areas of research? What is needed is for basic scientists and clinicians to work together, with NIAAA placing a very high priority for translational research and earmarking specific funding for that purpose.

- EL: When did you become a member of the ACNP?
- EN: I became a member in 1970, and am now a Life Fellow Emeritus.
- EL: And, what do you see as the most important contribution of the ACNP to our field?
- EN: ACNP is the premier organization for those of us who are trying to understand the brain-behavior connection. This connection can be better gleaned when one attends ACNP's annual meeting. There, in plenary sessions and symposia, select experts present their research or review the findings of others in various disciplines including pharmacology, biochemistry, neurophysiology and genetics. This has an important educational value to the attendees, as it updates them in recent developments in their own field of interest. Another exciting aspect of attending the ACNP annual meetings are the poster sessions. There, attendees have a chance to read about the most relevant developments in the field and engage in question/answer sessions with the presenters. I know personally that these interactions have frequently led to research collaborations between presenter and attendee.

There are many diverse functions that the ACNP performs. Here, I will mention only a few. Lobbying Congress to dedicate more research funds for the NIAAA, NIDA and NIMH is one of them. Another is setting ethical standards for researchers. ACNP also provides funds for young investigators to attend its annual meeting. The ACNP has developed the International Archives of Neuropsychopharmacology which gives the background and scientific accomplishments of some of its past and current members. It also sponsors the *American Journal of Neuropsychopharmacology.*

- EL: If you were talking to a young scientist that said I would like to go into understanding the genetics of alcohol and substance abuse, what would you give them for advice? You know, what would be the areas that they would work hard into becoming successful?
- EN: I would ask them what kind of knowledge or experience they have in this field. If they say little or none, then I would explain to them the fundamentals of genetics and how genetic techniques can be applied to understanding alcohol and other drug addiction. In addition, they will be asked to read primers on genetics written by distinguished scientists such as James Watson. They will be provided literature references on genetics/addictions studies. They will then be invited to return for a two hour tutorial per week where not only the materials read will be discussed but they will be invited to visit our laboratory to observe the genetic techniques we employ. If continued interest is shown, the

young scientist will be asked to collaborate in one of several ongoing studies in our laboratory.

- EL: So, of all of the papers that you have written and all of the experiments that you have done, what is the single most experiment that stands out in your mind as the most important to push yourself in the field forward, the one?
- EN: If I were to single out one paper as the most important one that I and my colleagues have published, that would have to be the 1990 paper in JAMA. That paper garnered great interest in the scientific community and in the general public, because it identified the first gene, DRD2, in alcoholism. However, at the same time it created controversy, as some simply did not believe that alcoholism had genetic underpinnings and a few others could not replicate the finding. Still, for us it created a treasure trove of activities. It led to exploration of the DRD2 gene's role in other addictive disorders, the phenotypic manifestations of the DRD2 in personality characteristics and cognitive functioning as well as the possible use of this gene in the prevention and treatment of alcoholism.
- EL: What do you think the role of controversy has been in pushing the field forward?
- EN: The controversy generated by publishing the association of the DRD2 gene with alcoholism has been good for the field. It has drawn the attention of a large number of scientists, both in the US and abroad, to replicate this finding. It has also attracted scientists in different disciplines who, with their unique approaches and techniques, have shed light on the underlying substrates that lead to this association. For the broader field of society, knowing that alcoholism has a genetic component has helped people realize that this disorder is not an issue of moral weakness but, rather, it is a disease just like any other disease.
- EL: What do you think the timeline is for the transition from where we are now to having someone come in and having a saliva sample predict what would be the appropriate treatment for them?
- EN: I mentioned earlier that we published a study in 1995 where we treated alcoholics with a dopamine agonist, bromocriptine. The best treatment outcome was observed in the "genetic" type of alcoholics, i.e., those who carried the DRD2 A1 allele, and no notable benefit was obtained in the "environmental" type of alcoholics, i.e., those who did not carry the DRD2 A1 allele. Whereas that study has been frequently cited in the literature, I am not aware of any treatment center where the two alcoholic types are differentially treated. To undertake such a study, and the time line can be now, the following procedure may be used. At intake, a saliva specimen is taken from the patient and sent to the

clinical laboratory where the DNA is isolated and the DRD2 alleltypes determined. Following this determination, the patients are placed in one of two treatment groups, an "environmental" or a "genetic" group. The "environmental" group, which usually develops the less severe form of alcoholism, will receive the current treatments which among others include individual psychotherapy, family/group counseling, or behavioral modification. The "genetic" group, which usually has the most severe form of alcoholism, will also be given the therapy that the "environmental" group receives but, in addition, they will be treated with bromocriptine or another D2 dopamine receptor agonist. Following the termination of their treatment in the hospital, which usually takes about a month, treatment will be continued on an outpatient basis. It is anticipated that the treatment of the "environmental" type will be discontinued, as they show improvement with time; however; in the case of the "genetic" type alcoholics, to sustain improvement they will have to be treated with a D2 dopamine agonist for the rest of their lives.

- EL: And, of course, you are probably speaking, not only of alcoholism, but of neuropsychiatric disorders, in general, is that right?
- EN: Yes, because I believe that most if not all neuropsychiatric disorders have a genetic basis. For example, in schizophrenia several genes have been implicated in this complex disorder. The DRD2 gene is one of them, where the A2 (major allele) compared to the the A1 (minor allele) has a higher density of brain D2 dopamine receptors, and is found to associate with schizophrenia. Autopsy studies have also shown a higher density of D2 dopamine receptors in brains of schizophrenic subjects compared to controls. It has been hypothesized that when these receptors are stimulated by internal or external cues, psychiatric symptoms ensue. To guell these symptoms, D2 dopamine antagonists have been and are still used. Unfortunately, hyperprolactinemia, a frequent side effect of these medications, results in a variety of negative symptoms, including depression, sexual dysfunction, amenorrhea, breast cancer, and osteoporosis. The question we raised was can we predict which of the schizophrenic patients develop these adverse events. In a study published in the British Journal of Psychiatry in August, 2004, we studied the efffect of DRD2 polymorphism on prolactin response to a variety of antipsychotic medications in schizophrenic patients. We found that patients with the DRD2 A1 allele treated with antipsychotic medications had higher prolactin levels than patients without this allele, and a higher percentage of patients with the DRD2 A1 allele compared with patients without this allele had hyperprolactinamia. It is suggested that the A1 allele of the DRD2 may be a useful clinical marker for the

identification of those prones for developing hyperprolactinamia and associated adverse effects.

- EL: Well, this has been a very beautiful story, the development of the field of pharmacogenetics as applied to alcoholism and neuropsychopharmacology, in general. Is there anything that I have forgotten to ask that would be an important message that we need to leave for ACNP and anybody watching?
- EN: No, you have raised good questions and I have tried to answer them. I have little further information to add.
- EL: Well, thank you very much.
- EN: Thank you Edythe.

CHARLES P. O'BRIEN

Interviewed by Leo E. Hollister & Thomas A. Ban Las Croabas, December 12, 1998

- 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 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, 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,

^{*} Charles P. O'Brien was born in New Orleans, Luisiana in 1939.

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 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. You had to know what was the oldest mental hospital in the country, what the real name of Freud's patient, the Wolf Man, was and those kind of things. 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 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 ones 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 ideas replayed in alcoholism. We discovered that naltrexone works in alcoholism, but all the alcohol specialists are still saying, "I don't believe in giving drugs to alcoholics" and it's the same kind of thing that I heard in the 1960s about depressed patients. 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 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 training at Queen Square.
- CO: I'm not sure about that, but 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 was drafted into the Navy, and, that's where I got interested in drug abuse. 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 and taking drugs either in Vietnam or when they returned to this country. 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. Active duty marines and navy men from Vietnam arrived in Philadelphia just 24 hours after returning from Vietnam. Some were already in drug withdrawal usually heroin. 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: From 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 ticket price reduction. 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: Actually, I did know him during the 1970s. As a matter of fact, there were three people who had a big influence on me as I was in training.

The first one was Matt Bach, who was a neurophysiologist. He worked with Horace Magoun. Bach did a lot of research on the reticular formation. My dissertation was on hypothalamic function. I was putting in electrodes and recording changes after stimulating them and all that kind of stuff. Bach 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 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. Neuronantomically, 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 on the brain.
- 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 who had a great influence on me was Abe Wikler. Since I have started to read about addiction, relapse, and conditioning has always been an important focus to me, 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 along the same line that you are doing but 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. All cue exposure studies 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, extinguish their conditioned responses. 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 sometime ago for Tom, but I can't recall.
- TB: It was around 1956, 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 Scientific 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 entire 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 we had was in 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 have just gradually grown in Philadelphia and in the VA as a whole. Our research has 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 as 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 for new treatments. We do things that compliment the clinical research; we do conditioning studies, drug discrimination, and the effects of drugs on self-administration, whether it's cocaine, opiates, nicotine or alcohol.
- TB: So, some of your research is 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: What ever 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 by Hal Altshuler, 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. I got alcohol treatment added to my naltrexone IND in 1983 and started try-ing it with alcoholics. Some of them seemed to lose their interest in alcohol. I wrote a protocol for a double blind study and gave it to a post doc in our program. We got it approved by the IND, but we hardly got any patients for the clinical trial. The recovering addict counselors

blocked us as much as they could because they didn't believe in using medications for alcoholism.

A young MD, PhD student at Penn, whose name was Joe Volpicelli, joined our program. He had published an animal study of post stressdrinking in rats. 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. After he joined us at the VA, I put him in charge of the study and he quickly began enthusiastically recruiting alcoholics. Our hypothesis was that alcohol activated the endogenous opioid system and naltrexone by blocking opioid receptors prevented some of the pleasure of drinking.

So, I went to DuPont-Merck 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 an NIAAA grant and they didn't fund us either. So I used our post docs and a psychiatric resident, who was doing an elective year with me. After we got a protocol through the Human Studies Committee, we started a double blind, placebo controlled trial with him in our alcohol program in about 1983. 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 we knew that it reduced drinking in animals and now we should find out whether it also works in humans. He told me that he was going to find a way to do the study 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.

No one was paying attention to our work and trying to replicate. Roger Meyer was a member of our scientific advisory board and he heard us present the data. He went back to Connecticut and convinced Stephanie O'Malley to do a clinical trial. She did an outpatient study with two kinds of psychosocial intervention 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"? 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 enterpreneurial 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, "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 β-carbolines.
- CO: β carbolines, yes, it's a condensation hypothesis. Actually, Ken Blum was another person associated with that and George Siggins and Floyd Bloom 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, but 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 β-endorphin, which, of course, is not the same thing as brain β-endorphin, there's evidence that people with a

strong family history of alcoholism get a large increase in β -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. There's a study that came up several years ago using an older PET process, the findings of which suggests that one 50 mg dose of naltrexone blocks, in the neighborhood of 80 to 85 percent of μ 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 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 people 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 them on with the opiate dependents 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 two studies with normals and we found some people just get very dysphoric on it. They just sort of lose their initiative and their ability to get anything done, 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 cold 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 measurements 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 the ASI. 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 kind of treatment actually occurs. 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 is 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 or 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 a very different from the match that NIAAA did where they matched very similar kinds of therapy and 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 seems that by now the ASI 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, either, minimal psychotherapy or 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..
- 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 addicts were not suitable for that kind of clinical research. But it turns out that they're, somewhat, difficult to do, 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 antidepressants 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 is 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. None of our patients 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 Association of Addiction Psychiatrists an award that 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 an-about 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 it 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 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 soar of positives was about in the neighborhood

10 or 11 percent or so. It was later in New York 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 like that 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 guestionnaire. 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 minorities.

- LH: Genocide hypothesis?
- CO: Yes, and, so, we have a couple of videos that have won awards and presented all over the country in which some NIH virologists 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 1987 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 '1970s and '80s, but in the late '80s, 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 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 MDs and PhDs in our post-doc program. One of my best trainees received the Elkes Award, the Joel Elkes Award of ACNP 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.

ROY PICKENS

Interviewed by Leo E. Hollister Washington, D.C., April 14, 1997

- 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, which you have your PhD in, 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.
- 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 cannulate 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.

^{*} Roy Pickens was born in Greenville, Alabama in 1939.

- 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 publication was in *Science* in 1962. 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 it was a call for people that might be interested. So, 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 on Non-narcotic Drugs and it was to study self-administration, 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, you know, became very important hallmarks of drug dependence.
- LH: Well, at that time, what was going on in Michigan? Were not 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, this 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 1960s until the 1970s.
- LH: That's right.
- RP: It was guite impressive. They used the substitution technique. You may have seen that with the 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 naive animals?
- RP: No, these animals that were involved in the substitution trials 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 Mannering, 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 selfadministration 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 that 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, but 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 and 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 selfadministration 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 genetic influenced some things and I would always point out the environmental 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 consultant ship with Hazelton 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 1,600 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 1,600 you'd have quite a few twins that come through there.
- LH: You could have 20 pairs.
- RP: 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 have 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 real 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, that 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 genegene 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 shows 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 that was brought to Baltimore when they closed down Lexington?
- RP: 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 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, it was settled definitively the nature of, say, alcohol withdrawal. I remember when I went to medical school we still believed that some toxin is involved from drinking that would cause the with-drawal symptoms. But in the 1940s we learned that it's simply the fact that you had changed yourselves and 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 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. Then, 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 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. There's 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. Now tell me this: when you start off 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: 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 every-thing. 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 Dolaphine, the phine from morphine and dola 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 dependencies that occur as a consequence of clinical use are miniscule 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 does 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, no, 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 with the genes.
- LH: Now, Pentazocine was a drug, I think, that looked pretty clean in the animal self-administrating, but, yet, turned out, clinically, to be of abuse potential.
- RP: That's kind of like 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 theses days
- RP: But, that area has changed a lot. If you go back, and look at what behavioral pharmacology was like in the 1970s 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 in 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.

BENY J. PRIMM*

Interviewed by Nancy Campbell Orlando, Florida, June 18, 2006

- NC: Can you tell me how you got to the University of Geneva for medical school?
- BP: In 1950 I finished college at West Virginia State College, which is now West Virginia State University. I was a member of the Reserve Officers Training Corps, ROTC, during the Korean War. I was a pre-med, biological science, and German major, and I knew I was going to get drafted. I even stayed an extra year to finish ROTC because I had transferred to West Virginia State College from another school. You had to be there four years to do ROTC. Although I was pre-med, my degree was a bachelor of science in education. I could go either into teaching and be a coach, because I was a basketball player, or I could end up going into the service. I knew I was going to get drafted even if I had taken one of those other jobs, so I took my commission and went into the 82nd n Airborne Division and was a paratrooper officer for four years at Fort Bragg, North Carolina. The 82nd n Airborne Division was a very elite division of the service. As a matter of fact, I was the first black officer integrated to command white troops in our country. Then I got hurt in a car wreck. When I came out of the hospital for my injury, Truman had declared that the officer corps would be integrated. There had been integration in the services in Korea, where white officers commanded black troops. There were always white officers commanding black troops, and some black officers commanded black troops, but no black officers commanded white troops. By division order I was sent from the hospital from my division to this completely white unit. As the ranking first lieutenant, I should have been assigned as a battery commander, but instead they made me a battalion intelligence officer that was two ranks above my qualifications. Then I was retired from the Army for my disability from my injury. I was then thirty percent disabled. I received thirty percent of my pay for the rest of my life, which went from \$80 at that time to today about \$500.

Anyway, I had a friend who I had grown up with who was an all-American runner and a national cross-country champion and honor student for NYU and he couldn't get into medical school. Instead of giving up and not going, he applied, was accepted, and went to the University of Geneva, where he had a couple of Jewish friends who had also applied to the University of Geneva. He was graduating from the

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University of Geneva Medical School at the time I was coming out of the service. We had been inseparable growing up and he suggested that I apply to European schools.

- NC: Where had you grown up?
- BP: Originally I was from West Virginia, but my family moved to New York when I was 12. I then grew up in New York. My friend came to see me at Fort Bragg to celebrate getting out of medical school. I had been hurt, and was in the process of getting a medical retirement. So he said, well, you've had German. Maybe you should apply to the German medical schools. So I applied to the University of Heidelberg in Germany, and the University of Innsbruck in Austria. I was accepted to both schools. I was discharged from the service September the 30th, 1953. On October 5th, I took a boat train to Halifax, Nova Scotia, and on October 6th, was sailing for Europe on the Queen Mary to go to med school at the University of Heidelberg. My family helped me make passage on the Queen Mary, which could not come into New York because there was a tugboat strike in New York. In order to get to the boat, I had to take a boat train from New York to Halifax, Nova Scotia. The Queen Mary had to go there because that was the closest port in the East where it could go into the harbor. The boat train took two and a half days to get up there. I took the Queen Mary and went to Europe and got off at Cherbourg and then took the boat train into the Gare Saint-Lazare. I never will forget it. It was that September. Matter of fact, I had on a seersucker suit.
- NC: Just like you do today.
- BP: Yes, I had on a seersucker suit just like this. I was a very meticulous guy, like I still am today. When we got into Germany, I had fallen asleep in my cabin. I still had my Army raincoat on because it was cold. This German conductor came in with this German hat. He woke me up, and I was startled. All I could remember was the Second World War, and I almost panicked and started to fight him because I was startled when I woke up.
- NC: How did you happen to go from the University of Heidelberg to the University of Geneva?
- BP: I couldn't get my GI Bill at the German schools, so I had only my retirement pay, which was about \$80 a month. That was 400 marks in 1953. I stayed at Heidelberg for a year, almost a year and a half. But I got married in 1952. My wife was a teacher, and I wanted her over there, so I figured I'd better find a way to get my GI bill and get the \$160 that the GI Bill paid plus my retirement pay of \$80 to make \$240. Then she could come over, and we could have an apartment. The only way you

could do that was either to go to an Italian school, a Swiss school, or a Dutch school. I said, what would be easier for me? Maybe I should try the Dutch school, make an application over there.

You go through the Ministry of Education in Holland. You don't go to the med school like you do here. The Ministry of Education accepts you for medical studies and they send you to one of the universities where there is a place available. So I made application, went over there and got an interview with the Ministry of Education. The guy who was the Deputy Minister of Education was from Nijmegen in Holland. I had on this Army raincoat with the 82nd Airborne and he thought I was one of the paratroopers that had freed his town in Nijmegen. He admitted me to school and wanted to send me to Nijmegen. I told him no, there were no black paratroopers in the Second World War. The black paratroopers only started after the Second World War. We saw no combat, but he didn't know that. He said lots of my colleagues were buried there, and I would do fine there.

When I went over to Nijmegen, they really didn't have a place for me so I came back and reported that. He says, well, we've got a place for you at Utrecht. So I went to Utrecht. I sat in the class there for a day or two, and the Dutch was so difficult, even with my German. I just said no, this ain't for me, and went back to Heidelberg and was, you know, very despondent, wanting to be with my wife and so forth. Then I said, let me try Switzerland. Let me try the German part of Switzerland.

So I went down to Basel, and talked to the Dean and was going to get admitted to Basel, or Zurich. The Schweitzer Deutsche was just as difficult as the Dutch was. I said, all right, what the hell am I doing here? So I called my friend and he said, maybe try Geneva, Beny. You'll do all right. You'll learn the language. It'll come easy for you, you'll go to class every day, and you'll end up speaking to anybody, and you'll learn the language. So I went down to Geneva. My friend had two friends who were still there in school, black guys named Charles E. Wilson and Charles Peter Felton. One of them was a fraternity brother in the black college fraternity, Alpha, so we bonded that way. He says, I'll take you to the Dean, better still, I'll take you to the Registrar and when I give you the sign, you cry. He says, Beny, you've got to do this. When we get to the Registrar, she goes over my transcript and says, I don't know whether you can make it or not here. You have a D here in genetics. I had gotten that D because, if you cut this man's class, your grade was reduced to a D. You could only cut his class three times. I cut six times, and he gave me a D. She said, that's important for medicine, genetics. To make a long story short, my friend gave me the sign. I heard later

on that this lady, Mademoiselle Grosselin, had dated a Moor and was very partial to what was going on in the United States with prejudices against blacks. She was very sympathetic to our cause. She saw me tearing, and she said, well, you have a good background you were a soldier, a paratrooper we're going to admit you. I don't know how you're going to make it, but I think you'll make it. I walked out of there the happiest guy in the world. I went back to Heidelberg, packed up my old car with my belongings, and came to Geneva and got a room. Then I went to Paris, and met my wife, who had come to Europe.

- NC: So she spent a few years there with you?
- BP: Yes, she spent two years there. My oldest daughters were born there. We had an apartment just like I dreamed. She enrolled in the school of music, and she was getting her masters in music. She had finished Fisk as music major and was getting her masters. She didn't know French, but she had had French in high school. When you go to University of Geneva, and you're a foreign student and don't know French, they assign you to a French class. You have to take this test to see where you fit into what level of the French class. They dictate to you a paragraph or two, and you have to write it. Then they grade that and according to what you get, they place you in beginning or right on up the line in terms of what class French you should be.

I got placed in the beginners' class. They have maybe 30 or 40 new students in different faculties. But you were all beginning to learn this, so you have a textbook and they would give all of us an assignment. When I would go home that night and read the assignment, I would memorize it. When you went back to class, the teacher would go from student to student, and you would read the next paragraph. When she would get to me, she would say Monsieur Primm, and I was supposed to go. I wouldn't have to look at the book. I would just go blah blah blah blah blah. I remember one day she looked at me, and I thought I had done something wrong. She said, Monsieur, after class, I want to see you. And I thought, what did I do wrong? My whole career counted on me knowing French.

Anyway, I went up to her after class. My wife was also in the class. She says, I don't want you to come back anymore. You can imagine, I'm 26 years old, and I've got my wife there, and I've put all my eggs in this one basket, and she didn't want me to come back to the class anymore. How was I going to learn French? She says, you're going to be okay. She says, I want you to do something, she said, and then she kind of leaned forward to give me some confidence. She said, I want you to speak to everybody you can, anytime you can have an

opportunity. I want you to go to class every day, she said, and don't be ashamed if you don't have the right verb or the whatever. You're going to be okay, she says. You'll see, she says, don't be discouraged. But you don't need to come here. My wife was furious because she had to continue. Six or seven months later I was taking notes half in English, half in French. I never studied a word of formal French except for that week and a half in that woman's class.

- NC: How did you become an anesthesiologist?
- BP: I came back to the United States, did an internship at Meadowbrook Hospital on Long Island, which is now Nassau County General Hospital. I was the first resident that they ever had in anesthesia, the chief resident, and I won the internship of the year award. I finished my anesthesiology residency and passed my boards and had passed my New York State board one year after I started my internship. Foreign medical graduates were considered second-class physicians. When all of that was over, I took my boards, as soon as I was eligible, because I had to make some money because by then we had a kid.
- NC: Can you tell me why you chose anesthesiology?
- BP: In January 1960, when I started my residency after finishing in December '59 from Geneva, I wanted to do OB-GYN. Getting an OB-GYN residency was very, very difficult, and extremely difficult for a foreign medical graduate and a foreign medical graduate who happened to be black. You could go to Harlem Hospital or Lincoln Hospital if you could get in, but the competition was very keen. You've got to remember that when I wanted to apply to medical school in 1950, there were 5,000 black applicants to medical schools that year in the entire United States. There was no admission to medical schools of blacks below the Mason-Dixon line to white-medical schools. None! Two medical schools accepted blacks, Howard and Meharry. They accepted about 180. Around the country there were schools like NYU that'd accept two, Harvard maybe three, University of Michigan four. So when I graduated from medical school that year, there were only about 227 African Americans who had graduated from medical school. A residency for a black guy was almost impossible if you hadn't gone to one of these schools. First they took the guys who went to Harvard or NYU or Michigan. A couple went to California and a couple may have gotten into Loma Linda University, but no one went below the Mason-Dixon-line. From the two guys who were in Geneva, one was from New Jersey, Chuck Wilson, and one was from Louisiana, Charles Peter Felton. The state of Louisiana paid his way to medical school because he was getting ready to apply to medical school at University of Louisiana, and they didn't want blacks to do

that so they paid his way at Geneva. That's how bad racism was, it was rampant. Chuck Wilson was from New Jersey and he was on the GI Bill like I was on the GI Bill at Geneva. When people ask me, why did you go over there to medical school I tell them.that I had no other way of getting to my goal.

I had always wanted to be a doctor from the time I was a little boy. My father was a funeral director and my mother was teacher and school principal. When I played with my brother, he would play the funeral director, and I would play the doctor. We bilt a small little city and we would have accidents, and I'd say people got killed, and he'd come in and bury them. That's what we did. So he became a funeral director, and I became a doctor.

- NC: Did you find anesthesiology interesting when you first encountered it?
- BP: Actually, not really. I thought it was a new residency that I would be able to get admitted to without a lot of fanfare, instead of trying to go OB-GYN where just didn't want black guys really doing physical exams on white women. It was just that bad. When I finished my residency I took my exam for the state boards, and I passed the first time and got my license. I was one of the few guys who were licensed in my intern class. I could go to work at other hospitals covering the emergency rooms with my license because we were only making about \$3,600 a year, \$300 a month.

Once I got my license, I went to work in different hospitals. I went to Good Samaritan Hospital in West Islip. I made \$3 an hour. I worked 36 hours on and 12 hours off at my internship and residency. The 12 hours I had off I would go and work in the other hospital and I would make \$36. That was a lot of money then, and I saved up enough to buy a house for my wife and kids.

I remember at Good Samaritan a woman who came in with an acute abdomen. I covered the emergency room. I palpated her, and I knew right away she had a ruptured ectopic pregnancy. I went into the ER. She had a little vaginal bleeding, a little spotting, but an acute abdomen. So I said, she's going to have to be examined. The nurse called me out because she had said something to the nurse. She said I don't want that nigger to touch me, and her husband said that, too, so I said okay. I said, I tell you that, she's going to die because she's got a ruptured ectopic pregnancy. So I said, I'm going to go back to the quarters and sleep. You let her know that if she isn't seen soon, she's going to bleed to death. She's bleeding internally, so she's going to die. Anyway, she changed her mind. That was the kind of thing you ran into. That was the kind of thing I ran into when I became a resident in anesthesia. People would be going for operations, and I'd go do the pre-op. They'd say, I don't want that nigger to put me to sleep. There was just that kind of prejudice on Long Island, where I did my residency. Things were not good.

- NC: How did you handle that? How did you cope with that?
- BP: I had encountered prejudice all the time in the service. When I went to jump school and when I went to the 82nd n Airborne Division, there were black showers for black officers and white showers for white officers. You couldn't go into restaurants in 1950, '51, '52, '53. The civil rights movement hadn't started yet. All that hadn't gone on so racism was the order of the day. There were whites that embraced me, but there were always whites that just hated black folk. We knew that. You had to be schizophrenic, in a way, because the only way I was going to get where I had to go was to be with white folks in terms of my residency in anesthesia and learning medicine. That's who controlled the hospitals so I did the best I could to cope with it. I had some bitterness, but I'd get over that anger very quickly because you'd have to do your work.
- NC: What drew you to start working in Harlem?
- BP: I started working in Harlem in 1963, three years after I finished my residency. There was a guy from Finland who was my junior resident in anesthesia. I taught him how to do anesthesia. He had come here from Finland, was married, was a heavy, heavy vodka drinker, and had three children. Even went on welfare while he was on because he had three children and he qualified even though he was on salary as a resident in anesthesia. When he was anticipating he was going to graduate, he got a job at North Shore General Hospital, which was in Nassau County. They needed an anesthesiologist, and I knew that, paying \$30,000 a year. Though I was the top guy in my class and had trained him and Dr. Lutzberg, who was the woman who came afterwards, they both got jobs at that place, but I couldn't because I was black. The only way I could get a job was at Harlem Hospital, where the chief of anesthesia was a black guy, Herbie Cave. Everybody knew about me and I went there and was making \$13,000 a year. I was very bitter about that.

Later on I became Chief of Anesthesia at Oyster Bay Hospital, which was an all-white hospital. People in Nassau County knew of this black guy who was an anesthesiologist that was so good at Nassau General because many of the doctors who were attendings at Nassau General Hospital were from Oyster Bay or North Shore or other places out there. So they would be surgeons who worked there as attending physicians, and when I was a resident I put their patients to sleep, because this was the public hospital in Nassau County. So they knew how good I was.

- NC: At this point, Henry K. Beecher at Mass General was criticizing the field for anesthesia-related mortality. He wrote two articles about excess mortality rates, anesthesia-related mortality. There was massive outcry from the field, criticizing Beecher for doing this. Would you have known about that at that time? Would that be something that you would remember?
- BP: Sure, I knew Beecher, but I knew him from attending conferences on anesthesia in Boston. He was a renowned anesthesiologist. He was at the place where anesthesia was pioneered, at Mass General. That's how I know him, from the history and I met him at conferences.
- NC: In 1963 you went to Harlem Hospital. Were you no longer working at all these different places at that point?
- BP: No. I did do some moonlighting, and I worked in Wyandanch, New York, in a general practitioner's office. I did some house calls and covered him on the weekends to make extra money to pay for the house.
- NC: When did you begin to get interested in drug addiction?
- BP: When I was at Harlem Hospital.
- NC: Up to that point had you ever known anyone who had a drug or alcohol problem?
- BP: You shied away from dealing with people like that. I mean, an addict was the scum of the earth.
- NC: How did you begin to realize the extent of the problem?
- BP: Because I handled emergency cases very well, they put me on the shift from 3:00 or 4:00 o'clock on Friday to Sunday morning. I was there during the weekend and that was my whole week's work. I was off the rest of the week, so I could do whatever I wanted to. Lots of emergency surgery came during my time there. All the time it was either indirectly or directly associated with substance abuse. One night this kid who had almost exsanguinated – bled to death - from a gunshot wound of the heart. We rushed him to the OR and opened his chest, and I could see he had another scar on his chest. He was just semiconscious, and he had been in the hospital a year before with a stab wound in the heart. But he was an addict and his admission to the hospital was associated with his addiction. Once I got his old chart, I read this. I did a study and wrote a paper after I saw that 90 percent of the emergency surgery done at Harlem Hospital on the weekends was either directly or indirectly associated with narcotic addiction.
- NC: Was that your first paper?

BP: Yes, that was my first. The Dean up at Columbia, Mel Yahr, at that time, found L-DOPA and was a big guy in Parkinson's disease research, saw the paper. There was an affiliation between Columbia and Harlem at the time. When he saw the paper, called me and said, Dr. Primm, maybe you should do what you have suggested. What I had suggested was that, if a person comes in the hospital and has a surgical or medical diagnosis, no matter what it was, and also happens to have a problem with substance abuse, that that person should be seen and something done about the substance abuse while they were more vulnerable and reachable in the hospital setting. He thought that was a great idea.

He spoke to the chief of anesthesia at the hospital, Dr. Cave. I already had done some very innovative things at Harlem Hospital. The first time they had a resuscitation team, I started it. They never had even a cart for a code blue, when somebody has a failing heart and you go to them. They didn't have anything like that going. I started all that at Harlem. So I was known as very innovative at the hospital and I was very friendly. I would get the student nurses to help me do all kinds of things, so I said, we should have a team of people that go in and see somebody who may have a surgical diagnosis or a medical diagnosis that also has a substance abuse problem, and talk to them about going into drug treatment, and get them into drug treatment.

- NC: What did drug treatment consist of that the time?
- BP: It wasn't much of anything. It was mostly therapeutic communities. I called this thing HOC, the Hospital Orientation Center, which had a staff of three people, me, a secretary, and another young fellow. We worked out of a closet, literally. That was my office. We set it up and started seeing people. We didn't have any place for people to go to get treatment. Therapeutic communities were just starting to get going. Phoenix House was going and there was Odyssey House, Exodus House, and the Addicts Rehabilitation Center. That was it in New York. They had limited space. Methadone was just starting in 1965 or '64 at Beth Israel Hospital downtown. If you were in Harlem, and you were addicted, and you wanted treatment, and you wanted to get on methadone, you had to go down to Beth Israel to be inducted, and stabilized. Then you were sent back up to Harlem, where they would dispense the medication. So I was kind of a revolutionary. I said, why do black people have to leave Harlem, the center of addiction, where black doctors are here in great numbers, and we're all smart, just as good as white doctors? Why send them downtown to a hospital where it's very difficult for me to even practice medicine, and put them on a substance that they're going to have to be on for the rest of their lives, supposedly, and then

send them back uptown for us to continue to refill their drug need? I said something's wrong with that. What are these white people doing, trying to enslave black folks and make us all into zombies?

- NC: Did you think that at the time?
- BP: Yes, I thought that. I'm kind of a revolutionary anyway. I said, what is this bullshit? I don't want this anymore. Dr. Trussell, who was the dean of the affiliation contract literally despised me because he thought I was going to ruin this whole thing that they had started that was going to save the world in terms of addiction.

Anyway, about a year later an institution was started up by a guy named Dr. Thomas Matthew. I was very well known by then to be interested in the addiction problem. Tom started up a thing called NEGRO, the National Economic Growth and Reconstruction Organization. NEGRO was to do healthcare, develop economic endeavors for black folk, to liberate us. Tom was a very prominent neurosurgeon, and I was known a very active and vocal anesthesiologist. He got me to come to work in the institution called Interfaith Hospital that he set up. I was going to do the anesthesia there, and he would do surgery, and we also would do work about the addicted. We would bring addicts in, detoxify them, do therapy, and so forth. I had this experience already with the Harlem Hospital Orientation Center. So I was the guv who was in charge of the hospital, where I was director of professional services. This was in the middle 1960s, '65, '66, '67. Then in '68, Bobby Kennedy was killed. When he was assassinated, Nick Katzenbach, who was attorney general, and Burke Marshall, that whole group of Democrats, came back to New York looking for a candidate for the presidency of the United States. New York City Mayor Lindsay wanted to switch from Republican to Democrat. When Bobby was killed, Mayor Lindsay was trying to position himself to become the Democratic presidential candidate. The problem of addiction in New York City was rampant and he was the mayor. One of the weak spots in his administration was that he didn't know what to do about addiction. Beth Israel Hospital had a very-closed methadone maintenance treatment program, which was supposedly the answer at the time. Riverside Hospital, the only hospital that was treating addicts, was closed because of its poor performance. It was on North Brothers Island. Dr. Trussell was chosen by the governor of New York, who was Tom Dewey at the time, to investigate Riverside, which closed in 1962 or '63. After he headed up this committee to investigate Riverside, Trussell then became Commissioner of Health in the City of New York. He knew of the work of Dole and Nyswander and got them a \$100,000 grant from a research foundation that allowed

them to continue their work with methadone maintenance at Beth Israel, and at Manhattan General, which then became the Morris Bernstein Institute. They then developed methadone maintenance and expanded the program even to Harlem Hospital, where there was a fellow that they trained named James Robertson, an MD. He was an internist, a general practitioner, who ran the Harlem methadone maintenance treatment program. They would send patients who were inducted at the Morris Bernstein Institute or Manhattan General, and keep them there for a couple of weeks or so and stabilize them on methadone. Then they were medicated at Harlem. That bothered doctors at Harlem, too.

The whole Tuskegee thing came out about that time, too, and experimenting on black people. Racism was still rampant. We had all kinds of cockamamie ideas about what was going on. It was so racist that there were very few, if any, black doctors on the staff of Beth Israel, or very few black doctors on the staff of any white hospital in New York, there were hardly any at Cornell, New York Hospital. Presbyterian had maybe 4 or 5 but that was it. They just didn't exist. We were all suspect. Being shut out and the racism toward us further exacerbated our feelings of distrust. These were real issues. If you put yourself in the position where you had done all this studying, passed all your exams, one, two, three, and then it's the white boys who had gone to American schools, who took the exam with you, who didn't pass the first time, who you have to listen to. If they failed, but passed the New York State Board the next time, they could get reciprocity to go to another state to practice. As a foreign graduate, I had to go to that other state and take an exam even though I passed the first time with a high mark. I was very angry. I had been a paratrooper, had been a Johnny Armstrong all-American boy, doing everything right.

- NC: Would it be fair to say that at some point you translated that anger and revolutionary spirit into starting your own institution?
- BP: Exactly. Let me tell you what happened there. The Vera Institute of Justice, which was headed up by Herb Sturz, was very close to Lindsay. Herb was a backroom negotiator when it came to politics. Burke Marshall was that in the Ford Foundation. Dick Katzenbach was vice president of IBM. They were all Kennedy people who needed to bolster the candidacy of John Lindsay and shore him up in terms of his approach to doing something about the addiction problem in the city. They knew the success of the methadone program. There was no methadone program in Brooklyn, where the problem was up and going, and still none really established in Harlem, except at Harlem Hospital, where it was hard to get on it. There was one in the Bronx already, with

Joyce Lowinson at Albert Einstein College of Medicine. But Harlem was really the center of addiction and there was nothing there. So they said, we need to start some drug treatment programs in Brooklyn and Harlem. They used the Model Cities initiative money. They got some money through Bert Brown, who was then at the National Institute of Mental Health. They spoke to Lois Chatham, who worked at the National Institute of Mental Health, to start a program in Brooklyn that would expand to treat 5,000 addicts, 2,500 in Brooklyn and 2,500 a little later in Harlem. Through the model cities program, a star-studded board of directors, and the Vera Institute of Justice, they found a way for Lindsay to take care of his addiction problem in the City of New York. They needed somebody to go into the black communities to explain the need for drug treatment programs and in particular to explain the need to expand methadone maintenance treatment, the Dole and Nyswander thing.

Well, there was this guy at the Harlem hospital named Beny Primm who had been very outspoken and had taken over some buildings in Harlem. I had taken over some abandoned buildings and a state building. By night I smuggled in beds, sheets, and medical equipment, and set up a detoxification center right on 125th Street in Harlem. I went underground through a garage, up into the building, and took the building. I set up detox right in this building, a whole hospital setting unbeknownst to the people who owned the building, which really belonged to the state. They didn't know what to do. I started treating addicts there the next day, detoxifying them, because there was no program in Harlem. They knew that here was this active guy who the community might believe in, and so they asked me to consult on their program that they wanted to start. So I did.

- NC: At that point did you believe in methadone maintenance?
- BP: I thought methadone was good, but you could go from methadone to abstinence. I didn't think you had to be on methadone ad infinitum, to stay on it for the rest of your life. I thought you could use it as a tool to get people into treatment, and start doing psychotherapy, and whatever else you needed to provide services that would then turn them around, so they would not necessarily be doing the criminal behavior and all that stuff.

I got chosen as a consultant to this program to go out and talk to residents in Brooklyn and I did. When the program was getting ready to get started, they needed somebody to direct it. I was running a detox center at Interfaith and doing all kind of revolutionary stuff in Harlem, so I knew the street people and was dealing with them. A lot of them were addicts. I had taken over offices in downtown New York, social service offices. I'd become known as a guy who was responsible, not the violent kind of a revolutionary type, but outspoken and really telling the truth. It's a wonder I never got put in jail or got beat up by the cops. It was amazing how I was treated, really.

After consulting with this program and talking about the need, the people in Brooklyn finally said, well, you can establish it in a model cities area. They got the building and said, well, Beny, what about you running the program? I said, you kidding me? I didn't run no methadone program. Why would I want to run a methadone program - put people on stuff for the rest of their lives? I was just dismissive of it. Then they said, you can run it like you want. This will be good research for you. Harvard will do the legal part to see the impact that your program will make on the criminal activity of these people. You'll have Jim Vornberg from Harvard doing the criminal evaluation. You'll have Herb Kleber at Yale to do the medical evaluation. Lukoff at Columbia will do the social. You'll have three evaluations. It was beginning to look pretty good to me but I said, no, I don't want that. They said, listen, why don't you give it a thought? I said no, I don't want that, I'm doing what I'm doing, and you all go ahead. But they kept coming back to me. They said, what would it take to get you to do this? I said, I don't want anything; I don't want to do it. They said, well, we'll pay you what you're making now and more. You don't have to be going to all these different hospitals doing anesthesia and hustling here and there. You can direct your mind to doing this research. We'll offer you \$40,000 a year.

In my anesthesia practice, after I paid off my nurse anesthetist, I was clearing about \$28,000, maybe. It was beginning to sound pretty good. No call schedule, no malpractice insurance, and I don't have to wear what these people in anesthesia wore. I was Chief of Anesthesia at Whitestone Hospital and the first year I was there they took 10 percent of whatever I made. Next year 15 percent. That year they were going to take 20 percent of whatever my gross was. I'm saying, what am I doing here? These guys are just taking my money for me to be here at the hospital doing work that they need to get done. This is ridiculous, a rip-off. So then Herb Kleber said, Beny, you've got to do this. We'll pay you \$45,000 a year and all your expenses if you run this program because we think you're the guy. I said okay, I'll do it. I'll do the medical but I don't want any bullshit with the administration. They had a guy, a lawyer, to do the administrative part.

NC: So that's how ARTC got started.

- BP: Yes, we had \$1.4 million or something like that through the Vera Institute of Justice and the City of New York Model Cities program. That's how the money flowed. Then I was in the papers. Dr. Dole said the ARTC thing was a 10-ton airplane with a one-horsepower motor that would never fly. I was the one-horsepower motor.
- NC: Why was Dole so skeptical?
- BP: They knew that I had been not a proponent of classical methadone maintenance. I started talking about neoclassical methadone maintenance and ways to do methadone to abstinence. They were variations on the theme as far as I was concerned. There's no set way to do anything, but they were unalterably opposed and rightfully so. They had put a lot of research and time into this, and I could understand that. Fran Gearing at Columbia, and Trussell, who was by then the Commissioner of Health to the City of New York were backing them. This guy Primm was up there making problems and was now going to start a program in Brooklyn. There were some scathing articles about me in *The New York Times*. They said I was killing people, giving children methadone, and manipulating the doses. They said people were dying from overdoses. All this was in the paper. They were tarring and feathering me.
- NC: How did you handle that? How did you respond to that?
- BP: I said, these people are just mean white people, the devil, not nice people.
- NC: So were you able to get that program up and going pretty quickly, though, despite the obstacles?
- BP: Yes, it started in October of 1969. As a doctor, as an anesthesiologist, I always said you've got to know the science behind this stuff. I said, I just can't be going out here running a methadone program, and they won't let me come over to Beth Israel and learn what they did. They won't share their information with me, so I said I've got to find a way to learn about this from a medical scientific point of view. I made an arrangement to go to the Addiction Research Center in Lexington. I went down to spend two weeks in 1968 with Don Jasinski.
- NC: They didn't like methadone at the ARC. They didn't like methadone maintenance. They had done initial studies on the drug after the Second World War, but they did not like Dole and Nyswander's maintenance approach at all.
- BP: Well, that's true. That's true. But they allowed me to come, probably because they had heard these things about me in New York. I said, let me go and learn from these white boys at the research center how to really do this thing. Plus they were not in favor of maintenance but they wanted to use it in whatever way they want to use it. So I spent

two weeks with Don Jasinski, Chuck Gorodetsky, Frank Fraser and Bill Martin. They all said, okay, come on, we'll teach you a little something. I went down there, and they were very nice to me.

- NC: What did you make of that place?
- BP: I thought it was wonderful. This was a very select group of guys. So I went there, and I lived at a hotel and went over there every day, just like I was going to work. I talked to the patients and the prisoners about methadone. Learned to see how it worked once when you gave it and all that. Chuck Gorodetzky really took a liking to me. They thought I was this crazy black guy from New York. They were very admiring of my spunk and we all became very good friends. We're very, very good friends now.
- NC: Did you learn a lot from them?
- BP: Yes, and then I heard about Jerry Jaffe out there in Chicago, running a program. He had been up at Einstein, did his residency, and then went out to the Illinois Drug Abuse Program. I thought that substance abuse should have all these modalities. Why should we just have people on methadone maintenance ad infinitum all their lives? We could have methadone maintenance and switch them over. They could go into a TC once they detox, and maybe they'd end up being drug free. So I heard about this guy out there, and I called him up and went out there. Jerry kind of looked at me like, what do you want to know this for? He was very frank with me. He didn't know where I was coming from.

We became very, very close. I stayed out there about two weeks. He had Safari House, and he had another place in a hospital where he was doing detox, and he was doing TC, and switching people from methadone maintenance to drug free. They were doing exceptionally well. I really admired him. He and Ed Senay taught me a lot about maintenance and the mixing of modalities. When I got back to New York, I said, this is what I'm going to do. I'm going to do it like Jerry Jaffe did in Chicago.

- NC: Was Jerry dealing with a lot of black people at IDAP?
- BP: Matt Wright, who was Jerry's right-hand guy, was an ex-addict. He ran Safari House. Then there was Joey Joya and David Deitch out there with him. That was it for black guys... I went out there just at the beginning, just before I went into ARTC.

I was looking for models to duplicate. I hadn't been working in addiction, and these guys had been working in addiction, with addicts. What did I know about addicts except for when they were on the operating table? At Interfaith Hospital, I was bringing them in, detoxifying them, keeping them for two weeks, and letting them go through therapy. It was like a revolving door. I did it for about two years or so before I went over to ARTC from '66, '67, and '68. In '69 I started ARTC. But in 1970, 1971, I was at a conference in Washington. I was in the back of the room because I want to slip out. I wasn't going to stay. Some guy comes in the back of the room and says, Dr. Jaffe is looking for you. It was a Secret Service guy. It scared me. He said, Dr. Jaffe wants to see you, so I saw Jerry, who says, I want you to go to Vietnam with me.

- NC: Tell me about your trip to Vietnam.
- BP: Jerry said, we're going to go over there because the President wants me to look at the drug problem. I'd like you to go with me. I said, I can't do that, you kidding me? Go to 'Nam? I said, I'm a retired Army officer and I missed combat. I don't want to get killed. He said, you're not going to get killed. He talked me into it, so I said okay and went home and told my wife. She says, Beny, you're crazy with this drug stuff. Please don't do this. I said, I think I have to do it. She says, I don't want you to do it. We've got kids, you've done your Army time, and now you're working with these addicts, too. I'm afraid. I said, well, don't be. I think I'm going to be all right.

They brought me to Washington to orient me to the whole trip. They brought my wife down to Washington the week before we went. They'd chosen who was going to accompany us on the trip. Seth Rosenberg was Jerry's assistant. Jeffrey Donfeld was on the domestic policy council. Me and Jerry and a couple of bodyguards were on the plane. We took the first free radical assay testing machine, EMIT, over there with us on the plane. The plane was a very private 747. My wife was to be on the plane with us, and we were going to drop her off in New York on the tarmac. This is what happened. We kept on to Alaska and stopped in Anchorage. They checked people coming back, their belongings, and they had dogs sniff out drugs in their belongings in Anchorage. We knew what we were going to be facing when we got over there because people were shipping drugs back home in their belongings. We flew from there to Taiwan and from there to Hong Kong and from Hong Kong to Saigon. We did the whole thing in Vietnam, set up drug testing, called it, the Pee House of the Harvest Moon. We had troughs where the guys would come in and pee, and waited while we observed them and tested their urine. Up to the rank of major, if they were positive we kept them and sent them to treatment.

- NC: How long were you there in Vietnam? What exactly did you do during the trip?
- BP: We were there about three weeks. We set up the testing program and set up treatment places in Vietnam, at the front lines, too. I remember

once we were in a plane, me, General Bernstein, and Jerry. They started vomiting, they got sick. The plane motors went out; thought we were going to crash. I said, here I am in this damn place, and didn't even have a chute. I said, what am I doing here? I had friends who were colonels who were over there in combat, who were in the 82nd with me.

Anyway, we flew up to the front. They got sick, and Jerry had to go to the hospital, so he was in the hospital for about ten days. So I had to run the whole thing by myself. We became very, very close. I had to talk to the generals and command them. I had the honorific rank of a major general in order to command them so that I would be able to get things done.

When we left Vietnam they asked me if there is anything I would like and I told them I would like to see couple of my friends. So, they sent two of my friends who were classmates and colonels now, to meet me at Admiral Nimitz's house in Hawaii for four days. They had R&R, rec and recuperation, and the house was stocked with steaks and liquor and everything we wanted. It was just wonderful. They didn't know how they even got there. I really learned what power was in this country. I was treated like a white boy. I hate to put it like that, I mean, I hate to put...

- NC: Better than most white boys, I think.
- BP: We were hobnobbing with the President. We came back and met at San Clemente with the President. We're sitting around the table like this. There I am, a black revolutionary in Harlem, taking over buildings, an ex-paratrooper type, now sitting with the President of the United States and telling him about substance abuse. He says, you guys got to write a book. I smoked a pipe then, and I think he got a little bit afraid because he didn't recognize it was a pipe until I put it on the table. Then he was more comfortable. There are pictures of all this, by the way. I have pictures of all of this stuff.

After that, when we came back, Jerry was the drug czar and he said, Beny, I want you to continue to come down. I said, Jerry, I've got to run my program. He says, you'll fly down here every day and fly back to New York and just help set up the office. And that's what I did.

- NC: How did you work out having your home in New York?
- BP: We would fly down in the morning, get up, go get the 7:00 o'clock shuttle or the 8:00 o'clock shuttle and be in Washington at 9:00, at my desk at 9:15 in the old executive office building. I did that for a year, year and a half about two or three times a week for the Special Action Office of Drug Abuse Prevention. They'd bring my wife down. My first job was to train all the people in the United States, at the Army facilities and the VA

hospitals, so that they would be able to assess soldiers coming back from Vietnam and to treat them right. So I would go to all the posts and train people all around the country. I brought them into Washington and trained them. I have pictures of all of these guys that I trained. We sent one team to Vietnam.

- NC: Was it about then that you started to be involved with CPDD?
- BP: That was in about 1972. The first two minorities were a woman and me, a black, on the Committee on Problems with Drug Dependence. That's when people like Hans Kosterlitz, John Hughes, and Eric Simon would come to this meeting. The committee was criticized for even funding Kosterlitz, who found enkephalin.

Have you read Stephen Jay Epstein's book, *Agency of Fear*, which was terribly critical of the CPDD? We were terribly vilified. I don't want to lose that history because that's important in building up to what's happened. What has happened now to enkephalins and endorphins has changed the field into this whole brain science thing.

- NC: Do you remember what happened the first time you attended a CPDD meeting in 1972?
- BP: I made a speech: "Methadone Is No Answer". I still have the speech. It's not only methadone. You have to do something else with methadone. I had come to that conclusion back then. I left SAODAP maybe a year before Jaffe did, but I was still consulting when he would call on me. Later I was on a NIDA advisory committee and then on the ADAMHA advisory committee.
- NC: What were those committees up to when you were on them?
- BP: Each department had an advisory committee. I was on the FDA advisory committee for a while that dealt with drugs and drugs of abuse. Then I became a member of the NIDA advisory committee in the 1980s.
- NC: How did the Urban Resource Institute (URI) come about?
- BP: URI is an offshoot of ARTC. I began to see all different social dislocations in the community that needed attention and said, you can't get the grants through the Addiction Research and Treatment Corporation. In New York State they just didn't want to give you a grant to do stuff on battered women or the developmental disabled under the name of addiction. So we needed another corporation. We set up another private nonprofit corporation to do other stuff. There we do an alcoholism program, we do a developmental disabled program, we do AIDS education, and we do a transportation program for people who are developmentally disabled. We also have intermediate care facilities for the severely disabled. We set that up in 1983 or '84.

- NC: Returning to Washington and your work at the federal level, tell me, didn't you work for Carlton Turner?
- BP: Yes, I did. Carlton had me as a consultant to his office. He was President Reagan's advisor on substance abuse. He was the so-called drug czar. The first real drug czar was William Bennett, because that was a cabinet post. Carlton had that kind of a role before, but he was not considered the drug czar because it wasn't a cabinet post until later. I used to consult with Carlton all the time. How I got introduced to Carlton was that I was on the Advisory Committee to the Food and Drug Administration. They had an advisory committee on drugs that had the potential to be addictive. I had been on that committee and had gone down to the University of Mississippi to the marijuana farm. A lot of work was being done there on marijuana by Dr. K. Foley and others. Before Carlton became the drug czar he had worked in the laboratory at the University of Mississippi. Every genus and species of marijuana is grown there so that they test the potency of marijuana. They look at tetrahydrocannabinoids and cannabinols and everything that comes out of marijuana.
- NC: What had your work had to do with marijuana?
- BP: I had not done any work on marijuana. I had gone to Vietnam and I was known as a guy who worked in substance abuse. So I got appointed to this committee. I had some background in pharmacology because in order to get your doctorate in medicine in Swiss medical schools you have to do a thesis and I did mine in pharmacology.
- NC: What was Carlton Turner like to work for?
- BP: He constantly wanted my input in terms of policy and ways to go at the federal level. He wanted my presence because, of my recognition in the black community. With me at his side, it made a way for him to be more accepted. He used me, but I didn't mind being used. You've got to be used in politics. But you use them, too, you know. That's important to me. He was good to work with. He was a good Southern boy, and Southern whites and blacks have a synergy. There's racism, we know that. But black women used to nurse their babies. Strom Thurmond had an affair with the maid that worked in his house and had a child by her. Not only were white southerners very closely related to blacks despite racism always being there. All her life she kept the secret and he even gave her money to go to college. So Carlton was just another good Southern guy. He was stymied by the administration when he was at the White House. He couldn't get much done. He couldn't get done all the things he thought was necessary, though we tried.
- NC: What would you say he was trying to do in terms of substance abuse and drug policy?

- BP: Status quo, keep things conservative. He pandered to the conservative side and he was controlled by them, really. He was safe for the administration, and he did some good stuff, but he mostly did nothing. He was a nice guy, a nice family guy.
- NC: What led you to your appointment to the Presidential Commission on HIV/AIDS?
- BP: I was on two presidential commissions. The first one was the Human Immunodeficiency Virus Epidemic Commission. I was appointed to in 1988 during the Reagan administration. That came about because of my consulting work with Carlton Turner. Being on the FDA Advisory Committee, and having gotten known by the Republican administration, when I went to Vietnam during the Nixon administration, led to my being appointed to the Human Immunodeficiency Virus Epidemic Committee formed in late 1987. They had a black on the committee, Woodrow (Woody) Meyers, and he became argumentative with the chairman and, of course, he was very critical of what the administration was doing. He got kicked off the committee and so did the chairman. I got a call that they wanted to talk to me. Bert Lee III, MD, at that time the president's physician and Yale classmate, called me. He had been aware of my work here in New York on substance abuse. They had problems with what they were going to do with substance abusers who had HIV. They thought I was a likely guy to be able to do something about that. I had been speaking about this strange lymphadenopathy, this associated virus that my patients had and he had gotten wind of that. He made a recommendation that I join the Human Immunodeficiency Virus Epidemic Committee.
- NC: Do you recall, Dr. Primm, when you first started seeing HIV in your patients?
- BP: Probably around 1983, I had a patient that had pan-lymphadenopathy in my Harlem clinic, and I tried to get this patient to have a biopsy. His mandible lymph nodes kept getting larger and larger, and he wouldn't agree to get a biopsy. He kept getting sicker and sicker and he later died of an opportunistic infection, pneumocystis carinii pneumonia. I began to talk about this problem in every medical conference that I attended, and how this was causing devastation in the black community, particularly among drug users. I had no idea that they were spreading this disease to other individuals. I began to read about it and I began to learn about what Luc Montagnier was doing at the University of Paris, and what the researcher Robert Gallo was doing here at the National Institutes of Health.

I began to think about what to do with addicts. I never associated it with injection drug use. I just knew that addicts had this and that I thought it might be sexually transmitted. I had an increase in tuberculosis among my patient population and so forth. In 1984 when they first identified the virus, I had an interest in it, and I would talk about it to the newspapers. That's how my interest got known. So when they needed to replace Woody Meyers, Bert Lee had read about some of the stuff I had done here in New York, I had been guoted a couple of times in The New York Times, and he recommended that I come on the commission. He talked to me and said that the president would like for me to come out to California and join this commission. I consented to do that and went out to the first meeting in Los Angeles at a hotel at the airport. I was there representing what to do with persons who became infected with HIV who happened to be substance abusers. I was to help to write the chapter in the book to advise the president about what to do about this problem.

We went around to multiple cities throughout the United States. I remember we met in San Francisco. It was a very charged meeting. Then there was a very charged meeting in Miami and New York. Then there was ACT UP, the AIDs Coalition to Unleash Power. They were a group that was very radical. They would disrupt the meetings that we would have in different cities, these town hall meetings. I thought there was no need for this, and said that I would go down and talk to them. They had respect for me from having worked in substance abuse and taken over buildings in Harlem years and years ago. They trusted me and they would cool out, and allow us to go on with the meeting. For these very conservative people on the advisory committee, they were mesmerized by my ability to do that. I can remember in Miami, the Haitians were going to take over the meeting and they did. I spoke French, so I cooled them out and they had their meeting with me on the sidewalk, and the meeting was able to take place and go forward and we were able to satisfy lots of their demands. I would talk to them. I became that kind of a person on that advisory commission to the president. There were a lot of bigwigs on that commission; there was Cardinal O'Connor, who was cardinal here in New York; there was Bill Bennett's father; there was Admiral Watkins. It was a star-studded group of people. I became pretty well known and I helped to write the chapter. We came out with recommendations to the president in 1988. Of course, Bert Lee was a classmate of George Herbert Walker Bush at Yale, and they were friends. He was one of Reagan's physicians. He

liked me. I was the only black at that time on the commission. So that's how I got introduced first to HIV and AIDs.

When Bush was thinking of running for president, he had a problem with the whole addiction situation. They didn't like what was going on there, and so I got a call to come to Washington to meet the vice president of the United States and to choose four or five people to come with me and talk to him about what he should do for substance abuse in case he became president. Some of the people who were on the staff of President Reagan's HIV Epidemic Commission had recommended me to Vice President Bush because I knew something about substance abuse. I chose four or five people and we went there and spent two-and-a-half hours with the vice president talking about what we thought he should do if he became president. Indeed, he became president. So I had been an adviser to the National Institute on Drug Abuse and an adviser to the Alcohol, Drug Abuse, and Mental Health Administration, and had been making suggestions there also simultaneously. There was an overlap. Now we've got these three different things through which I had been known: one was'the marijuana farm and the drug abuse situation with Carlton Turner; two, the President's Advisory Commission; and, three, they had my resume there to become the ambassador to Haiti. I had gone to 'Nam and I had done some really good things and I was a black guy and they needed black representation. So when my resume went over the White House to be vetted for the ambassadorial post in Haiti, I had even gone to Haiti to look at the situation. My wife was very sick at the time, and once I had looked at it, I didn't really want to go, but the ambassadorial post was awfully attractive. The White House personnel office saw my resume and decided that this guy doesn't need to be going to Haiti, he needs to be serving on the President's Advisory Committee for HIV. So I did that.

Then when George Bush became president, he invited me to come down on the boat, to come down to Mississippi with him, and I did. Three or four weeks later, I get a call from Bob Trachtenburg to come down and meet with him and Fred Goodwin. They said, Beny, you're on the advisory committee, but the President wants you to do something else. I said, no, no, no, no, no, I'm fine where I am, I just want to run my program now and be cool. I had just finished doing a thing with the Presidential Advisory Committee on the Human Immunodeficiency Virus epidemic. They said, no, there's something that we want you to do. We want you to do what you have been advocating all along. So we want you to do this job as the Director of the Office of Treatment Improvement. We want you to head it up and get it started. You don't have any competition. This is the job. The President wants you to do this and we want you do to this, and that's that. I said, but you don't pay enough money for me. They said, you don't have to come here as an employee. We'll pay your company for you to be here. I said, wow.

And that's what they did. When Mr. Bush was getting elected and having the Republican National Convention in New Orleans, they asked me to come and be on the boat with him coming down the Mississippi into New Orleans. He was going to choose his Vice President, Dan Quayle, that day, and I knew him. I didn't know that it was going to be Dan Quayle, but I knew that was what was going to happen. So I got on the boat north of New Orleans in the Mississippi and came down the river with him and then into New Orleans. Saw him, and he waved and talked to me. Then I didn't see him anymore.

- NC: Tell us what the Office of Treatment Improvement was.
- BP: The Office of Treatment Improvement was in the ADAMHA, the Alcohol, Drug Abuse, and Mental Health Administration. There was an Office of Prevention and the Office of Treatment Improvement, under ADAMHA. Then ADAMHA evolved into SAMHSA, which had the Center for Substance Abuse Treatment (CSAT) and the Center for Substance Abuse Prevention (CSAP) and the Center for Mental Health Services (CMHS).
- NC: Did you sense a rift between substance abuse research and treatment at that time?
- BP: Yes. I had problems with that rift between research and treatment. I did not want to get involved in an intramural kind of war like what went on. I think there was some resentment on the part of NIDA that some of their funds were taken away to form OTI. When the NIMH moved from the ADAMHA over into NIH, there was this elitism that was created that prevention was not really science, and science was everything that had to be under NIH, and NIMH was science, and so forth and so on.
- NC: Are you saying that there was an elitism created at NIDA by that split?
- BP: It was always there, I probably always felt something like that, but it became more apparent during that period of time. I could see us being together. I thought it would destroy substance abuse as we knew it. Of course I still had influence at NIDA because of my associations with the College of Problems of Drug Dependence (CPDD) and the people who ran NIDA, and the fact that I'm a member of the American College of Neuropsychopharmacology. Goodwin and company, people like that, liked me. To tell you the truth, I think it helped to have a little color around for them, too. Even though there were certain areas I was locked out of, that I was not that privy to, they were pretty accepting of me. It

allowed me to bring along people, who were even more capable than I am in terms of their own preparation for the kind of research that goes on, which has been a godsend for the field. That's sort of my role. I know also that my role was to get some things done politically. I'm very happy with what I've done in this field. I saw a need for young, white or black, didn't matter to me because my Army experience was such that, if we got something going, I don't care what you are. I see all my relationships like that. With Jerry Jaffe, it's like he's my brother, there ain't white boys or Jews. He's my brother his kids are like my kids. My kids are like his kids. They're all successful, they're just good kids. Jim Anthony is like a son to me. I've been a champion of women's involvement in this field. I look at Maxine Stitzer, Loretta Finnegan, Joyce Lowinson, Karol Kaltenbach, and Mary Jeanne Kreek, and all of the women that I know who have done so much in this field and I champion their causes.

- NC: What did directing the Office of Treatment Improvement enable you to do?
- BP: I made the changes that I always wanted to make. I was able to talk about comprehensiveness and that methadone should have this, this, this, this, and drug abuse should have this, this, this, and this. That was implemented. I'm just ecstatic about that. It revolutionized drug treatment. I was able to get representation from Native Americans, Hispanics, and blacks involved in choosing grantees and on the different committees. I talked about integrating HIV identification and care for those people in substance abuse programs. They had to go together. At that time we already had a way to find seropositivity in the population. We had tests to do that. Tests were being done and the people in my program were finding that 20, 30, 40 percent of them were HIV-infected. So when I went to Washington for OTI, it was on my mind that you gotta do something about HIV among substance abusers, or you're not going to be able to do anything about this problem. It had to be integrated into the treatment process. I began to talk about comprehensiveness. I began to talk about the "supermarket of services". In other words, if you had a drug treatment program, you had to have all these other things as well. You had to have comprehensive care. If you just did methadone and didn't do anything else about the person's social dislocations, you weren't going to do anything about the disease and most of them will become recidivists. I had become pretty convinced that you had to do comprehensive care, and that's the only care that the federal government should be funding in drug treatment programs. I thought that I should be a spokesperson and make sure that's done while I was

down there and able to influence substance abuse treatment and how it would go in our nation. That's what I did.

I became more and more involved with AIDS. Then the president's advisory book came out and I was mentioned therein as having contributed to it. So my HIV work just mushroomed. I was being asked to speak about HIV and its impact in the African American community all over the country. I would get people interested in it in different parts of the country and people would start to do something about it. I became nationally known as doing something about this problem.

In 1998 after being an adviser to the CDC and speaking all over the place about this disease, they called together about 14 African Americans to Atlanta to tell us how the problem had been burgeoning among African Americans in the country, and how bad it was. After the first day, they had told us all the data, the epidemiology, and I was meeting with some of the group that night just sitting in the bar and we talked about how negligent the CDC had been in not making this a public thing. If these numbers had been in white folk, this whole country would have been in an uproar. We needed to try to force them to do what we thought was necessary to combat the further spread of this disease among African Americans and Latinos. There weren't any Latinos with us, but we included them anyway. We decided that night to take over the meeting the next day. I had been pretty experienced in seeing people take over meetings and buildings to try to get people to do what I thought was right. We had become a little bit more sophisticated than in the earlier things I had done. We began that night to write a paper that we were going to put on the chairs of all the other invitees to say that we wanted to call a National Health Emergency for this problem of HIV in African Americans and Latinos. We went out to Kinko's and early that morning, we had a paper on the chairs of everybody who was going to be at the meeting. We chose someone who was going to take over the meeting. It was Reverend Yvette Flunder from Oakland, California. But Yvette didn't come down on time, and I was there on time. So everybody said, "Well, Dr. Primm, you're the senior person here, you take over since she's not here". Yvette was a fiery, well spoken black woman, and a really great minister. So I took over the meeting and I demanded that the CDC call a National Health Emergency. We demanded to see the Director of the CDC, and said she should be here talking to us and the meeting shouldn't go on without it. We said, "We're going to run the meeting and tell you all what to do for our people". Naturally, that didn't go over very well but it went over well enough. The Director of the center for HIV and STDs was Helene Gayle,
now president of CARE and Chairman of the President's Advisory Commission on AIDS. She had been a mentee of mine. I was an adviser to the Student National Medical Association, and she was president of the SNMA at the time that they had had to declare bankruptcy. I helped her get out of bankruptcy and I was like a father to her. She understood what we were trying to do. That day and the next day, she and the director of the CDC were supposed to be going to Washington to speak to the Appropriations Committee to renew the grant for CDC. Our demand that they show up at this meeting and speak to us, and if they didn't we were going to be even more disruptive, worked. They consented to our demand and came to the meeting, both she and the director of the CDC. But then they had to leave because they had to catch a plane.

I immediately knew what I had to do. If they're going to leave, and go to Washington to go before the Appropriations Committee, I gotta get to Washington as well, so that when they testify before congress, before the committee, then I have to get some people in Congress to ask them some questions about why they have been so negligent in not notifying the African American community beforehand about the problem that has really gotten out of hand. So when they flew to Washington, I flew to Washington and I met with Congressman Lou Stokes, who was a member of the Appropriations Committee, and I met with Congressman Nita Lowey, who was also a member of the Appropriations Committee. I got Lou's legislative aide to get him to ask the questions concerning the negligence of the CDC. He had no idea of the numbers, which were astronomical compared to whites and others. He was very concerned and of course made a very passionate interrogation of both Helene and the Director of the CDC. They were asked questions about why the numbers were so great and why they hadn't done something to focus more specifically on that population.

Let me tell you how the 13 of us got to the CDC in the first place. There were people working in the Division of HIV and STDs and Tuberculosis who were black folk who would call people like ourselves, activists, and let us know what was going on so we had an idea, but we had no idea it was so bad. To show you how bad things were, there were people who saw the data and the epidemiological reports and had become alarmed. The top people were so afraid that they would be accused of stigmatizing black folk that they were reluctant to do anything. That happens all the time at the federal government. They were reluctant to do anything that may be something else added to black folks' burden.

So we were being informed by interested people about these kinds of situations. Had we not had that, we never would have been able to

be effective to get Congress to do what they did. Later on, I had gone to the Congressional Black Caucus because through Lou Stokes, who was chairman of the Health Advisory Committee of the Congressional Black Caucus, I was able to make a speech that spring to them. They became up in arms about it and in speaking to them I challenged David Satcher, who was the Surgeon General. I hated to do that as David and I had been very good friends for years when he was president of Meharry. I demanded that the Secretary of HHS, who was Donna Shalala, do something about HIV at the time, and do it not only because it was right to do so but because of these numbers. It was shameful. They couldn't get a national health emergency called because that would have created some kind of response that they only do when there is a major epidemic. So it went back and forth and then Maxine Waters became enamored with this whole problem and got most of the women in the Congressional Black Caucus to go along with her. With me and Deborah Fraser-Howze here in New York, they came up with having a town hall meeting in Washington and invite activists like ourselves, from around the country to come to Washington and be demonstrative and have a meeting at the Rayburn building to discuss what should be done about this. Eleanor Holmes Norton and of course Maxine Waters, Barbara Lee, Dr. Donna Christensen from the Virgin Islands, were all extremely active to bring this to the fore and to demand that President Clinton declare an emergency in the African American community. They got to the president and we had the meeting in Washington. We "bussed", people down to Washington from New York and from Philadelphia and from Richmond and Baltimore, and had a major all-day meeting with members of the Congressional Black Caucus with a lot of fanfare and certainly a press conference. The president was notified and ended up declaring not a health emergency but that it was a problem in communities of color, not only the African American community but that it was a major problem in our nation. He ended up appropriating 156 million dollars to do something about the problem. I ended up being the spokesperson because I guess I had the grayest hair and a well-known name.

- NC: Were you still working for the federal government then? How long were you at the Office of Treatment Improvement?
- BP: I was at OTI about two years, and then it became CSAT. I was the first director of CSAT. I left in the spring of 1993. Clinton was elected in November of '92 and I stayed after his election. I was still director until the spring of the next year. So by 1998, I had left CSAT, which stayed head-less for a while, and then Lisa Scheckel, who had been my deputy, was acting director of CSAT. I never had a government check.

I was on loan from my corporation to the federal government and the government paid the Addiction Research and Treatment Corporation that wasn't mine because it's a nonprofit organization, but I had started it and that's where I had worked. When I left, I went right back to my job as executive director of ARTC.

- NC: What federal roles did you play after that? When did your work with the next presidential commission start?
- BP: After all that stuff with the Clinton administration in 1998, getting him to declare that there was a problem and to give us the money, I became a member of the Advisory Committee to the CDC and was one of the first members of the Joint Advisory Commission to the CDC at HRSA (Health Resources and Services Administration). The Joint Advisory Commission came out of what I called the Linkage Initiative. I sponsored a conference that brought together all of the different acronyms in the federal government-representatives from HRSA, SAMHSA, and the CDC, that had anything to do with HIV and AIDs. Orrin Hatch was a sponsor of this Linkage Initiative with me, and Fred Goodwin, who was then head of ADAMHA.

Then I got a call from Secretary Sullivan about serving on the Advisory Commission on HIV and AIDs of President George Bush. Lou was co-chairman of the advisory commission and I had worked under him during the George Herbert Walker Bush administration. He was secretary of HHS and he knew about my work on HIV and thought I would be a good member of the president's advisory commission. Dr. Coburn, who was then a senator, was co-chair, so I went and became a member of the commission. I was appointed and immediately served on the subcommittee of treatment and domestic committee. There were two committees, one was the domestic committee and the other was the international committee. I was assigned to the treatment and domestic committee. I had quite an ample voice on almost every issue. Normally, you are appointed for three years, but when my three years were up, they felt very strongly that my contributions had been such that they wanted me to stay over and I was held over for another two years. I was on that commission longer than any other single person. I have now been off the committee for about a year and a half.

- NC: What do you feel you were able to accomplish on that committee?
- BP: I began to have great influence in terms of focus not only on the African American community but also the Puerto Rican community in Puerto Rico, that still have inadequate help for their HIV problem. It's rampant, especially among injection drug users. My pet peeve was also about testing in the prison system and knowing their status and getting

treated early. That took on a very important focus for the administration. I insisted that testing be universal and trying to stop people from having to go through such rigmarole just to get tested, in terms of consent forms and so forth. If you try to get people to sign consents, it scares them that they are consenting to be tested and so forth. To make treatment available to everyone who tests positive, in my own program, for example, I make sure that you have a yearly physical. If you are being treated by us, naturally, we do the viral load. But you may not be being treated by us, but you're HIV positive and you're being treated elsewhere. But we can monitor how well your treatment is being done by looking at your viral load. Those people whose loads are still high, and are in treatment are contagious in the community. That's why the disease continues to spread so widely in the African American community. It's not only injection drug users but those people who are HIV positive, who get on treatment and who may not be following their treatment as they should. As a consequence they still have viral load and are still heavily contagious. I think people should, when they are tested and are found to be positive, wait until the viral load is 250. You ought to be treating these people when the viral load is 500 or less because they'll do better. There are new studies out that indicate that. Treatment outcome is a hell of a lot better if you begin to treat people with HAART (Highly Active Anti Retroviral Therapy) when their Cluster of Differentiation (CD) 4 counts are higher than normally believed. In Africa, of course, you don't have the money, so they wait until the CD4 count is 250. Well, people's immune system is pretty battered by that time. I think we ought to begin to treat people when CD4 counts are 500.

- NC: At your program, ARTC, have you been able to put into practice the kind of drug treatment and HIV treatment that you see as ideal.
- BP: Yes, I have. I have comprehensive care, as illustrated by what I call my "supermarket of services". I have a supermarket shopping cart with all the things that I offer and should be offered for comprehensive care for the treatment of addiction. I'm a proponent of that being done in all substance abuse treatment programs. Unless you do that, your outcome is not going to be as successful as it would be if you did that.
- NC: Would you consider that one of your major contributions to the field of addiction? Is that what you would want to be remembered for?
- BP: Absolutely.
- NC: What else would you want to add to the list of your contributions to the field of addiction? What else would be on that list?

BP: If you are using medically assisted addiction treatment, using methadone or buprenorphine, that you include other ancillary services. That's the comprehensiveness but also develop vocational services along with this. I have a Culinary Arts Academy, for example, where I train people to work in kitchens, hotels, schools, and so forth for 14 weeks and give them a certificate if they pass the standard test. Then they have a certificate that they can go and get a job so they finally have something other than themselves to offer up to people. I have people now who have graduated doing catering work for other companies. I think that to me is demonstrative. I also have an artist-in-residence, and we're doing art therapy. We're integrating it into our treatment process. I have my developmentally disabled patients and drug abuse treatment patients doing artwork so that as they are completing a piece of art, they are also helping themselves realize that a process may be slow but if you work on it, you can complete your rehab and complete your artwork. It takes time and it creates patience and it creates an understanding of this disease, that this is not something that you can get rid of overnight. That has been a contribution that I'm trying to make and I'm demonstrating it in my own program.

This is a chronic re-occurring disorder, addiction. You may ameliorate it, you may reduce it, but there's always the possibility that it can be rekindled by just going into a neighborhood where drugs are being sold. It doesn't have to be. Certainly, you can become abstinent but for me, a goal of abstinence is a goal to failure in treating the addicted. You can achieve abstinence but you have to be ever careful monitoring your temptation. I have characterized addiction as a chronic, relapsing disorder.

- NC: Often, the definition of addiction as a "chronic, relapsing disorder" contains the word "brain". Do you see addiction as a "chronic, relapsing brain disorder"?
- BP: My focus has been more on the social than it has been on neurology, on the brain situation. However, I think if you have become so programmed by the use of drugs, that your brain has become accustomed to that feeling and chemical change, that indeed there are brain changes that may be irreversible when you take exogenous substances. The irreversibility of that makes you always liable to suggestions. That's why people shouldn't necessarily go back to the neighborhood where copping takes place, because all of a sudden that triggers something in the brain that changes their focus on abstinence to an uncontrollable compulsion to get involved again. They end up starting all over again. So I'm under the impression from my years of being involved in this that

there are brain changes. And those changes are in many cases irreversible and permanent. That may be why the explanation by Dole and Nyswander in terms of methadone is so important to be considered. It's now established, I think that the brain is involved in this whole situation, and that these changes take place with short and long term use. You and I know if you have postoperative pain and you have not had drugs before, we long remember the immediate relief that you get when you are administered a narcotic. I do. Though the pain is not removed, your perception of the pain is different. It makes changes in perception in the brain when you get the drug, and you never forget that.

JOSEPH C. SCHOOLAR

Interviewed by David Healy Las Croabas, Puerto Rico, December 16, 1998

- DH: This is Wednesday, the 16th of December 1998, 10:05 in the morning. I'm David Healy and on behalf of ACNP at the ACNP Annual Meeting in Puerto Rico, I'm going to interview Joseph Schoolar.* Joseph, can we go all the way back? Can I ask you when you were born and where and how you ended up doing the kind of career you have done?
- I was born in 1928 in a little hamlet called Marks, Mississippi and grew up JS: there in the Delta. After the Second World War, I went to the University of Tennessee for a Bachelor's and Master's degree and worked at Oak Ridge and was an instructor in Biochemistry there and my chief was from the University of Chicago, so when he went back to Chicago he invited me to go with him for a dual degree program. So I got a PhD there in Pharmacology in 1957, focusing on the central nervous system and ordering graphic studies. We developed a system for doing vein autoradiograms in experiments on animals. And, then, after the PhD I went to medical school and actually was slated to go into internal medicine at the Peter Bent Brigham, but a friend of mine said before you do that, go to Texas and look at Baylor and the Houston State Psychiatric Institute; it's a very interesting place. So I went there and I've been there since the end of my internship, which was in 1961. So, actually, I've been there thirty five years.
- DH: Okay. Let me go back here. Why did you want to go into pharmacology at all and why did you want to go it in this area? Were there any influences that had led you down these roads?
- JS: I don't think any specific influences, just a general interest in the central nervous system. I had done my master's work on the Effects of Radiation on Neuroblast Cell Development. I can't point to any one thing.
- DH: Okay, if you're doing a PhD on CNS Pharmacology in the mid to late 1950s, what were the drugs? What were the issues?
- JS: Well, at that time we were trying to determine, principally two things. In my laboratory with Lloyd Roth and Charles Barlow, we were trying to map out the blood supply to the brain and see what the influence of blood supply had to do with what drugs went where. So, we used, chiefly, organic iodides in those days and it was a very simple approach. We gave the radiolabeled organic iodide to the animal and, then, at various times sacrificed the animal, had profused the blood out, and we

^{*} Joseph C. Schoolar was born in Marks, Mississippi in 1928.

could see where the drug went. For this, awe developed a system of using a photographic densitometric step tablet. That's where we get comparative densities. And, we did that for a number of years for different drugs. There were a lot of soluble, lipid soluble drugs. The other thing that Roth, himself, was working on more specifically was metabolic studies in the brain, studies of glucose metabolism.

- DH: Was there a feeling at the time that the work you were doing was going to shed much light on what the drugs did?
- JS: Well, yes, of course, there was the long view that this would be helpful, but this was at the time science for the sake of science. Shortly thereafter Comroe's paper came out that said that of all the advances that were made in medicine sixty percent of them came out of the basic science laboratory. We had to pay some attention, of course, to people who funded us. Multiple Sclerosis Foundation of America, for example, gave us a grant and, so, we were doing studies on myelinization, myelinization rates indirectly, things of this sort, so it was both actually, but we didn't have a pinpoint end purpose to see what this drug does for a given patient.
- DH: Okay. At thetime you did your PhD I have the feeling that the kind of research you were doing could easily come into neurology, but not quite so obviously into psychiatry.
- JS: Oh, that's right. That's exactly right. My interest in psychiatry came out of, I think, a personal thing. In my medical class; I believe there were 60 of us and, if I remember correctly, 23 wound up in psychiatry.
- DH: That's extraordinary. There must have been something about that class. What was it?
- JS: I don't know. We had some intriguing teachers. I don't think they were any better than the teachers who taught us anything else. This was the beginning of cardiovascular surgery and people were very interested in that. I don't know why. I don't know.
- DH: Extraordinary.
- JS: It was very interesting.
- DH: You were trained in Chicago, first of all, Carl Rogers, of course, was there. Did he have an influence of any sort?
- JS: No, I always thought that he was a little bombastic and I just didn't go over to his part of the campus; he just didn't appeal to me. People who did appeal were Bruno Bettelheim who was on the campus, right across the campus. His books were interesting. I didn't meet Bettelheim. Nobody met Bettelheim much. He sort of kept to himself. But, there was a great deal of discussion about the Nature of Humanity and I think that was influential. Reisman was there and he had just written *The*

Lonely Crowd. I used to sneak out of pathology lab and go hear Paul Tillich lectures and things of that sort influenced me.

- DH: But, this is a very philosophical kind of psychiatry.
- JS: Well, that was the sway at that time. Chlorpromazine had just come out and psychiatry at Chicago at that time was pretty analytically oriented. I would say almost exclusively analytically oriented; although, they did use some medication, but we didn't, number one, have many drugs and, number two, I don't remember any pioneering influence or interest in seeing exactly what these drugs would do. It was more analytically oriented psychodynamically oriented at that time.
- DH: At this point, you would have been quite happy to go down that line of training.
- JS: No, I really was not convinced that psychoanalytically oriented psychiatry was where the answer was. We had theories then of the, so called, icebox schizophrenogenic mother causing schizophrenia. Well, you didn't have to be too alert to see that there was a lot wrong with that theory. I never was headed down the psychoanalytic route, personally.
- DH: When you trained in psychiatry, did you get to see the old hospitals, those big wards. What was it like in psychiatry?
- The first, old state hospital that I remember was back in Tennessee and JS: that was the East Tennessee State Hospital. I can remember driving around it, but in school, I think the Elgin State Hospital in Illinois was the first one I actually went into and spent any time and was able to see what went on and so on. This was probably in 1956 or '57 and it was a huge state hospital. It was at the time that they were beginning to use phenothiazines in the state hospitals. I think they were using also reserpine or something like that and I asked one of the doctors why he was using that particular drug and he said, well, because the drug house gave us a lot of samples. They were just beginning to use medication, Until, I guess it was the mid-1960s, or even later, when the big exodus from the state hospitals began to occur psychiatry became much more an outpatient practice than it was originally. In my early days in psychiatry in state hospitals in Texas, for example, the Austin State Hospital was a huge hospital right in the city of Austin. I can't remember how many patients they had there, but it was in the low thousands, I believer, fifteen hundred to two thousand, but that's a guess; I can't really remember, and as time went on they began to develop outpatient clinics and the hospital by that time had come to be known as the Texas Research Institute of Brain Sciences, and people began to recognize that, it was much more humane to treat patients, most patients, as an outpatient. There's still a place for the state hospitals, of course. But,

across the country, there were experiments done. Jonathan Cole did some experiments at Harvard and well we had the same thing in Texas. We had developed outpatient clinics to handle most patients.

- DK: Okay, you've trained in medicine up in Chicago. Then, you have this idea that maybe you should go down to Houston, so you went. What was the situation in Houston? Why did you go down to Houston? Why did people think that the Houston Psychiatric Institute was interesting?
- JS: Well, I had a friend, with whom I'd been in physiology class. He was actually a Dominican priest, who had been sent there, and he came back across the campus and asked me what I was going to do and I said to him I was going to Peter Bent Brigham and he invited me go down to look at Baylor and the Houston State Psychiatric Institute. So, I went and I was very intrigued by the people there. Dr. William Langland was there, who had been at Payne Whitney, and he had come down to be the head of psychiatry at Baylor, and Dr. Kinross-Wright, John Kinross-Wright was there, who was doing a lot of interesting work in psychiatry and psychopharmacology at that time. And, they had this institute, a research institute that was very intriguing. Then, I'm a Southerner, so there was, I'm sure, some conscious or unconscious pull there and, so, all of it added together that I went there for residency and then stayed.
- DH: Residency there at that point in time would have involved psychodynamic training?
- JS: Yes, psychodynamic training and a third of it was neurology, two thirds of it psychiatry and that was psychodynamic and also a good bit of training in psychopharmacology. The drugs were coming out very rapidly. This was 1961 to middle of '64 and, so, we had tricyclic antidepressants available and phenothiazines; new drugs began to come out pretty rapidly, so we got a lot of training in psychopharmacology at that time.
- DH: Right. Okay, just to go on, how did the antidepressants look to you guys then? Clearly, Thorazine (chlorpromazine) produced a huge breakthrough and people like Kinross-Wright were among the first in the country to use it, right?
- JS: Right.
- DH: Did the antidepressants play quite as well? I mean, there was a little bit of controversy at the time; it seemed to be, some in the conntry were unpersuaded that these drugs really worked.
- JS: Well, we were persuaded and we used them. Maybe we weren't as critical as in other parts of the country. Patients would come in and they'd get Thorazine or Stelazine (trifluoperazine) or one of the other substituted phenothiazines and antidepressants. The big one in those

days was imipramine and, then, also Elavil (amitriptyline). Mesoridazine sold as Serentil. So, the new drugs were coming out pretty rapidly and we used them. We used them a lot. In fact, we had a rule that if you had a depressed patient who was agitated, you gave them Elavil. If you had a depressed patient who was not agitated and retarded, you gave them imipramine.

- DH: Right. And, how did this compare to ECT? Did it compare well?
- JS: Yes, it did. It really did. When I was early in training, we did a lot of ECT. I'd go in first thing in the morning, 7:00 AM, and do all the ECT's that I had to do as a resident but before I finished my residency this was no longer the case. The number of ECTs given went down.
- DH: Substantially?
- JS: Yes, substantially
- DH: On that score, how many patients did you have to look after? I mean, there were obviously much fewer people actually doing psychiatry at the time than there are now, and there were much more patients per resident than there would be now.
- JS: I don't think so. I really don't think so. We were under the mantle of Baylor College of Medicine and it was a training experience. My first inpatient service was in the old Jefferson Davis Hospital in Houston and we had a ward there that had maybe 35 patients, inpatients, or something of that sort and, as I remember, there were three of us, so we were doing okay. And, we had a mixture of therapies, ECT's and supportive psychotherapy, but we were also training in dynamic psychotherapy, as well.
- DH: Sure. Once the drugs began improving the the mental state of the patient, and please correct me if I'm wrong, more things were actually happening on the wards in terms of occupational therapy and various other activities before then now. In the kind of the district general hospital unit that I work on nothing happens these days. People now come into the hospital and after getting their pills are sitting in the ward and get bored out of their mind. They often leave, because it's so boring. But this was not the case in the 1960s; there was a combination of non-pharmacological therapy with the the pharmacological therapy; it was more than just drugs being given, right?
- JS: Oh, yes, a lot more. We had a theraoeutic milieu. And, you're quite right. Occupational therapy was very important. Group therapy was important. We had at TRIMS an art therapist and we'd have discussions in which the patients were included about the art that they had produced. There was a great deal of social support, so drugs were an absolute sine qua non of treatment, but it went far beyond drug

treatment. I would say that when I was in training at Baylor while drug therapy started and increased, psychodynamic psychotherapy stayed about the same. It was a very important element; it was a therapeutic milieu.

- DH: Given all that, I have this hunch that there's something pragmatic about what you guys were doing down in Texas. Up in the east coast there seems to be these wars between the analysts and the drug therapists. Did that play down in Texas?
- JS: Oh, yes, it played to some degree. The analysts were said to act and think themselves superior as psychiatrists and so on. But, this never did really get in our way very much. Many of the people who were our teachers had had analyses or had had some analytic experience including my second chief there, and he brought in a group of analysts to enlarge the department, so we felt a great deal of influence of that, not a war though. I don't think it was quite as vitriolic as I seem to believe that it was on the east coast.
- DH: Sure.
- JS: There was still an important analytic influence. The first chief, when I went there in 1961, was William Layman; He'd been at the Payne Whitney Clinic and he was not an analyst. He was very interested in research. He was very interested in the concept of time and measuring time and he was a very impressive brilliant individual, almost encyclopedic mind the kind that would just draw a resident to him. He was not an analyst and, so, there was not very much analytic influence at that time, I would say. The other people in the department were Kinross-Wright and Eugene Kahn, who had come down from Yale; he wasn't an analyst. He was interested in Kraepelin and spent his time doing history of Kraepelin and an analysis of Kraepelin's work and so on. And, the other people in the department were, by and large not analysts. But, then, after Layman left, Shervert Frazier came in and I think, speaking privately, I haven't asked Sherv about this, but I think he had sort of a love/hate relationship with analysts. He knew a lot of analysts. He'd worked with a lot of analysts at the New York State Psychiatric Institute and at Mayo's and he brought a lot of analysts into Houston. The chief among them was Eldon Bouk and, so, we got quite a psychodynamic influence at that time and I would say, sort of an analytically based influence. Even though you were on the wards, you had a lot of psychodynamic psychiatry in your training, so that influence was there. It was either or.
- DH: What about the influence of the St. Louis group?
- JS: Well, it was known as the place of biological psychiatry. They were quite scholarly at Washington U. They just said, psychiatry is biological and

that's it, as far as I know, which I think was a very strong and good balancing influence. You need a place like that. They stood out in that fashion. We were never that oriented toward biology, exclusively. Now, Kinross-Wright, an Englishman, had no interest in analysis, he was definitely a biological psychiatrist and he's the one who stimulated all the drug studies that we did and got people in to do the drug studies and so on. So, we had both of those.

- DH: Could you let me know a bit more about him, because clearly, in one sense, history has been a little unkind to him, in that he gets portrayed as the man who pushed the doses of chlorpromazine up to really high levels, but he was also doing a lot of other work on things like conditioning. Is this right?
- JS: When you say conditioning, you mean like conditioned reflexes?
- DH: Yes, that kind of stuff.
- JS: He might have been.
- DH: How did he look to you at the time, as a man? Can you fill me in about that? You said he's from England.
- JS: Yes, from England.
- DH: When did he come over?
- JS: I don't know when he came over, but he came to Texas, I believe, from North Carolina and, in maybe 1956 or '57 came to Baylor, but that's a guess. And, he was very interested in the study of drugs and the application of CNS medication and psychopharmacological agents to a large patient population. There's a sort of an interesting story there, as it has been told to me. There was a man in Holland named Korito, who was doing some outpatient studies with drugs and getting patients out of the hospitals and having clinics with medicated patients and so on, and Eugen Kahn read the European literature, I don't know whether Kinross-Wrright did or not, but at any rate Kahn and Kinross-Wright were talking about this, and as the story has been related to me, Kinross-Wright got in touch with Heinz Lehmann and he and Lehmann discussed this and actually Kinross-Wright set up the first psychopharmacology clinic at TRIMS with a man named Kanellos Charalampous.
- DH: That's an unusual name.
- JS: Yes. Charalampous was a medical student at Baylor and worked at the VA Hospital and when Kinross-Wright and Gates and Pokorny did some of their early chlorpromazine studies, he was the medical student who did all the histories and followed the patients and things of this sort, or at least assisted in a great way and, then, when he graduated and finished his residency he joined Kinross-Wright in the psychopharma-cology clinic and continued there for a number of years until he went to

Oklahoma under Jolly West. And, so, in the psychopharmacology clinic indoles and phenothiazines were used and studied in the treatment of psychoses. There was a little benzodiazepine work done by Irvin Kraft in children, but the big thrust of it was the antipsychotic drug. reserach Then, by this time, James Claghorn had joined Kinross-Wright and William McIsaac and, so, they had guite a critical mass there and I think they did a couple of impressive studies. One of them was the labeling of drugs radioactively. They could be studied in animals. We had an animal colony that included monkeys and rats and mice. It cost us a lot of money to keep that colony going. We could do metabolic studies; and behavioral studies in animals with Hal Olshever, who was a behavioral psychologist and pharmacologist. The synthesizing and radioactive labeling of drugs was under Beng Ho. Some members of that team are members of this college. Ho is a member. I don't think Claghorn is a member, but certainly Ho is. So, there was an effort to make the studies controlled, experimentally exact and well thought out and well done from a variety of standpoints. So, I think that was one of the unique things about the Texas Research Institute. Then, after awhile, a clinical laboratory was set up in Huntsville, the so called Wynne Unit, and a lot of drugs were tested there and, all in all, it was a very productive unit I think. While it lasted, that clinic tested about upwards of a hundred drugs and, of course, most of them didn't make the market. It was considered to be very valuable, to stop a drug that was thought to be worthless. I think Kinross-Wright started one of the first six of the early clinical drug evaluation units. With Charalampous he did some early Phase II studies and a lot of Phase III studies. And, the residents were, to some extent, involved in this but, by and large, it was Charalampous and the nurses that they trained to do the busy work and the instruments that they used for evaluation.

- DH: Did the psychopharmacology clinic that was being run there come before the first early clinical drug evaluation units and, in some sense, provide a model for them or did they both come at pretty much the same time?
- JS: Pretty much the same time. I think, actually, the psychopharmacology clinic came first and, then, the early clinical drug evaluation unit came in. All of this was within a year or two of each other.
- DH: Who were the other units around the country? You said this was one of six.
- JS: I can't tell you where they were.
- DH: Heinz Lehmann and Tom Ban, I think, had one. I could be wrong on this.

- JS: No, no, I think you're correct, but I can't tell you. I'd be guessing. I never did know. I was just told that there were five others.
- DH: Did you get involved with this clinic?
- JS: Well, only to a certain degree, with my little finger. I was one of the evaluators who went with Clyde Warren every Thursday to the Wynne Unit to evaluate patients and, also, in the outpatient clinic we had drugs that were being tried and, so, I would evaluate those patients and so on, but I was never a major player in that.
- DH: So, you weren't at any of the first NCDEU meetings where all the units got together?
- JS: No and that is why I don't know where they were. You're right; I never did go to any of them.
- DH: What were you doing as your own research at this point? You mentioned radiolabeled drugs, in the light of your PhD; I wonder whether this is the kind of thing you began to get into?
- JS: Well, I did some studies in rats, chiefly on drugs of abuse. We did cocaine and LSD, chiefly those two. There was also a man, Heikkila, Juhana Idänpään-Heikkila wit his wife, working with us who had come from Helsinki and on two different occasions spent, I think, two years with us. He is a pharmacologist and she's a psychiatrist. And, so, we did those studies and using the same audiographic technique that I'd developed at Chicago. And, then, I became very involved in substance abuse and about 1965, I guess, I put some 3 x 5 card notices around the campus, saying that I was interested in patients who were abusing drugs and almost overnight I was overwhelmed, because this was the beginning of the increase in, particularly young people who were using LSD and all the drugs. So I got very active in clinical research. We had a training program. The residents would rotate through from other hospitals on our program.
- DH: Why did you get interested in this area, because it's always been a bit of an off area within psychiatry and an awful lot of people feel you can't cure these people, so they tend to...
- JS: Well, it may have been an off area in psychiatry but not in classical pharmacology, the pharmacology of the opioids and central nervous system, the pain killers and mostly the opioids, is a very classical area of pharmacology, so it's not off to one side at all.
- DH: Clinically though, it's a tricky group of patients to work with. James Woods' in his interview was saying that that there was a group in Lexington, Abe Wikler, Harris Isbell, Bill Martin, ivolved in early research in this area; did you link with those?

- JS: Yes, Martin and I were good friends and we worked together a lot. Isbell and Wikler were older, but I had their books. I had read their stuff when I was a graduate student in Chicago and that influenced me. The research done at Lexington and at Ft. Worth, by Maddox was unique. So, yes I was in contact with them. What else did Woods say about them?
- DH: Well, what I understood was that I guess, in the 1950s, the idea was that central in addiction is the withdrawal, that some drugs cause withdrawal when you halt them, so the addict keeps on having them in order to avoid the withdrawal. It moved on then, I guess, in the early '60s by Bill Martin, more than by anyone else that it is not just it's not just withdrawal to a group of drugs but that there is a kind of people, kind of psychopathic people, get hooked on these drugs... There are issues to do with the individual, even before they have the drug that we need to take into account. And, then, in the mid 1960s, issues related to behavioral pharmacology came to the forefront, like abuse liability of the drug itself, quite apart from the individual who had a problem from any withdrawal that it might cause. How did these issues look to you?
- Well, understandably, to tease out and categorize the main areas in JS: this is very difficult. In the early days, when Isbell and Wikler and, even Martin, were there, they were dealing with opioids and the one thing that adds a new dimension, an additional dimension, to this whole consideration is the fact that a patient can be off opioids for years, but they get the yen and they go back to them. And in Woodlawn experience, that was repeated by others, opium and our heroin addicts, who were totally off the medication and so on, if they return to the place where they used to have ther drug experience their salivation would go up; their heart rate would go up; their pupil size would change and so on. And this this was not drug-induced, so there's a great deal of expectation and emotionality and psychophysiological components to this yearning. In the '60s, I saw many people taking opioids, barbiturates, amphetamines and also hallucinogens, and it was a large group of adolescents that we saw. And, so, when Bill Martin said that they were sociopaths, we had discussions that the criteria oof sociopathy was not met by all the substance abusers at all. I saw a lot of confused adolescents involved in substance abuse, because they were antiauthoritarian or they were lonely or they were depressed, or caught in a crack between some-sort of a dysfunctional family difficulty and so on. These weren't traditional sociopaths and, with treatment, a lot of these people I have been able to keep up with over the last twenty or thirty years; they've come out of

it and they've done extremely well. And, classically, a sociopath never comes out of it. So, you have to be careful with the term.

- DH: So, it seems there was a wave of people beginning to take LSD during the '60s. Had you got the clinic up and going before the wave hit?
- JS: Well, in the beginning of the wave. I could see it coming, but didn't know it was going to be as big as it was, so I was at the beginning of the curve, I guess. So, it was a good time to become very involved, because there were not that many people working on it at that time.
- DH: How many other people were there? They were the people in Lexington...
- JS: Well, in Lexington, they weren't working with hallucinogens.
- DH: Not working with hallucinogens, not at all...
- JS: But, they had done work with amphetamines, but mostly with opioids, and not much with barbiturates. Well, I don't know how many people were working in the area. There was Division of Narcotics, what was called narcotic abuse or something like that, in the National Institute of Mental Health, and Sid Cohen was the head.
- DH: Yes. Let me know more about him.
- JS: His background, I can't really tell you. He was from California, I believe, but when I met him he was head of that Division at the National Institute of Mental Health that was only a division then. Now, later, they changed it to an institute with its own standing and he had with him a staff of, I don't know how many, people who were psychologists and career health providers with various training. I don't know how many physicians or psychiatrists. I don't think Sid was a psychiatrist. I'm not sure, but it expanded a lot at about that time. They set up various committees and began to give out grants and things of this sort and, so, I spent a lot of my time reviewing grants and going to Washington and sitting on those committees and things of that sort. It was very interesting and pretty heady. You felt that you were on the cutting edge, so to speak.
- DH: Heady in the sense that you thought you could crack the problem?
- JS: That it was a big problem and something had to be done about and with. One of the big questions then was the whole methadone question and I remember they got me in Washington once and asked if I were Chief would I be in favor of using methadone, and by that time I said, yes, without hesitation that I'd use methadone, and I didn't realize it was as quite a political issue as it, I guess, was, but it clearly helped a lot of patients and we, by the way, had a large methadone clinic in Houston. We had, I think, 500 patients in our methadone clinic there that by that time had been set up.
- DH: Who are the other people from the hallucinogen field; obviously Leo Hollister was doing an awful lot of work?

- JS: Leo Hollister was; that's right, in marijuana mostly, but that's right, he did a lot of work in hallucinogens and so on. Reese Jones was another one. He was from San Francisco, and he's a college member, I think, and he did work in marijuana.
- DH: And, there were also, two other people who were actually in the college at the time, there was Freedman, Danny Freedman, and Daniel Efron was also involved with it.
- JS: Yes, Efron was, very early on. Who was the other one?
- DH: Freedman, Danny Freedman.
- JS: Oh, Daniel X., oh yes, yes, he had been at Yale and he did some of the very early work on LSD. Then, he went to Chicago as head of the department. Oh, he was a powerful person. He was such a fine gentleman. I really got to be close to him. Unfortunately, he died; I think it was last year.
- DH: What do you suppose his actual contributions to the field were? Can you pin them down to us, the LSD work he did, the basic work he did, but after that his work got more kind of political type, I guess?
- JS: Yes, that's right and organizational. Danny was on every committee that you can imagine and he did a lot of organizational political work and was very effective in that regard, quite effective.
- DH: I know Arnie Mandel was in this area.
- JS: Yes, he was in San Diego. I can't remember the detals. Somebody told me there's a book about it, but I never read it.
- DH: Okay. How do you read the hallucinogen story now? It happened during the '60s. It was part of the counterculture, but to some extent it reemerged a little bit with the use of PCP during the '80s. How do you read it all now? What do you think was going on?
- JS: Well, I think you're right in your statement that it was a counterculture thing and when I was in college people would walk around with a book of French poetry under their arm, or philosophy and so on. Well, in the '60s, a lot of the people that I talked to were reading Carlos Castaneda and it was just the "in" thing to do and so on. This was, I think, a large component of that. There was also a lot of, as you say, the philosophical and emotional countercultural elements of the '60s. People were sick of the Vietnam War. They were sicker a little bit later on. It was the part of the rebound phenomenon from the conservatism, I think, of the '50s and so on and, of course, the sociologist have really had a heyday writing about this stuff and I think their theory is as good as anybody's theory.
- DH: Okay. So, we're here in the '60s and you've got the clinic going. Where does the drug abuse story go from there for you?

- JS: Well, I spent a lot of my time doing what I've just told you and working with the youngsters and so on. But, we also established a substance abuse clinic for, what Bill Martin would have called a sociopathic type, as it were, for heroin addicts, opioid addicts, and so we used methadone. I had been to Rockefeller and spent some time with Dole and Nyswander, so I brought back the techniques and set up a lab there at TRIMS. So, we had a big effort going there in methadone maintenance. Now, of course, the effort was always to get patients off the opioid. We didn't just get them on it and keep them on it, but there was a residual amount of patients that we realized would be always be on an opioid and, so, we put them on methadone and we tried to get the dose down as low as possible. Jaffe had some studies then that showed that patients did just as well on, I think it was 37.5 mg of methadone a day, as they did on 100 mg a day. Well, we were never able to corroborate that but we did get it down low. And, their employment rate went up to maybe sixty percent from about twenty percent and patients, with, adverse encounters went way down and so we felt that was a successful experience for these patients. We continued that until we closed the clinic in about 1982, I guess, something of that sort.
- DH: Why did you close it?
- JS: Political. It was political, I think. We were giving methadone and, by that time, the sway in Washington was that we ought to use some sort of sociological approach and not use methadone. It seems to me, I can't be sure, that methadone had been outlawed by that time in Oklahoma and there was just a swell of opinion away from methadone into other types of treatment and we lost our funding. We lost our grant, so we closed it.
- DH: Looking at it now, do you think this was a backwards move?
- JS: Yes, I think it was. I think that now and I thought that then. I'm not saying that one should give methadone to all opiate addicts. I think that each individual addict has to be evaluated. You've got to have a lot of social support and individualized treatment regimen and a totality for this patient and so on, but I don't think that you should just, out of hand, say that methadone has no place in treatment.
- DH: How about the issues that will be thrown at you, this is not a real medical disease; this is a self inflicted condition?
- JS: If it looks like a duck and it walks like a duck and quacks like a duck, it's probably a duck.
- DH: So, you're quite happy with the medical model?
- JS: Well, I don't think it matters, really. I mean, I wasn't trying to be flip.
- DH: No, no, no.

- JS: If you have a patient who is taking a medication here or an element like opium and so on, whether you call it a medical disease or whether you call it a social disease with medical attributes and so on, I think is sort of lead to nothing. You've got to treat the patient either way and, so, I don't think it matters a great deal. Now, individually, it may matter. Now, there is something about patients, who, as we were talking earlier, been off heroin for two and a half months, let's say, or a year and a half, and goes back to it that is, not medical. I mean, there's no pharmacological reason why he should go back to it, that we know, and it's hard to imagine that there would be a pharmacological reason for that. But, nonetheless, they go back. It's a part of the phenomena and, so, you have to treat that.
- DH: Sure, sure. Okay, so you've seen the wave of hallucinogens crash over the '60s. You've been involved with the methadone and the clinic gets halted in the early '80s. Did you get involved with any other drugs, cocaine, etc., etc.?
- JS: Oh, yes, right. We got involved with all of them, because we had patients sent to us, who were taking all of them. In those days, it was extremely rare to see a patient who had taken only one drug and who was taking only one drug.
- DH: Even way back in the '60s?
- JS: Oh, yes, right. Whatever they could get their hands on is what they took. Now, they had their preferred drug and I guess the opioids were the one class of drugs that were the preferred.
- DH: Can you describe for us what the cocaine story was like? When did it begin?
- JS: I think in my experience the drug abuse era started in about 1963, '64, or somewhere along in there, and peaked in about 1970 to '72, '73, '74, somewhere along in there, so the curve would go something like that. But, then, cocaine came back up, the stimulants. Early on stimulants meant amphetamines, but now, in the second wave, stimulant meant cocaine and, so, yes, that was later. And, there were many people who were pure cocaine abusers and, counter to what I said earlier, these patients were likely to be abusing just cocaine.
- DH: Right.
- JS: Not always, but likely.
- DH: How did the problem look to you, how serious a problem did it look?
- JS: Well, it was quite a serious problem. Here again, from where I sat, in academia and in a university medical school and so on, it was different, I think. For example, I didn't get involved so much with the crack cocaine abusers. Now, some of the people in our drug abuse

section did, earlier, but mine was more the affluent people who were using cocaine and so on, so it was a little bit different, but it was quite a serious situation the more we began to learn about it, for example, when this professional basketball player died suddenly, allegedly, from having taken cocaine and had a myocardial infarction. I began to look at this in our area and I talked to the lady who ran the cardiac clinic at the Bentall General Hospital and she said that earlier the cardiac clinic was full of people who were in their sixties and seventies and so on, now, a third of them were in their twenties, people who were afraid they had myocardial infarctions or who had, indeed had a myocardial infarction from cocaine use.

- DH: Gosh!
- JS: A very, very significant change.
- DH: Sure, sure. Okay, could I move you on; you got involved with ACNP, when? When did you get involved, originally?
- JS: ACNP, oh, in the '60s, I don't remember. Let's see, the meeting that was in Washington, was the 25th anniversary. It seems to me, back years ago, they had a meeting in Washington to celebrate.
- DH: The 25th anniversary, yes.
- JS: I believe the 25th. I had been in a number of years by that time. I don't know when I became a member, but it was in the 1960s.
- DH: Yes, okay. What were the meetings like during the '60s? Obviously, it's a huge meeting now, but what was it like during the '60s?
- JS: Well, it was smaller then. They were always at the Caribe Hilton in San Juan. One of the things I mentioned to Eva Killiam was if ever she got to be President she should make the meeting in St. Louis, where it would be a lot more central. She became President, I think, but she never did it. They liked the Caribe. It was smaller, but they were always very good meetings, a lot of good pharmacology. I can remember when the dopamine theory was first promulgated. Ed Domino gave a talk right here in Puerto Rico that really laid it out. They've always been good meetings.
- DH: I have a feeling though that in the early days when they were smaller, more intimate, where you all knew each other and there was the opportunity to sit around the pool during the afternoon, the early afternoon and that a great deal more change happened then than happens now. Have I got the wrong impression?
- JS: I don't know. I think your impression is probably correct, but that hasn't been a big issue with me. I'm sort of a compulsive and I go to all the meetings, anyway. But, you're probably correct.

- DH: As regards to substance abuse, has ACNP been a good forum, or have you guys needed to create other forums, as well?
- JS: ACNP has not had substance abuse as one of its prime areas of focus and, yes, there are other forums. There's one, American Academy of Addiction Psychiatry. I'm a charter member of that. And the Association for Medical Education & Research into Substance Abuse (AMERSA) or something like that. That's been a very good forum and there have been one or two others that sprung up about in the '60's or '70's.
- DH: Okay, but you've needed these other forums?
- JS: Well, yes, I'd say. They sprang up and they have continued, so I guess we needed them.
- DH: Have you had a role in any of the other societies?
- JS: I was a member of all of them in the beginning, each of them, and chaired various committees and went to all the meetings and gave some papers and things of this sort. Sure, I had a role in them, most of them, many of them.
- DH: Okay. When you raise the issue of the papers you gave, what do you consider your most important work?
- JS: In substance abuse?
- DH: Either that or any other area.
- JS: Anything else?
- DH: Yes.
- JS: Oh, that's a difficult question to answer. I've been a researcher; I've been a teacher and I've been a clinician and I think that it would be sort of like trying to describe a three legged stool. If you take one of those legs away you wouldn't have a stool any more. I liked the early research, laboratory research that I did. I certainly have always liked the teaching. I gave the big pharmacology lectures at Baylor for twenty-eight years on the central nervous system and drug aspects and psychopharmacology and things of that sort and that was interesting. But, the clinical work, might be the most important, how can you say? I don't know the answer to that; I don't know. There's been no one thing that anybody would ever connect me with, unless it would be the development of the brain autoradiography technique. I used to get a lot of appreciation for that, but that was in the mid 1950s.
- DH: You said you were working on this, as you said it, but, gosh, that was awfully early to be working on that and I can't think of anyone who would have been working on it earlier. Did you actually develop it?
- JS: That's what I was told. I don't know. I had been at Oak Ridge, the Oak Ridge Laboratories, and, of course, radiation was what we dealt with in radioactive materials, and so when I went to Chicago, and I went

to Chicago, I believe in '53, I had to select something for a PhD doctoral effort, and so I developed the autoradiographic technique, in brain. Autoradiograms had been known before that. There were autoradiograms that were done in Oak Ridge. I can't remember the exact origin of that. But, in brain, I think we were the first. At least, that's what I was told.

- DH: Right. When you radiolabeled drugs down in Houston, what drugs were you radiolabeling?
- JS: LSD and mescaline. We did LSD and we did marijuana and we did cocaine, I believe.
- DH: What did the autoradiography of these compounds show?
- JS: It showed where the drugs went in the body and we thought that would be valuable to know if they went to a certain part of the brain more so than other parts of the brain, but we were under no illusion that this would say that this is where the drug had its greatest action. We were simply doing drug studies in brain tissue in order to see where it went and the object, then, was to coordinate these findings with the metabolic indices. I had some ideas of doing metabolic studies in various particular parts of the brain, but I never did get into that, because I got off over into clinical studies.
- DH: Okay. When you move into clinical stuff, you have to take all of the issues into account including the social situation of the patient. But just to come back to the monkey population, because when you mentioned that first, what hit me was that there were two or three things you guys could have done with these. One of the things is that you give them the various drugs and autoradiograph them, or you could have been looking at the impact of the drugs on animals in group settings. Were you able to marry the two together?
- JS: Nop. Observing them in group setting is behavioral pharmacology and that was done by Harold Altshuler.
- DH: The idea is that you can give a drug to one animal and see one thing, but if you give the drug to a group of animals, you see something else.
- JS: Right. That was done, by Harold Altshuler, who was a behavioral pharmacologist at TRIMS. I don't think though that he put a great deal of emphasis on the group part but he did do behavioral studies. But there was a lot more to do than we could do, so we were going in, I guess, the direction that we thought was most fruitful at the time.
- DH: Sure, sure.
- JS: What I'm saying is that we knew at the time that were a lot of other things that we could be doing or would like to be doing.

- DH: Looking back now, drug abuse, it's an area of clinical psychiatry that has to be one of the hardest areas to work in, because the public attitude to the problem. I'm not sure I can see the public will to pay for the treatment to solve the problem. How is it all going to play out, do you think? Are we always going to have a drug abuse problem, or are we going to be able to lick it or what's the interplay between the science and the public view of the issues?
- JS: Well, I agree with you that it's a hard sell to the public and, not just because some people think that it is the individual who brought this on himself, but it's more than that. I think, the smoker brought on himself COPD or lung cancer or something, he brought that on himself, but society looks differently on the smoker from the way they look on the alcoholic or the other substance abusers, so it goes beyond that. I think there is an element of something deep within the core of society that makes it difficult to accept the fact that substance abuse is an illness. And, that's why I don't like to get off into the deep discussion about whether it's the illness or whether it isn't an illness. We could talk about that, but I think it's almost a fruitless, existential reality; it is, so we have to deal with it. But, to answer your question I think we'll always have obesity and we'll always have alcoholism. We'll always have some degree of substance abuse.
- DH: On that one, I'm not sure we always will have obesity, because I think the pharmaceutical companies think they're actually going to produce an agent that will help solve this and they're onto any medicine to try to reduce weight, because they know they'll be able to sell it. People will pay for it, but in terms of trying to get anyone to pay for treatment of substance abuse, well, the addict won't pay for it, necessarily. Society won't pay for the addict. It's a different ballgame. It will be much harder to encourage industry to want to get involved with this area, won't it?
- JS: Yes, you're right and I agree with you, obesity is a different kettle of fish and, so, I was just trying to think of things that I, as a human, could do to myself that I could refrain from doing to myself and therefore, circumvent certain conditions or diseases. So, generally speaking, I don't look for a perfect world. I mean, we've never had one and why should we expect one now?
- DH: I think that's extremely sobering and obviously a clearly right statement, but with ACNP meetings now you're at a point where the neuroscience has really begun to develop and there's really great hope where you have to know breakthroughs in regards to drugs for forty years or so, well, there will be, too.

- JS: I think there will be. We're becoming much more precise in the areas of the brain and the G-proteins and the genes that encode with this and and this is all absolutely wonderful and this is the cutting edge. There's nothing in medicine, there's nothing in biology that is more exciting, but who knows, twenty five years from now, when I walk in that door and I am depressed and you could say, well, you need some 2D6 devolution and some 3A4 increase and by that time philosophy may be the thing we're all after. You see, we don't know where society is going.
- DH: Do you think we'll go back?
- Sure. I think we'll go back to something. Sure, this is the ACNP meet-JS: ing. If you go to other meetings, people don't care what's happening in the central nervous system. What they're interested in is science vs. religious precepts. That's what's important to them and they're wondering whether the pendulum is going to swing back a little bit in spirituality vs. secularism and so on. They're not interested in brain chemistry, so that may have an influence that will influence what happens.. After all, philosophically, one could pose the question that in the long run, what difference will it make? In the short run, it makes all the difference whether you can treat a substance abuser or whether you can treat a schizophrenic, or whether you can treat an addicted depressive. It makes all the difference in the world and those of us in ACNP are dedicating our lives to this, but in the long run, in the greater scope of things, if you take the history of diseases throughout the history of mankind, are you going to change the curve? We don't know.
- DH: A perfect point, I think. Do you think there are any other areas that I've left out?
- JS: No, I don't think so.
- DH: I think we've actually hit the key ones.
- JS: Well, we hit the key ones. I thought this was going to be the history of the Texas Research Institute of Mental Sciences and I wanted to be sure to get in the names of the people who have contributed so very much.
- DH: Have we left any people out that you want to mention?
- JS: I think we've mentioned the major ones. We didn't mention Burch. He did a lot of work on electroencephalography in patients. At one time, he had hoped to sort of automate the EEG and, then, do a sort of the signature of various types of emotional aberrations. People like Johnston did a lot of training and I mentioned Gates and his work in gerontology and Garner, along with him, and Hartford, who is a member of the college here, and I mentioned Charalampous and Claghorn. I'm just going

through my mind. McIsaac did a lot of the early medicinal chemistry work that was done at TRIMS. I just want to be sure to get them in.

- DH: Get them in.
- JS: Get them in and give them credit.
- DH: Sure, sure. I think your view about the short to the long run is very interesting. We are heavily focused here at the ACNP meetings on the short run, what can be done for the individual patient.
- JS: That's our job.
- DH: Should we bring some of the longer run view into the meetings as well, though? Should we include more on that?
- JS: No, I don't think you have to be all things to all men. I think it would be a mistake to try. A long time ago, I read the history of tuberculosis, a review of the entire field. I think it was in *Scientific American* and it was written by a man, whom I knew, and so I talked to him about this thing and this history and what he really showed was that we really hadn't done much for the shape of humanity, in all of our contributing to tuberculosis. Now, if you ask people who are tubercular, we've done everything, so I think we have to keep both in mind is all I'm saying.
- DH: Right. Okay. Joseph, thank you very much.
- JS: I enjoyed it.

MARC SCHUCKIT

Interviewed by Andrea Tone San Juan, Puerto Rico, December 13, 2004

- AT: Good morning. My name is Dr. Andrea Tone; we're at the 2004 ACNP Annual Meeting in Puerto Rico and today I'm interviewing Dr. Marc Schuckit.* Thank you very much for joining us.
- MS: My pleasure.
- AT: I just want to start with some basic questions and ask, first of all, how you got interested in the field of psychiatry?
- MS: Getting into psychiatry was pretty easy for me, for some reason, maybe, through novels, perhaps through reading history, whatever. I went to college, thinking that I was probably going to go to medical school and in medical school, probably, become a psychiatrist. The issue was that I thought I was going to become a psychoanalyst and when I got to medical school, I, actually, chose the best medical school that gave me the best scholarship, which is, perhaps, not the best way to do things, but that's what I did. And, it turned out to be Washington University, St. Louis, and I learned that psychiatry was something quite different than I thought it was, that, actually, psychiatry was much more disciplined and focused and I found that even more attractive than I had the original thought of what a psychiatrist was.
- AT: What was your original thought as to what a psychiatrist was?
- MS: Probably, mostly, what you see in movies and read about in books, that they talk to people help them go back through their histories and through piecing things together, make them understand themselves better, which is probably true, that they function better, which often happens. But this wasn't certainly a way that I felt I was going to be able to help the largest number of people possible. So, when I got to Washington University, St. Louis, I, basically, needed a job. I was working part-time and was looking, first day of medical school, at the bulletin board and the bulletin board had on it that this doctor was doing a study, following up thirty year old men in St. Louis and trying to take a look at what happened during their lives, etc. I applied for the job and it turned out to be Lee Robbins, a sociologist, the best researchers I've ever worked with and she taught me not only about how to do research, but also to love research. And, from her, when that project ended, I was looking for another job about two years later, and got one with George Winokur who was interested in what was running in families of people, who had depressive disorder. And, he taught me not only the

^{*} Marc Schuckit was born in Milwaukee, Wisconsin in 1944.

methodology that he and Lee Robbins used, but, also, gave me the opportunity to start learning about something I'd never thought about before, which was alcoholism. So, psychiatry wasn't a surprise to me. What was a surprise to me was that I became interested in research and research has become the center of my academic life. And, the major reason for that is that I had such incredible mentors. I was at Washington University in St. Louis at a time when the people, who were prominent there were very diagnosis oriented, used diagnosis to predict clinical course. At that time, Eli Robbins, who I also had the chance to work with, was the Chair of the department. In addition to Lee Robbins and to George Winokur, Donald Goodwin was there and he taught me a lot about genetics. Actually, he's probably the best writer I've ever worked with and he taught me about writing papers. And, Sam Guse was there as well. Sam was a model of almost anything that you would want to do in research and in academics. So, I really found my way into academics, into psychopharmacology, into careful diagnostic approaches by a feat of great luck.

- AT: Often, these people are just referred to as the St. Louis school, right? They really did stand out in the history of psychiatry.
- MS: As I became more interested it became obvious to me that there were some places in Europe where psychiatry was approached in a simlar way. The Maudsley seemed to be one of those places. I don't know whether that was right or not, but that's certainly what I was seeing as a medical student. And, then, you had the group in Stockholm, people at the Karolinska that seemed to have a similar approach.
- AT: How was psychoanalysis treated in the curriculum?
- MS: It was a part of the curriculum, for sure, and there were courses that we had, when I was a resident. The prior Chair of the department to Eli Robbins had been Dr. Gilday and Dr. Gilday was psychoanalytically oriented. His wife, a physician was also psychoanalytically oriented. And I was encouraged to ask the wife of Dr. Gilday to supervise me so that I could learn something about Jungian analysis. The fact that there were analysts on the faculty was very important and we took advantage of it, but it wasn't what that place was about.
- AT: So, tell me about some of your early research. I understood from you that you became increasingly interested in alcoholism. Is that right?
- MS: Right. The first thing that happened that got me interested in alcoholism was that if you're studying disorders in relatively young men in the United States, there ain't nothing to compare to the rate of alcoholism and the problems that people acquire in the context of alcoholism. So, Lee Robbins gave me very good solid basis to consider looking at

some of the data that she had, regarding alcoholism, and she gave me free reign. She said, "Good, you're interested in that. Why don't you talk with me about some of the analyses you might do"? And, in those days we were using IBM counter sorters for our data and she taught me how to do that; she guided me as I analyzed some data and wrote a paper, as a medical student. And, then, when I went to work with George Winokur, he had chosen families that were rich, both in depressive disorder and alcoholism. He was very interested in the depressive disorder and, also, interested in alcoholism, but he wasn't as focused on alcoholism. George Winokur was studying not very highly functional group of families loaded with psychiatric disorders, and alcoholism was running as strongly in these families as any other disorders. I asked him once whether one could tease out whether this familial nature of alcoholism was genetically influenced. George said that it would be a little difficult to do. But there was a paper written by Rudin about this in the early years of the twentieth century. He did it by breaking up families, so, you've got full siblings sharing fifty percent of their genes; you've got half siblings, basically, sharing twenty-five percent of their genes and, then, you can look at, who's got whose genes or what load from father or from mother, and who raised them? And, so, with George's guidance, with Lee Robbins looking over my shoulder and with the help of a guy named, Pitts, I was trying to make sense out of the pattern that was coming up. Dr. Pitts was, also, very helpful to me then in the writing up findings. I started analyzing and published soon after medical school, an article that was a half sibling study of alcoholism. Now, at this time, information was, also, being gathered on genetics in a much more direct way by adopted-away children and that was being done in Scandinavia, because in the United States you couldn't get adoption records. So, if you wanted to separate genetics and environment, you had two choices. One was, you do an adoption study and find children whose biological parents have X, but who were raised by people without X, and the reverse. And, twin studies were another way to do it, which is a little more complicated, but where you look at the level of similarity among identical twins, who share a hundred percent of their genes, compared to fraternal twins that only share fifty percent of their genes, and if a disorder is much more similar in identical twin pairs than in fraternal twin pairs, it, not only, indicates that genes are contributing to the risk, but, also, tell you the proportion of the heritability or the inheritance that's related to genes. The twin studies had, already been published at the time by a guy in Finland and another in Sweeden and they were looking like genetics was important in alcoholism, but

the adopted-away studies by Donald Goodwin, Finny Schulsinger and another fairly large group of people from Washington University and from the Karolinska Institute, had not yet been published as yet.

- AT: What does adopted-away mean?
- MS: You weren't raised by your biological parents, you were adopted. In the two adoption studies, they didn't know who their biological parents were and didn't know anything about their biological parents. That's the best way to do an adoption study. The trouble with the half sibling approach is, that you can't guarantee the kid didn't know that the father, who never raised him, was an alcoholic. You can be in the adoption studies, a little more fancy, and you can say, let's take a look at the number of years the kid was raised by the biological parent with the disorder, and does that correlate with the kid's risk for the disorder?

So, coming back to why I got interested in alcoholism and in genetics was the result of a series of thigs. Lee Robbins got me into a study on alcoholism that was highly interesting. George Winokur got me into a study of families. Even before I graduated medical school, George said, "Well, if you're really interested in genes vs. environment, try this half sibling approach, which is like an adoption study, but easier to get data" and by the time I was a third year resident, I had a paper come out. I had a number of small papers come out asubsequently includig the paper that was related to an adoption type study, using a US sample, where the data was very clear that it was alcoholism in the biological parent that predicted the risk for alcoholism in their offspring, and that the alcoholism in any of the families that raised them didn't seem to be related to the risk for alcoholism. That doesn't say it's not important being raised by an alcoholic or not. It's just saying, it does not have the same impact as of a biological parent. Now, by the time I'm a resident, I got really lucky, because I asked George Winokur, "Would you mind, I just saw this announcement for something called the Hoffheimer Award", if we submit our paper for that? And, he said, "Sure, go ahead". So, I submitted the paper and it won the award.

- AT: That's fantastic.
- MS: So, now, if I'm going to stay in academics, why should I change my field of research?
- AT: At that point, you sort of have to stick with it.
- MS: And, I sticked with the genetics of alcoholism.
- AT: Let me ask you, how was that paper received at the time? How did it overturn traditional understandings about alcoholism? I guess they emphasized the environment much more until you came along.

- MS: By the time our paper was published in the Archives of General Psychiatry, I was building upon Kai's twin work and on a highly flawed adoption type study in the United States in 1948, by a woman named Roe. Then our study was published and the adoption study from Sweden, with Goodwin as the senior author. But, ours was one of the first modern adoption studies in the United States. So, it was part of a picture of many different studies done by different people.that hopefully turned people to, say, yes, it looks like alcoholism is genetically influenced. I, personally, don't think that ours was the most powerful of the papers. I think some of the earlier twin studies done in Scandinavia and I think the larger study done with twin adoption by Goodwin were more important, but it was part of the picture. Now, the next step, if you like, is to say, all right, so it's genetically influenced. You know, environment has to be important because if you don't drink, you don't become an alcoholic. So, alcohol is necessary but not sufficient to cause alcoholism. There must be some environmental stuff out there. And, if you step back from the data and, especially, if you're fortunate enough, like I was, to, also, be a clinician, so I get to see patients and talk to patients, you realize it's not terribly likely everybody inherits the same thing that contributes to alcoholism. After ending my residency, I had to do two years in the military and during that period of time I decided that I don't want to do any more adoption type studies and .there is no real reason for me to get interested in twin studies. I don't have huge numbers of twins available to me. So, where do I take these studies or where do I take these data, next? One of the ideas I had was, that alcoholism must be heterogeneous; there must be different things that contribute to the cause. So, I thought if I want to do a study of what's inherited in alcoholism, then, I need to identify people first who metabolize alcohol totally differently. For example, about fifty percent of Asians; when they drink, they turn red. Some of them, about ten percent of the total, when they drink, they get very sick, couldn't drink at all. They seem to be the only ones who have this flush.
- AT: I have this flush, too.
- MS: Actually, the Caucasian flush is a little different and it's probably a different set of mechanisms. The Asian flush looks like you went outside and you had goggles on and you sat in the sun, in the most intense sun you can think of; you are bright red, often, with kind of white around the eyes. It's really very striking. It can be a gradation of things, but in its' extended form, or its' extreme form, that's pretty much what it looks like.

Now, the second thing, and, actually this comes from studies that I was doing with George Winokur and Jim Halikas, is that there are some people, who seem, from an early age, to be extremely impulsive, often violent, don't do well in school, and commit crimes; almost all of them become alcoholic. But, there's this pre-existing stuff that is probably related to major personality characteristics, high levels of impulsivity or dis-inhibition. In adulthood, it's called antisocial personality disorder, with repetitive criminal acts, violent criminal acts, in the extreme form. I put this aside so, because very few alcoholics have it and it seems also, related to drug dependence and gambling and all sorts of other things.

So, what am I going to study? Falling back on the fact that I was originally interested in I thought that "there's going to be a group of people out there who when they drink alcohol, it makes them feel normal, who don't feel normal, and never felt normal before".

Now, I was done with my two years in the Navy and I was finishing up my residency at the University of California, San Diego Medical School (UCSD), at the medical school where I'm still now. In the Navy and at UCSD, I started to ask groups of alcoholics, tell me what it was like early when you drank, early in your drinking career, and, darned, if most of them didn't say, oh, alcohol didn't affect me very much. I was the designated driver, often. I could drink everybody else under the table. So, I, not knowing which theory would be right, continued a theory related to, maybe there are some other differences in metabolism of alcohol. Maybe there are some differences in personality and maybe there are some differences in the intensity with which alcohol has an effect. And, I put together a study.

There was, actually, a small hiatus. There were three years when I was at the University of Washington after I finished my residency and my two-years in the Navy. It was at the University of Washington where I did all the pilot work for the study. I took a group of people, who were at high risk for alcoholism, children of alcoholics. Looked at their metabolism and personality characteristics and intensity of response to alcohol by taking people only, who were old enough to give informed consent, i.e., eighteen yers or older, and have had some experience with alcohol. I gave them alcohol, studied their metabolism and, also, gave them alcohol and looked at the intensity of response to alcohol. And, we published the findings of the pilot study which showed that children of alcoholics, compared to children of non-alcoholics had a different intensity of response to alcohol. It turned out to be about forty percent of the children of alcoholics seemed to be responding less to

the alcohol. Having those pile of data, moving back to UCSD, we, then, built on that.

Now, eight years have passed, that I started out with kids, roughly, age twenty in San Diego; those kids are now in their late twenties. So I thought why don't we take the next step and find out whether the level of response to alcohol predicts alcoholism and drug dependence? There were 453 guys in this sample that I have accumulated over the years. The women are, also, interesting, but the major population is men. We got all but 4 of the 453 to go through an interview, a urine sample, and blood sample. We also had an interview with somebody about them to tell us their psychiatric, alcohol and drug history, in case these guys are under reporting. The urine samples and the blood samples are for state markers of heavy drinking. That's likely to change if you're drinking six or eight more drinks a day on a regular basis. Having all that information, what we found was that the initial level of response to alcohol, roughly, age twenty in the San Diego sample, was a very powerful predictor of who became alcoholic. It predicted both alcohol abuse and dependence, predicting dependence more strongly than it did abuse. It did not predict marijuana dependence, cocaine dependence, heroin dependence, despite the fact that a Southern California population in the 1970s had a lot of drug use. The sons of alcoholics did show a higher rate of alcoholism than the sons of non-alcoholics and the low level of response to alcohol was an excellent predictor among any of the populations, but, especially, the sons of alcoholics and who became alcoholic and who didn't. There was no difference on psychiatric disorders between the populations and no difference on level of response to alcohol, predicting psychiatric disorders.

- AT: Did you control for women who drank while pregnant? Was that ever an issue?
- MS: Yes. In this kind of talk, where we're just kind of chatting, there's a lot of methodological details that I skipped over, so there may be people, who listen to this tape, who would be very interested in pulling some of the articles, but yours is a very important question. The 453 guys, whom we studied, all had an alcoholic father, no alcoholic mother. We have a small sample that we looked at with an alcoholic mother, but only if the alcoholism in the mother developed after the birth of the child. It didn't matter, father or mother, regarding level of response to alcohol or prediction of alcoholism. But, the majority of the 453 sample that I basically built the study, turned out deliberately to be sons of alcoholic fathers, so that we avoided fetal alcohol effect, at least. In human work, you can

never control everything, so I can't guarantee you that mothers, drinking two or three times a week, one or two drinks per occasion, didn't have an effect. The animal work would not, to me anyway, indicate that that was likely.

- AT: Very interesting.
- MS: So, where do we go from there? Now, I don't want to start another follow up study. It takes a lot of time. It's a lot of effort.
- AT: You're very good at explaining things. Are you a professor? If not, you should be.
- MS: Oh, thank you, yes. I spend a lot of time teaching. I love it. So, now, we're at a point where level of response to alcohol turns to be a good predictor of alcoholism. How do we know whether the level of response is genetically influenced? Well, for that, thank God, I have colleagues, who publish. The University of Colorado has one of the groups, who publish about the importance of genes vs. environment in animal models, regarding various aspects such as sleep time or un-coordination in the animals and sure looks at genetics. In my own samples, as things developed over the years, I'm able to look at level of response to alcohol in people who are related to each other vs. unrelated and it correlates much more strongly in related people than in unrelateds. There's a wonderful work by a guy named Andy Heath and another name, Nick Martin, where they're able to look at level of response to alcohol in identical vs. fraternal twins. So, a little bit of our work, a lot of other people's work is developing fairly convincing evidence that a level of response to alcohol is genetically related. Now, we come to an interesting spot, which is something that I've never dreamed of when I started this study that noow it's even possible to look for the genes that are contributing to the level of response to alcohol. But I'd better not forget the fact that both the level of response to alcohol and the risk of alcoholism are about fifty percent environment and about fifty percent genes. So, I'm trying to look, beginning about twelve years ago, on how the level of response to alcohol and genes that affects it work with the environment in increasing or modifying the risk for alcoholism, while looking for the genes, themselves. And, for that, it's a whole new set of directions. One of the beauties about research and, research in psychopharmacology is an excellent example of this, is if you're in this business and get bored, it's your fault, because every few years along the road, there is this, where do I take the research next? I'm very fortunate to be at UCSD, where there are a lot of really good geneticists and to collaborate with people at University of California San Francisco, the Gallo Institute, where there are some awesome geneticists, and start to search for

genes, related to the level of response to alcohol, as one of the roads I am following. For that, we've used two different approaches, both brand new skills for me. One of the approaches and it something that we're doing now with the group at UCSF. University of California San Francisco, is to say, well, what genes do the animals show that seem to be related to the level of response and, then, are there similar genes in people and can you test a group of individuals, who are clearly high responders and low responders and see if the gene forms differ among them? You take the candidate gene that's developed in the animals. And, you look at the association between that gene form and level of response to alcohol in humans. It's too early in this work for us to say whether we're using that method in a way that's going to bear fruit, but there are a couple of genes, one of which done in collaboration with David Goldman's group at the National Alcohol Institute, and that particular gene is the LA form of the serotonin transporter. In psychopharmacology, a lot of people are interested in the gene forms that affect how rapidly the cell takes up serotonin from the space between cells and that up-take of serotonin into the cells, especially the presynaptic cell, the cell that originally released it, is controlled, in part, by the serotonin transporter. And, the S form of the serotonin transporter is probably very important in anxiety and depression and stress handling. The L form, especially the LA form, our data would say, are related to very rapid uptake of serotonin from the space between cells and seems to be strongly related to the level of response to alcohol. We have one paper that we published with David Goldman's group that shows this relationship between the LA form of the serotonin transporter and the level of response to alcohol and alcoholism in a small, fortyish, sample... Then, we have a replication, which is really an expansion of the earlier sample, which is now in press, that shows the LA form appears to be operating and, then, somebody, Christine Barr, not long ago, published a paper from the National Institutes of Health where, in monkeys, the LA form is related to, both, how much the monkey drinks and related to the intensity of response to alcohol. I don't know how these experients will will turn out. What I do know is how much fun I'm having. And I also know the wondrous people that I'm continuing to work with, who are teaching me more and more about methods.

By the way with the group at the UCSF we are doing, now, a typical linkage study. You look at large numbers of people levels of response to alcohol, this time, using a retrospective questionnaire that they fill out. And, then, you ask the computer to tell you whether there's a particular chromosome or a section of a chromosome, not a particular
gene, that might be related to the level of response to alcohol and you look across large studies to do this. We're also pursuing that and part of that is done with the collaborative study, the genetics of alcoholism. We've published several papers with Kirk Wilcoxson, who's no longer at UCSF..But, let me put that aside a second. Remember, early on, the first person to teach me about research was a sociologist. I never forgot the importance of environment and I know that half the picture of how level of response, as a genetically influenced characteristic, relates to the alcoholism risk. Part of that has got to be how this level of response to alcohol, exposure to alcohol is acting in the context of environmental events. So, we currently have two papers in press right now, where we're doing something that five years ago I'd never heard of, called structural equation modeling in which a variety of things about a person, their family history of alcoholism, their level of response to alcohol, their self report of levels of life stress, how they cope with stress, drinking among peers, expectations or attitudes towards the effects of alcohol, using some examples, are studied. Now, I've got all these balls in the air. I know about John Jones, so there is 150 or 300 John Jones. This is, also, done in women, as well. The computer, now, says, okay, what do you think the model is? How do you think these are all fitting together? The family history affects level of response; family history impacts on alcoholic outcome, but a significant proportion of that relationship goes through level of response to alcohol. That level of response relates to whether you pick heavy drinking peers or not, which would also add to the alcoholism risk and relates to what you would expect alcohol to do. So, we put together a model, a close colleague and I, Tom Smith of how the level of response to alcohol might fit into all these other things that are going on in a person's life. And, then, you test them. You go to the computer and the computer looks it up, looks at how everything is related to everything else, and how each is related to outcome and tells you whether your model makes sense, whether it's functioning. And, the models, that we've chosen, related to many of the variables I've just talked about, appear to be operating and impacting on the level of response to alcohol and how it goes on to alcoholism and it's the clue for us, about things in peoples' lives that we might be able to change, to help prevent alcoholism before it begins. If you know genetically characteristics, such as level of response to alcohol and you know how it's operating, regarding expectations in a specific way the effects of alcohol, for example, or the impact of heavy drinking in peers, you might be able to start modeling prevention programs, based on this whole group of events that seem to be contributing to the alcoholism risk.

- AT: I was going to ask you that question.
- MS: Things going on parallel, the structural equation models and the search for genes, how do they interact? And, what we are starting to do now is to take a look at specific genes that may be or maybe not, contributing to level of response to alcohol. Come back to the equation model; pull out level of response; put in the gene. And, see, people have the gene, don't have the gene, how does that effect how things are in the model? With the hopes that we'll understand more about the specific biological vulnerability and that will help with prevention, we might start to pick up hints about neurochemical approaches that could be useful in treatment to pick up information about the importance of additional variables, such as peer drinking or attitudes towards alcohol and what specific attitudes towards alcohol seem to be most salient here in trying to put together treatment. Now, can we go back and look at, among those people, who happened to enter treatment, did the specific gene form that they have impact on how they responded to a particular medication? Now, we're talking, pie in the sky. Right now, we're just starting to look at those kinds of things, but it could turn out, for example, that we can learn more about who is likely to respond to acamprosate, a new drug just about to be marketed in the US. So, let's try to search for both the genes and the environment, as they're relating to each other and causing the alcoholism risk, and have implications, both, for prevention and for treatment.
- AT: Let me ask you a question that takes you back to something you said at the beginning of our conversation when you were saying that many people suffer from alcoholism and the rates are alarmingly high and I wonder, as we sit here at the ACNP meeting, if you feel that alcoholism has been given its' proper due by psychiatric associations and the larger community?
- MS: What person studying anything doesn't think that they're the stepchildren of their field, and I'm not different. I understand that the lifetime risk for alcoholism in men is at least fifteen percent and in women, eight, maybe ten percent, a disorder that cuts their life short by probably an average of about ten to fifteen years. If you take a look at that information and, then, you look at the other side, what the average physician knows about alcohol or drug dependence when they graduate medical school, how many hours have they had in alcohol and drug dependence you would see the problem. And, if you take a look at the budget of the

National Alcohol Institute, for example, compared to other institutes, you would see that the other institutes have much higher budgets. I don't want to take any money from them, but if you take a look at the field of alcoholism, it is, in many ways, not recognized for the remarkable discipline of the research, the really impressive levels of findings, the great importance, as a public health issue, and the fact that nobody can, basically, function as a professional in the mental health field without knowing a lot about alcohol and drugs. Drugs, of course, are very important, as well. And, that's all historical, happenstance. Whether it'll change or not is beyond my control. All I can say is I'm really happy to be working in that field and I think we are in a field that has dramatic levels of public impact.

- AT: I'm going to push you on this point. If you look at the programs at ACNP or CINP, there's not a lot of intellectual space being devoted to alcoholism. Why is that?
- MS: I don't know. Let me give you some theories and I'm not saying any of these are correct. The same people, who are on the program committee and got the education in their PhD program or their MD program on alcohol or drugs, is the average person out there, so they don't, necessarily, come from institutions that have trained them about how exciting and important alcohol and drugs are, but as they put together programs, they fall back on, and I would, as well, what's most interesting to them. And, I think that has a major contribution. Then, if we were to take a look at, well, at least up until very recent years there hasn't been a tremendous amount of interest or very exciting findings regarding treatment of alcoholism, drug dependence a little better, but not a lot of interest. There are not a lot of corporations out there strongly interested in alcohol or drug treatment. I think that's changing and I think we may see some symposia, not just ACNP, but like American Psychiatric Association and other meetings, of focusing more on alcohol and drug treatment. From the standpoint of the interest of other researchers in the alcohol and drug field, I don't know what's going to happen. I might be overvaluing what it is I'm seeing in the area of alcohol and drug research but I think it's tremendously exciting. But, if I'm not overvaluating it, then, it's going to take training and interest from very early on, during medical school, during a PhD program, of mentors to try and get people into the field and into research and of getting the word out there of how exciting and important this field can be. And, if that is a reflection or a major reason of why there is not more emphasis on alcohol and drugs in many national meetings, it's going to take a while for that to change.

- AT: It's wonderful to interview someone so enthusiastic about his work. Are you going to stick with alcoholism? Do you have any regrets that you went down this path?
- MS: Oh, no, none at all. I have no regrets that I've been in the alcoholism field at all. It's been tremendously fascinating and I have no plans to switch. However, if somebody walked into my office and said, listen, we're really interested that you should switch and study griznip and this terrible disorder that people know almost nothing about is worth studying and we're going to fund you more than you can dream of for the next ten years, I'd say where do I start reading about griznip? Because, what I'm really interested in is, I really love doing research. Alcoholism has given me everything I could possibly ask for. Through my studies in alcoholism, I've learned to do research, as best I can. I've learned epidemiology. I've learned family work. I've learned treatment stuff. I've learned how one asks if something is genetically influenced, how one starts to look for genes, environment, interactions between the two. I am perfectly happy to stay where I am, but I love doing research and I would switch to griznip and find it a great challenge if the opportunity came up.
- AT: That's wonderful. Do you still see patients?
- MS: I do, maybe, three patient hours a week. I am so into my research that it would be somewhat cheating patients. When I'm going for a walk and my mind is wandering about things, it's often coming back to problems in the research that I'm doing, how am I getting around that roadblock? I think that wonderfully skilled dedicated clinicians when they're walking and looking at the birds, their brain is functioning about their patients, so, I don't think I'd be doing my patients a lot of good if I had a large practice. A few, I've got a few gray cells there that can work with that. In addition, I just don't have the time. That is, a research career is time wise, all consuming. It's not that you can say to yourself, or at least I've never been able to say to myself, ah, I've accomplished everything I set out this week. I really have nothing more to do. You just can't do that and, so it becomes tremendously consuming in a way that's just fascinating and not at all intrusive, because my family is more important than my work, but within my work, my research is a very important part of my being. And, I don't really have the time to take on a lot of other patients, but probably about three patient hours a week.
- AT: Are they mainly patients with alcoholism?
- MS: Actually, I love treating people with depression, because they almost all get well and I love treating people with major anxiety disorders, like panic disorder, because they just feel so awful, not that I would ever

wish anyone to feel awful, but I know how well they're going to do. And, so, it's probably equally divided between substance abuse disorders, anxiety and depression and most of my patients are medical students, who come knock on my door or faculty, and, occasionally, somebody else. I, also, run an alcohol and drug treatment program through the university and that is at the San Diego VA Medical Center, which is our major teaching hospital right on our campus. And, I love that, because we constantly have medical students rotating through, psychiatric residents rotating through and all of the more challenging patients are presented to me. I wish the patients were closer, but, at least, observation of clinical cases and how they do over time is available to me.

- AT: An observation, Malcolm X only needed five hours of sleep per night and I'm guessing you're the same. I wouldn't know how you multi task so effectively, otherwise.
- MS: Thank you. I need eight and if I don't get eight for successive nights, my brain doesn't quite work the way it normally should. Oh boy, would I love to be one of those people, who only needed four or five hours of sleep a night.
- AT: I'm afraid a biographer of you will probably grab onto that statement. We know conclusively you need eight hours a night. A couple of final questions and, then, I need to let you go. The DSM, I see that you were on the task force and that's such a controversial diagnostic manual and I wonder what your experiences were on that task force. Tell us what you think about some of the controversies. Does it really explain anything? Do we have too many descriptions of disorders that it's become a useless tool?
- MS: Since the time of the Civil War, it certainly was fairly obvious that you can't have large numbers of people, who are being impaired, without a way of communicating about the level of impairment. So, you need some sort of jargon to be able to pick up what the kinds of cases are you're talking about. Once you become interested in these cases and you want to treat them, you have to have some standardized accepted way of defining this thing so that researcher A and researcher B are studying something that is, at least, overlapping enough to give some possibility of generalization from one study to the other. So, we must have a diagnostic manual, I think. Now, comes the issue of in psychiatry you have a bunch of different kinds of approaches, cognitive behavioral kinds of approaches, psychodynamic kinds of approaches, and they're going to disagree about how to put a diagnostic manual together and they're going to disagree about the optimal way of

defining anything. And, then, you've got other problems. You want your diagnostic approach to be useful in men and women, older people, younger people, people in Thailand, people in Poughkeepsie, so you have to make compromises where things are defined in a broad enough way that clinicians in all these different places can know when they're talking about major depressive disorder or alcohol dependence, this is what you mean. The diagnostic manuals of the American Psychiatric Association's or the World Health Organization's are kind of broad outlines of what this disorder is. It is a compromise of different approaches, each being given the respect they deserve in order to come up with this manual. And, DSM-IV and ICD 10, are both wonderfully useful. They can't be perfect, because there are always compromises of different divisions of mental health research and the need to apply to different cultures, different age groups, etc. So, they're going to be broad. Now, you can't use that for research, very well, and if you want to do research on it, you've got to operationalize all of these things. How long is several weeks or more? What does almost every day mean? What does insomnia mean? You've got to operationalize them. So, the people, who are doing research, I think, should be looking at the DSM's as a political, epidemiological oriented manual that needs to be modified for research and that this manual will never perfectly fit research and clinical needs and will never perfectly fit all the different types of approaches to psychiatry. This is a long-winded response. The DSM's are doing as good as anything like that can do. DSM-V is starting its' planning phase now, as a series of committees. I'm on the committee regarding alcohol and drugs. There's somebody from the WHO on the committee as a Co-Chair with me and, then, there are a broad number of peoples on that committee. Somewhere in four or five years from now, a committee to, actually, write DSM-V is put together. I would advise, nobody will listen to me, but I would advise DSM-V, keep the diagnostic criteria broad, useful, simple, and for clinicians. ACNP, maybe, should put together a diagnostic tool for research, based on DSM-V and try and get the different types of people with different types of background to agree on research definitions. But, I think, DSM is doing as well as it can under the circumstances it is functioning.

- AT: Two more questions and, then, one off the record question. How has psychiatry changed since you entered the field, question one, and, then, question two, what do you think your key contributions have been to psychiatry, at this point?
- MS: How has psychiatry changed? The major thing that I've noticed is, indeed, when I was in medical school and found myself, fortunately,

to be at Washington University St. Louis, I was part of a minority of people thinking and taught that you can define psychiatric disorders, that you can predict clinical course, that you can select treatments, based on data rather than opinion. The rest of psychiatry didn't seem to be in that direction and that's changed. Now, psychoanalysis, for example, has an important role, but not the major role, in psychiatry and the importance of focusing on the best diagnosis that you can come up with and the appropriate use of psychopharmacology help with the other approaches of psychiatry. The core of what your approaches are in treatment; that's all changed dramatically since I entered medical school in 1964. It's just changed dramatically. And, I think it's been a good change, and it's is not that psychoanalysis, shouldn't be there, but I think that, considering the fact that there are a lot of people out there who need help, that the time we're allowed to spend with patients is somewhat limited, this data based structured approach is a very good direction for psychiatry to have gone. A second major change has been the remarkable scope of enhanced knowledge that we have of brain neurochemistry and of brain electrophysiology and overall brain functioning. Yet, there is so much to be learned that those of us doing research in this field we're never going to get bored, because there is so much out there still to learn.

- AT: What do you see your key contributions to the field as being?
- MS: I hope I've helped people to recognize that alcohol and drug dependency are terribly important clinical conditions. Obviously, I haven't had as much of an impact as I would like, but I hope that I've helped to, in one way among many other people, to get the information about alcohol and drugs out there to clinicians and to other researchers. I hope I could be considered as part of the cadre of people, who are able to say, this disorder can, not only be crisply defined, but it looks like it's genetically influenced and convince people, who come in with an open mind, that there's a genetic influence here. I hope that I've been able to add to the understanding of the heterogeneity of the genetic risk for alcoholism. It's not one characteristic that's inherited. It's many different ones that are inherited. And, that the intensity with which one responds to alcohol is part of that picture and is, itself, genetically influenced. Well, I hope that if you and I meet again in a few years, I'll be able to say to you that I am now able to tell families of alcoholics and clinicians and other researchers specific genes that contribute, and some clues as to what it is that we might be able to do in prevention and to enhance treatment. I'm very fortunate to have stumbled into this area. I'm very fortunate that the areas of research that I've been following have been productive

and I don't kid myself, I am one of many different people, who are following similar lines of research and I think, together as a whole, we add, I think, a significant amount. Any one of us, individually, adds a bit.

- AT: Is there anything you would like to add?
- MS: No, just what a nice thing you're doing. This was great fun.
- AT: Thank you.

CHARLES R. SCHUSTER

Interviewed by Thomas A. Ban Acapulco, Mexico, December 13, 1999

- TB: We are at the 38th t Annual Meeting of the American College of Neuropsychopharmacology at the Acapulco Princess in Acapulco, Mexico. It is December 13, 1999, and I will be interviewing Dr. Charles Schuster* for the Archives of the American College of Neuropsychopharmacology. I am Thomas Ban. Can we begin with where you were born and when? If you could say something about your family, educational background and, then, we move on from that.
- CS: Well, I was born in 1930 in Woodbury, New Jersey. My mother and father were both, I would say, very inquisitive, intellectually inquisitive people. My mother was a musician and influenced me very, very much in my early career choice to become a musician. On the other hand, my father had been in the medical corps in the first World War and when he got out, he decided that he wanted to go into some branch of medicine, but he became very intrigued with a branch of medicine, at that time, which was called Naturopathy, which interestingly enough espouses principles, which we today would call Holistic Medicine or Preventative Medicine. As a child, for example, I never had candy until I went to school, because it was not in my home. We had very little salt. We had a variety of dietary restrictions, which were based upon principles of health, and I think, probably, have served me well, because I'm probably much healthier because of it. My father got out of that profession for a variety of reasons, not the least of it for which it was nice, financially, and went back into his family business, which was in the food business. But, I was very much influenced by his interest in health issues and his interest in the relationship of diet and lifestyle, etc., to health. Well, my mother was, as I said, a music teacher and a musician and I began, by the age of 5, to play trumpet. I had an older sister, who was seven years older than I am, and by the time I was 10 or 11, she was 17 or 18, and going to a college in the area. My sister was a very beautiful young woman, who wrote poetry and liked jazz, and a lot of the jazz musicians, who would come to Philadelphia and the Camden area where I was living, were very interested in her, because she was a very attractive and she would invite them to come to our house on Saturday afternoon. We had, of course, a large grand piano because my mother was a music teacher and some of the top jazz stars of the 1940's, came to my home on Saturday afternoon and would play. Well, I was a little

^{*} Charles R. Schuster was born in Woodbury, New Jersey in 1930. Schuster died in 2011.

kid. I was 12, and they would say, oh, you've got a trumpet there, why don't you play with us? So, I started playing with some very noteworthy people at a very early age and I'd been studying trumpet since I was five, so, you know, I could play. I started playing in nightclubs by the time I was 13, and didn't spend a heck of a lot of time on my high school studies. I will be honest about that. I spent more time playing jazz in nightclubs and continued to do that throughout high school and, as a consequence of that, I couldn't get into a very good college. So I went to a local community college and continued to play jazz until I was about 18, at which time I became very frightened, because many of the young musicians that I had grown up with and was working with had passed beyond smoking marijuana and had started to inject heroin. Frankly, it scared me to death and I retired essentially, from the music business at about the age of 18 or 19, because I could not see myself going down that pathway.

- TB: What did you do after that?
- CS: I, then, began to get a little bit more serious about school and got through my community college with sufficiently good grades and I was able to get into Gettysburg College, which I graduated from in 1951. My sister had gone to college and she was interested in Psychology and, so, when I started college I found Psychology to be, not only of interest, but, perhaps, easier for me, because she had taught me a lot about it and, so, I just gravitated into studying, both Psychology and Biology in my college career. When I got out of college, which would have been in 1951, my sister was married and she was married to a great guy, who had just gotten out of the Marine Corps, and I thought, boy, wouldn't it be neat if I could follow his career? I'm going to enlist in the marines. Well, I went over and, you have to understand in 1951, if you didn't enlist in the Marine Corps you would be drafted in the Army. So, I decided I would enlist in the Marine Corps and I went through all the physicals, was accepted directly into becoming an officer, because I had a Bachelor's Degree from Gettysburg College, and it was then that they discovered that they had not done a dental exam on me, so I went through the dental exam and I was missing one molar on one side and they said, sorry, but you cannot become a Marine Corps officer unless you are physically perfect and missing one tooth disgualifies you. So, there I was, I was not going into the Marine Corps. I hadn't made plans for graduate school, but I knew someone who was going out to the University of New Mexico where they had a Master's Degree program in Psychology and I decided that, well, maybe they will take me and I called up and I talked to the Chairman of the department and I guess I must

have convinced him that I should go there and he, fortunately, admitted me, even though I hadn't gone through all the usual procedures. So, I went to the University of New Mexico, and entered their graduate program. I had teacher by the name of George Maxwell Peterson and nobody that I know of could have made the neuroanatomy and neurophysiology of the central nervous system more exciting than he did. He did rat studies in terms of how cortical lesions would affect various complex performances like maze performances and I decided, well. you know, that's what I will do and for my Master's thesis, I severed the corpus callosum in rats and looked at a variety of tasks, including tasks of handadnes. One of the other interests that Dr. Peterson had was in the cortical region that controlled handadness and he'd shown, many years before that the destruction of as little as 3 percent of the cerebral cortex on the dominant side in the right region could convert a right handed rat to an ambidextrous rat. Well, he wondered whether or not if we severed the corpus callosum that would have an impact on the dominance that was expressed through handadness, so, I did that. Frankly, I didn't find anything. I cut the largest fiber track in the central nervous system and the rats still learned the mazes well. They did all of the handadness studies, the same as before they had in corpus callosi transected rats So, I really didn't find anything very important about this, but I did learn how to do research from him and how to analyze data and so forth and I'm very indebted to him for that experience. Of course, many years later, people who are a lot smarter than I was came along and did studies where they covered the eye of an animal and after they had transected corpus callosum showed that they were, essentially, learning with one half their brain and not the other half. But I wasn't smart enough to have done those studies.

- TB: What did you do after you got your degree?
- CS: Well, I left the University of New Mexico to enlist in the Air Force to do research. I had a Master's Degree in Psychology and they were taking people directly into officer's training to do Psychological research.

Well, something that I haven't mentioned was that while I was at the University of New Mexico I had been involved in an activity that, at that time, was fairly novel; I had played with a lot of African American musicians and it turned out that when I got to Albuquerque, it was segregated, and we could not eat together in the town with many of my black friends on campus, who were fellow graduate students. We could eat together on campus, but things were strictly segregated and, so, I began working with a group of people, who were working on getting an anti-segregation ordinance passed through the city and we were successful in doing that. It was one of the first anti-segregation ordinances passes in the United States.

TB: What year was that?

CS: This would have been in 1950, the first year I was in graduate school. We enlisted the aid of people from CORE and from other African American organizations to come there and we had civil disobedience. We would sit in the Rexall Drug Store at lunchtime with 10 white individuals and 1 black and if they wouldn't serve him, we wouldn't leave the scene and they would have to get the police and escort us out. And we created a lot of civil disobedience to bring attention to this. We also organized a national boycott of some of these stores, which were in Albuquerque, that were part of a chain. Some of the leaders of this organization that I was working with were known card carrying Communists and this was the McCarthy era. So, after I enlisted into the Air Force, they never called me up, because I found out subsequently, that I was declared a security risk because of the fact that some of the people involved in this activity of getting this anti-segregation ordinance passed were Communists and the Air Force, I presume, was afraid to call me up, because, I had told them about this when I went and had my interviews, because I was not hiding anything and I was not and I never had been a Communist. But, I had worked with these people, and they were devoted to getting this anti-segregation ordinance through, and so was I. To make a very long story short, I had made no plans to go past my Master's Degree at that moment. I was going into the Air Force. By that time, I was married. I had a child and, suddenly, the Air Force didn't call me up, so I came back to the East Coast, which is where my family was, and I looked around for various kinds of jobs. I was very fortunate to get a job at Temple Medical School as an assistant instructor in Endocrine Biology. Well, I'll be honest, I didn't know very much about Endocrine Biology, but they needed someone, essentially, to be a glorified technician to do bioassay procedures and I was familiar with operative procedures in small animals because of my training and my Master's Degree. So, I went to work at Temple Medical School in 1953, and I did all of what were, the bioassays. We had to ovariectomize mice and, then, inject them with urine extracts from women in which the estrogen had been extracted and, then, you would look for the presence of quantified epithelial cells in a vaginal smear, which was the indication that estrogen had been secreted. Anyway, I learned a lot about surgery in mose. In the second year I was there, they had a visiting scientist from Israel, whose name was Bernhard Zondek, and Bernhard Zondek was the father of the Ascheim-Zondek pregnancy test, a verv

revered endocrinologist, who had moved from Germany to Israel, and he came to Temple to spend a year, teaching and so forth. Well, I was assigned to be his research assistant. I had a great deal of respect for Dr. Zondek, he was a superb clinician, but I will say, in all candor that his science left something to be desired. One of the first things I was charged with doing was to do some research with rabbits with him and we would, again, be doing vaginal smears, looking for guantified epithelial cells and I would get these things and I'd look at them under the microscope and I would say, oh, you see, there's some quantified epithelial cells. No, no, no, he would say. So the next day I'd bring them back and they were not labeled the same way and I would find that he changed his opinion. I don't know what was going wrong there, but, anyway, I got the privilege of working with him and he said to me, ah, my boy, your future is assured, you worked with Bernhard Zondek. Well, about that time, Smith, Kline and French Laboratories, which was in Philadelphia, a little ways away from Temple Medical School, but on the same subway line, advertised for a research assistant, somebody with some training in Psychology, and I said, ooh, I'm going to go look there, because that'll pay a lot better than Temple Medical School that was paying me \$212 a month at the time and in 1953, even then, that was not a lot of money when you were married and had a child. So, I went to this job and it turned out that they wanted someone to be the assistant for a person by the name of Donald Bullock.

- TB: What year was that?
- CS: I can't tell you the exact year, but I worked at Temple for three years, this would have been 1956, approximately, and Smith, Kline and French had, of course, obtained Thorazine (chlorpromazine) from Rhone-Poulanc by then and decided that this was such a blockbuster that they wanted to get someone who could screen for them other psychoactive agents that might have therapeutic benefit. They didn't know how to do this, and nobody knew how to do this, and this psychologist, Don Bullock, who was trained at Columbia University, and had been working at the University of Buffalo, but was paralyzed from the waist on down from polio, sold them the idea of setting up a lab for him so that he could test their compounds in a variety of different animal types of procedures to see whether or not they had psychoactive properties.
- TB: Wasn't Len Cook there at the time?
- CS: Well, Len Cook was there. He was the head of the unit and he was using a classical avoidance procedure for screening of chlorpromazine like drugs, but we wanted to diversify from that, so Don Bullock needed an assistant. He was not hired, incidentally by Smith, Kline and French,

because he was a Psychologist. They gave him a grant and a dog room in the back of the laboratory and that's where I was hired to come and be his assistant. And I learned a great deal about, what we now call, Skinnerian psychology or operant conditioning, because that was Bullock's background and his training. I worked there for six months with him and one Friday afternoon, he was summoned to a meeting and came back and said, "Bob, pack my things", and I said "what do you mean"? And, he said "well, I've got to be out of here by 5:00 o'clock". Well, Don had a temper and would speak up at meetings about what he thought were stupid things that certain other people in the company were doing and, so, they decided that they were not going to renew his grant, and, rather than keeping him around any longer, they said, he had to depart. So, here I'd had six months crash training in operant conditioning and psychopharmacology and my job, I thought was over. So, I helped him pack up and helped him get all of his stuff out and to his car. He drove a car, a special car for someone who didn't have use of their legs, and he went on his way. Monday morning came. I came into the lab and I was sitting there and I wasn't doing anything. Then, E. J. Fellows, the director of Biological Sciences came past and said "well what's going on; why aren't you working"? I said "well, you know, my boss got fired on Friday", and he said, "well, you're in charge now". Well, Len Cook became very interested in the lab and we worked together. I had two consultants, Carl Prebome, who was, of course, a psychiatrist and had done a lot of research on brain function, and a psychologist, by the name of Charles Furster, who was an expert in pperant conditioning and the principles of Skinnerian Psychology. So, for the next two years, I ran this lab, developed new behavioral assays and screened compounds for Smith, Kline and French. And the company started to expand. We got technicians and, suddenly, the board of directors said, wait a minute, who is is in charge of that program and when they said, Mr. Schuster, they said, we've to get somebody in there, with a PhD. And, they decided to get a person with a doctorate, so that was Roger Kelleher, who is now deceased.

- TB: When did you go back to school to get your PhD?
- CS: Well, I decided that I would go back to school at that point and get my doctorate. That year, Joe Brady had been the lecturer and he came to Temple Medical School and gave his talk on the Executive Monkey who had to made decision all the time vs. a yoked control, who did not. The monkey, who had to make the decision, had to decide when to respond and when not to respond in order to avoid an electric shock. The monkey over here got the electric shocks if the executive monkey

didn't behave properly, so they were equated in terms of shocks, but, at that time, Joe reported that the executive monkey, who had to work 24 hours a day doing all these things to avoid shock, developed ulcers, whereas, the monkey, who received just as many shocks but didn't have to worry, didn't have a responsibility, didn't get ulcers. So he was giving this lecture and I went to hear it and when I told him that I wanted to go back to school he said, well, do you know something about Psychopharmacology? And, I said, yes, and he said, well, we just got a grant at the University of Maryland to set up a Psychopharmacology laboratory. Why don't you come down there and I will pay you as an Instructor, because you know something and you can finish up your doctorate at the same time while helping us set up this lab? So, I went to the University of Maryland, then, around 1958, and helped them set up one of the first academic Psychopharmacology labs. It was in an old abandoned Army building and it was a great place. There were a number of people there, who went on to do important things. Pete Grossman was a student there, who wrote a textbook on Physiological Psychology, later, and, many people went through this lab.

- TB: Could you say something more about the work you did with Joe Brady?
- CS: Well, Joe Brady was a fascinating guy and I'm sure, probably, will be interviewed for ACNP History, but Joe was, not only a Professor at the University of Maryland, he was also a Colonel in the Army over at Walter Reed Army Institute of Research. So, he could go back and forth between these two, and he had all of these draftees, who were PhD psychologists, and he could get them assigned to Walter Reed. So, Walter Reed was a real hot bed of intellectual activity, and as I said before he had this new Psychopharm laboratory over at the University of Maryland. Well, students at the University of Maryland could go over to Walter Reed and do things over there and vice versa. So, I went over to Walter Reed and there was an endocrinologist there by the name of Jim Mason, who had Rhesus monkeys, who were catheterized in their jugular veins in order to be able to remove blood repeatedly so that he wouldn't have to go in and hassle with them and stress them. He was trying to study hormones, and if he had to go in and wrestle with them to get a blood sample by venous-puncture that would have stressed them and it might have changed the hormonal picture. So he put these catheters in permanently and, the monkeys could run around their cage when they weren't in the study, but when they were in the study, he could put them into a chair, hook up a line from another room and had a direct access to the venous blood supply of the monkey. And, I looked at this and I said, wait a minute, if he can take stuff out, I

can put things in. My experience as a young jazz musician came back to me and that is, those guys were always main-lining heroin and mainlining other drugs, putting them into their venous system. I was trained as an operant psychologist and I wondered whether or not if we put a drug into that, we can train an animal to perform some type of behavioral response in order to get that drug. And that began my career in drug abuse a field that I've been with ever since, which is now almost 40 years. I was very lucky to have been in a situation where I could learn how to do this type of catheterization from Jim Mason and the people at Walter Reed. We got monkeys and we did the surgery over at Walter Reed, transfer them back over to the University of Maryland, and we began to study whether or not if we had a drug in a syringe and we made the syringe active if the animal pressed the lever, whether or not they would press the lever in order to get a drug. And it turned out that after a number of false starts and playing around that we were able to show that animals, Rhesus monkeys, would work for the same drugs that people abuse and, drugs that people found neutral, the monkeys found neutral, and, drugs that people find diversive, the animals would actually learn to perform a response to avoid getting the injection of those drugs. So, it appeared as if the animals would find to be positively reinforcing the same drugs that people got in trouble with. At the same time as I made these discoveries there were other people, who were also doing smilar work. It was sort of a Zeitgeist phenomenon. Everything was coming together. The Department of PhramacologySo, at the University of Michigan, was run at the time by a very famous harmacologist, by the name of Maurice Seevers...

- TB: Wasn't Seevers one of the early researchers in the drug abuse field?
- CS: Dr. Seevers had been in the area of drug abuse research since the late 1920s and ran a department that had a heavy investment in drug abuse research. They had developed a similar technique to the one that we developed at the University of Maryland.and when I began first doing these studies I had the audacity to write to Dr. Seevers and say, we want to find out whether or not animals will self-administer morphine. Could you please tell me what dose of the drug to use? And, I love this, he wrote back and said, if you have to ask that question, you shouldn't be doing these studies. Go to the library; look it up. I mean, do your own. Well, obviously, it was a naive question on my part. A couple of years later, after a meeting, at which he and I was giving a report on my research on this, he said to one of his young faculty members, go on and recruit that guy to come to the University of Michigan. And I did. I went to the University of Michigan in 1962, after

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I got my PhD from Maryland and was doing the type of research, this drug self-administration research that I've been describing. I'd gotten a grant from NIMH and I remember it was a grant for \$26,000.00 that paid my salary and for all the monkeys, paid for all the equipment, paid for all the research, maybe, even a half technician or something. So, I went to the University of Michigan in '62 as an assistant professor of Pharmacology. I was not a well trained pharmacologist at that point, but, suddenly I was in a Department of Pharmacology, and I had to be in charge of a lab and do heart/lung preparations, stop/flow kidney preparations, etc. Well, here I was a psychologist with some training in Biology. I was not a pharmacologist, but over the next 6 or 7 years I learned a lot about Pharmacology. The other thing that took place was that you had to attend every single pharmacology lecture. All the faculty in the department sat at the rear of the auditorium that the medical students were in and after the lecture was over, all the faculty would go for coffee and we would discuss the pros and cons of the lecture that had been given that day. So, when it was my turn to lecture about psychoactive drugs, being a non pharmacologist, I felt very much on the spot and I probably worked much harder than many of the rest of them, because I was intimidated, but got by. About that time, I decided that there was no textbook in, what we call, Behavioral Pharmacology and one of my old friends from the University of Maryland, who had gone to the University of Minnesota, and I got together and we wrote the first textbook in Behavioral Pharmacology, which was Thompson and Schuster's Textbook. It did pretty well and I'm still very, very proud of that book, because I think it was important, in terms of helping to get people with an interest in behavior aware of the fact that you could learn a lot about behavior from pharmacological probes and we could learn a lot about how drugs effect behavior by using sound and sophisticated behavioral procedures and that's what we stressed in that textbook.

- TB: What year was your textbook published?
- CS: The textbook was published in the early 1960's. I think it was about 1963.
- TB: 1963.
- CS: It was probably a little later. I'm sorry. It would have been '64 or '65. I stayed at the University of Michigan and, as I said, learned a lot about Pharmacology while continued my research in drug self-administration. I worked there with Jim Woods, who is, of course, a member of ACNP, and one of the foremost psychopharmacologists working in the opiate pharmacology area. Jim was originally my technician there and he had finished everything, but hadn't written up his dissertation. So,

I kept bugging him to do it, and he didn't get around to doing until I announced that I was going to leave. I was going to leave, because a guy by the name of Jerry Jaffe, Jerome Jaffe, was one of a really smart young psychiatrists, pharmacologist, had been recruited by the University of Chicago in the state of Illinois to set up the first monomodality drug abuse treatment program in the US. It was called the Illinois Drug Abuse Program. It was centered at the University of Chicago, but had clinics and facilities all over the state. Well, for some reason, he was intrigued with the research I did and; although, I did monkey research and rat research and pigeon research, he said, come on over and become associate administrator and do human research in the area of drug abuse. I said, wow, that's neat. That's a real challenge.

- TB: What year was that?
- CS: I went to the University of Chicago in about 1967 or '68. I say, '67 or '68, because I stayed half time at Michigan for a year and half time at the University of Chicago, because I had graduate students, who were finishing up at the University of Michigan. Finally I got over there and was in the Department of Psychiatry and Pharmacology at the University of Chicago. At that time, the Chairman of that department was Danny Freedman, who was just an absolute delight and a source of great intellectual stimulation to me and everyone in the department. When I got over there I started to do human research. But I also hungered to set up an animal research laboratory, as well, because there were many questions that I wanted to ask that I couldn't answer in humans because of ethical and considerations. So, I wanted to have a situation in which I could do human research and animal research, as well. And, so, I was fortunate to be able to set up a large animal laboratory, while at the same time. I was able to conduct human research in the clinics that we had for the Illinois Drug Abuse Program. We did some of the first studies with a maintenance medication for the treatment of opiate addiction, back then.
- TB: What was the drug?
- CS: It was LAAM, or L- α acetyl methadol. Jerry Jaffe got a call from a psychiatrist on the West Coast, who said, you know, I've got a bottle of this stuff, called L- α -acetyl methadol, and Fraser had studied this at the Addiction Research Center in Lexington, Kentucky, years before, and shown that it has the action of a very long acting opiate. It was a Merck compound and originally when they put it out for the treatment of cancer pain, they ran into some overdosage problem, because they didn't realize that one dose would last for two days. So, they gave cumulative doses and dropped the drug when after they ran into a few death. Well,

we got this bottle of L- α acetyl methadol, which at this point was 15 years old, so Jerry said, hey, we should try this on a couple of methadone patients and if it's really long acting, maybe we can use it instead of methadone and we will only have to dose them every couple of days instead of every day. So, the first thing we had to do was to decide whether this drug in this bottle was still good. So, I went to Christian Ikizdere, who was the chemist for the IDAP program, and he said, well, give me some. He ran it and a thin layer of chromatography came out with one spot, so, he said, okay, it is fine for humans. Now, that one spot could have been something other than LAAM, but we said, okay, it's going to be okay. Well, we didn't know exactly what dose, but we were conservative, so I called up the local methadone clinic and I talked to Ed Washington, who was the person who ran it, and I said, send me over 4 people, who are willing participate in an experiment, and he sent over 4 people. Well, I thought to myself, I will explain to them what we were going to do, that we are going to give them a new medication that we thought might be as good as methadone, but it might last longer, and they said, okay, and they will say we'll participate in this. Now, you have to bear in mind, there was no human investigations committee at the time; there was no nothing about passing any ethics test, etc. We knew very little about this compound, but we knew that it had been given to humans and we knew the right dose, approximately. But, I said to myself, OK, let's not do this quite yet. In our methadone clinics, we gave out methadone in different flavored Kool-Aid. We had clinics that were labeled like Rooting Tooting Raspberry Clinic, because that was the flavor of Kool-Aid. We had Lefty Lemon. That was another clinic. So, these guys came from a Raspberry Clinic and I decided to give them their methadone that day, but I changed it to Lefty Lemon, not in their usual Raspberry, but I didn't tell them that. All I can say is that I am very fortunate that I did not give them LAAM because if I had we wouldn't have L- α acetyl methadol on the market today, because within 30 minutes after I gave them their regular dose of methadone, but in a different vehicle, a lot of them had hysterical paralysis in the legs. I didn't know it was hysterical paralysis. They couldn't walk. One developed a panic state and two of them were fine. Well, if I had given them the new medication at that point, I can assure you I would have never given anybody else this, because what was essentially a placebo intervention, the thought that they had received new medication instead of methadone was sufficient to produce these responses. So, I called up Ed Washington and I said, hey, you know, don't send over any of those crazy people that are going to react to this kind of thing; I need

some stable people. So, he sent over some more people and we began to do research, then, with L- α acetyl methadol.

- TB: When did this happen? Was this in the '70s?
- CS: That was in the early 1970's and LAAM was only marketed, I believe, in 1993, which tells you something about drug development when there's not a large market for it, as there isn't for treatment for the heroin addiction. So, it was about that time that I was admitted into the American College of Neuropsychopharmacology. Let me go back just a moment to reflect about my first trip to ACNP.
- TB: When was that?
- CS: That was actually back when I was at the University of Michigan in the '60s, and I was coming down, at that point, to a meeting that was being held in Puerto Rico, but not at the Caribe Hilton where most of the meetings are held that I've gone to since then, but it was in another, hotel, at the Sheraton probably. I had never been to ACNP before and I was coming to give a talk on opiate pharmacology. My co-author was a very eminent young guy by the name Julian Burreal, who was an MD, PhD pharmacologist, and an absolutely delightful scholar. He was the co-author, but he didn't get to go on the trip. They would only pay for one of us, so I boarded the plane with my slides and with my paper. I got to Miami and had to transfer planes to go to Puerto Rico and after Isat down in the seat, the gentleman next to me started talking to me and he asked, what are you going to Puerto Rico for? And, when I told him, he said, well, that's where I was going. And, I told him, fantastic. He said, my name is Bill Krivoy and I do opiate pharmacology research. And, I said, oh, well, I'm giving a paper on opiate pharmacology. He said I guess you've reviewed all my work and I thought, no, I haven't, no, what am I getting myself in for here? Well, it turned out that Dr. Krivoy had done some excellent work on spinal function with opiates and spinal reflexes, but that was not the thrust of my talk. But I was scared to death, because, here I am going to this meeting with all these preeminent people and the guy sitting next to me says, you must be quoting all of my work, and his name is not in the list of my references. Well, I got there and I gave the talk and got through it and he was in the audience, but he didn't say anything, but it was my first experience. And, one of the things that for me the most impressive about the meeting was the fact that there were not only pharmacological researchers such as I was and people with an interest in psychology, but there were clinicians. There was a complete mix of people and, so, they asked questions that were very different than if I'd gone to an ASPET meeting, because they asked about clinical relevance for things that I was

doing in animals. And I think that's one of the things that turned me on about ACNP from the very start; the mixture of disciplines, which were brought together, and the kind of people that one was privileged to meet so you got asked questions that you wouldn't get asked, ordinarily., And, I wasn't necessarily able to answer them, but I went home thinking about them and they may have become some of the impetus for the next research that I did.

- TB: At the University of Chicago?
- CS: Well, let me just say that I continued, at the University of Chicago to do research. I actually left the Illinois Drug Abuse Program for a couple of reasons. I was interested in treatment and treatment research, but at that time there was some real constraints about being able to do things within the context of a state managed program, in terms of changing things or doing studies where you would have a control group. When Jerry Jaffe and I first started the program, we had this, what now is, obviously, a very naive kind of concept that we were going to bring heroin addicts in, because the problem that they were interested in at that point was heroin addiction, and we were going to randomly assign them to, either a therapeutic community, to methadone, to detoxification followed by after care counseling, or to a waiting list control group. Well, the first thing that happened, I got the names of the first people and started to do this, was that my secretary said, I won't type this list, because you've got a waiting list control group in there and it's unethical; you can't let just people, who want to come into treatment, stay on the street for awhile. And, I can say, we really have never had a control group of that sort in the area of methadone maintenance. Although, there's no question, through a variety of other studies, we've established the efficacy of methadone, but without having a no treatment control. So, we didn't have that. The next thing we discovered, you can't randomly assign people to grossly different kinds of therapies. Fifty five year old heroin addicts, when we assigned them to a therapeutic community and they were told, you're going to have to grow up all over again; we're going to reduce you to being an infant and you're going to have to learn responsibility and grow up, came back to us, said, are you nuts that I'going to go and spend a year in that place? No. It was not appropriate for these older heroin addicts and, so, we gradually learned that we could not randomly assign people to all of these diverse kinds of areas, but we did begin to do a few studies. I decided that I would, rather than doing treatment research at that time, I would rather leave the IDAP program and go into laboratory research in, both, animals and humans. And, so, we founded the Drug Abuse

Research Center at the University of Chicago and we were able to get NIMH funding and, then, subsequently, NIDA funding for supporting this. And, in the laboratory, at that time, were some important people, who are members of ACNP, one of whom also happens to be my wife and that is Dr. Chris-Ellen Johanson, who was a Fellow this Society and was a graduate student at the University of Chicago and did research in the primate laboratory there. Dr. Marian Fischman was also a Fellow in this Socieity, who first did animal research, looking at the neurotoxicity of methamphetamine, a topic that we're going to discuss here in 1999, tomorrow night. I'm part of a panel to discuss that, and many, many other people, but those are just two of the people that popped to mind. Both of them went from doing primate research to doing human research. Dr. Fischman started doing human research with me at the University of Chicago at a time when cocaine started to be a drug that came to prominence in the United States. When we looked at the data and saw that there had really been no human studies done, essentially since Sigmund Freud had done studies, using himself as experimental subject, we decided that it might be time for us to do some human research with cocaine. Well, to say that we ran into some obstacles is to put it a little bit mildly.

- TB: What kind of obstacles?
- CS: The first thing was, the FDA said, well, if you're going to use people to do human cocaine research, you have to screen them and establish that they've been using cocaine three to four times a day, every day, for the past three months. Well, that was not the way cocaine was used at that time. It was used in binges and guit. So, we, then, had to a small epidemiological study to show the binge pattern of cocaine use, rather than the fact that it was like heroin taken regularly every day. We came back to the FDA and were able to show them that this was not the pattern of use of cocaine and that we needed to bring people in who used it in a binge fashion. There was also great concern because cocaine is not only a psychoactive agent, but also has local anesthetic properties, that it would cause a conduction block in the heart and many of my MD colleagues and many of the fathers in drug abuse research said, oh, boy, you're really stepping in dangerous grounds to use cocaine in humans, because it may ice them, that is, cause this conduction block in the heart. And, I said to them, well, you know, I've been doing Rhesus monkey research, now for 15 years with cocaine and I've never seen an untoward death that was not dose related. I told them that I've never seen anything at moderate doses, and that we're very conservative and we will be not putting anyone at great risk. We, obviously,

got cardiologists to be involved in this research and Dr. Fischman and I began to do this. The first thing was, we had to get the Provost to sign off on the grant and I remember him saying this to me, "Schuster, if you hurt somebody with this research, your career is ended". And I said "well, you know, I think it is very vitally important research". I think that the animal research that we've done for the past number of years indicates we can do this and I can say that we've been doing cocaine research for somem time now and we have never run into any really adverse events that were life threatening to individuals. So, my only point here is that we began to do, what I think was very important laboratory human research there and that is something that I continue to do today.

- TB: When did you move to NIDA?
- CS: In 1986, at sort of the peak of my career at the University of Chicago, I got a call from some people in the Federal Government, saying that there was position open, the Directorship of the National Institute on Drug Abuse, and I said, are you kidding? Everybody knows that first of all, I was declared a security risk back in the McCarthy era, everybody knows that I was a young jazz musician because I've openly discussed this and that I'd smoked marijuana, and above all of these things I'm a known card carrying Democrat and this is a Republican administration. They said, well, come down and interview for this, anyway. So, I went down to Washington and I interviewed for the job, and I can tell you, there was a member of the Parents movement there. The Parents movement was very active at that time and continues to be active in terms of Drug Abuse Prevention and one of the people, on that committee was Shirley Colletti from Florida. She started prevention programs, treatment programs and has done a dynamite job down there. She was on this committee and when I walked out, for whatever reason, she said, that's the person that we want to be the director of NIDA, and she was persuasive. And, so, I left my position at the University of Chicago in 1986, and went to the National Institute on Drug Abuse as the Director of the Institute. I knew NIDA a little bit, because I'd been on study sections and I had been there as a consultant to them on many occasions, but there's nothing like walking into the director's office and realizing that, suddenly, you're in control, so to speak. I found out how little control, maybe, you have after awhile, but, theoretically, you're in control of the major institution in the world that provided funding and direction for drug abuse research. At the time I went there, the budget was 85 million dollars a year and that was an astronomical amount of

money, but I was there a short while and things began to happen. A basketball player at the University of Maryland died of an over-dosage.

- TB: Who was the player?
- CS: His name was Len Bias and he hit the newspapers. He had been signed to the professional NBA at an astronomical amount of money, because he was an incredible basketball player. Obviously, clearly a healthy physical specimen and he had overdosed on cocaine and died and newspaper headlines went out, like all over the country, about this. Congress just became possessed with the idea of cocaine and the horror that it presented to us. At the same time, it was being established that HIV infection in AIDS was being transmitted by drug abusers, who were sharing needles, particularly in New York City where the rates of HIV infection were escalating. So, in the next six years that I was at the National Institute on Drug Abuse, the budget went from 85 million to over 400 million, because of the incredible public clamor for doing something about the problem of cocaine addiction and doing something about the problem the spread of HIV infection amongst those, who are using illicit drugs, particularly by the IV route. It was an incredible experience to be in Washington at that period of time and to have a role in attempting to develop a research base for trying to help those, who were out in the community, trying to deal with the reality of these problems, and that is cocaine use and spread of HIV infection through dirty needles. I can say that there were a variety of very positive things that happened, in terms of the government, at that time. Now, you have to understand that as an institute director, I could not lobby Congress for money for my institute. That was against the rules. You can't do that. You could be dismissed for lobbying Congress, directly, for money. And I was breaking the rules. What happened was that I was told that a person, named Mr. Conti wanted to put about a 10 to 15 tmillion dollar proposal into the NIDA but he wanted his name on it and I said, fine. I was, that day, in New York City and listening to the AIDS statistics. And by the time I got back to my hotel about 5:30, I was really depressed, because HIV infection was going up, up, up, it was getting up to thirty-five to forty percent of the intravenous drug using population in New York City and there was no solution in sight. The thought of this spreading across the United States was just horrific, so I could, with a great deal of passion and emotion, call and say to a congressman, that we need 10 to 15 million dollars to establish a Medication Development Division in order to develop new medications for the treatment of heroin addiction. because if we don't have options, besides methadone, I'm afraid we

will not be able to totally cope with the problem of HIV infection and its' spread amongst heroin users.

- TB: How did he respond?
- CS: He said, well, how much do you think that will cost? And, I said, again, well, around 10 to 15 million dollars. And, what you find out in the government is, once you get sort of a named area of research by Congress, that's sort of like a bucket or a basket into which money can then be put in the subsequent years. And, of course, the Medication Development Division at NIDA has grown and has been responsible for a number of activities over the years and I'm very glad that I selected that particular area to be the emphasis that Mr. Conti put in there. I can say that, and, here I will be very blunt, because I want it to be recorded for history, that there was a great deal of animosity towards drug abusers in many aspects of the government during the Reagan administration. During that time, I had the privilege of going around the world on Air Force One, spending three weeks with Attorney General Meese, Frank Lawn, who was head of the Drug Enforcement Agency, and the Governor of Oklahoma, Frank Keating. We all went around the world together on Air Force One to the drug producing countries and they went off to see the police and the people charged with supply reduction and I went to the demand reduction people in those countries. Many of the people on the plane, who accompanied them, in talking to them about drug abusers, referred to them in extremely derogatory terms. Some even espoused the principles that maybe it was modern day evolution to let them have all the drugs they wanted to, so they just overdosed and died. AIDS was a natural God's way of punishing homosexuals and drug abusers. This was common banter and it was a very difficult time for me to be on that plane, because there was not much point in trying to argue. I argued a little bit rationally one time with someone who said that drugs were simply modern day evolution; let those junkies overdose and die. I said, well, you know, there's only one problem. They usually don't overdose until after they reproduce, so it is not going to work. As I say, it was the attitude toward drug abusers. Then, Leslie Clarke, the director of CSEP had the major initiatives to try to overcome this stigmatization, because when people are stigmatized this way, they won't come in for treatment until they are really desperate, in other words, until it's almost too late to do things that we could have done much more effectively years earlier.
- TB: Until when did you stay with NIDA?
- CS: In 1992, I left the directorship of the National Institute on Drug Abuse, for personal reasons, and there was a little bit of a problem, because my

colleague and wife, Dr. Johanson, had been selected, after two nationwide searches, to be a Branch Chief in the Intramural program that I directed and that was found to be OK by many people until it reached certain high level positions and they felt that that was unethical. And, I said, well, if she cannot take this position, then, I no longer will be the Director of the National Institute on Drug Abuse, so I resigned. She took the position and I joined her at the Addiction Research Center as a Senior Research Fellow there and we stayed there for 3 years until Dr. Tommy Hudeyat at Wayne State University School of Medicine offered us a position that we couldn't refuse and, so, we've gone to Wayne State University in Detroit where we have laboratories, and direct a number of drug abuse treatment programs and research. Although, I'm technically more than old enough to retire, I have no intention of doing it in the foreseeable future and I'm as excited about everything I'm doing today as I was about anything I've done in my life. We're doing a lot of research with behavior in conjunction with pharmacological interventions for the treatment of heroin addiction and cocaine addiction; doing a lot of work on smoking cessation problems and in the development of new medications to assist people in that area. And we've done some recent studies on cocaine addiction in individuals, who meet the criteria for adult ADHD, or ADD, and, so, we've got a lot of interesting things going there. I'm very excited about the research and hope to be able to continue to contribute to it for some years to come.

- TB: You did research in many areas within the field of addiction. What would you consider your most important contribution?
- CS: Well, I would say a couple of things. I think we advanced the field of drug abuse immensely when we were able to show that organisms, other than humans, would self-administer drugs and that they would do so in a way that was lawful and, I mean, lawful from the pharmacological viewpoint, that you couldn't attribute this to many of the psychological theories that had surrounded drugs of abuse in the past. I can remember that there was one analyst, and I don't remember the name, who wrote, saying that individuals became addicted to heroin because it decreased their sex drive and if they had any latent homosexual tendencies for which their super-ego produced great guilt, they could resolve this by taking heroin. Well, I looked at my monkeys and I thought we should look at some other reasons. Now, I'm not saying that there aren't psychological factors, co-morbidities and a variety of other things that influence the propensity of people to take drugs. There's a variety of ways in which mood disorders that could be genetically determined might influence the propensity to take drugs. But, I

would still argue that I have rarely, if ever, seen a Rhesus monkey that will not self-administer cocaine after they've had some experience with it, and that's true for most of the rat strains that have been looked at. I think that organisms, which ingested these things and found them immediately reinforcing, were those who survived, so, we laid down these tracks in the brain, in the mesolimbic subcortical dopaminergic pathways, and others. So those were laid down to evolutionary mechanisms and they're responsible for the fact that drugs of abuse, which have the capacity to interact with those brain systems, are so insidious, because they can directly produce the kind of experience, which many of us get from other activities which we find reinforcing.

- TB: So, you recognized that drugs of abuse could produce the kind of experience that we find reinforcing.
- CS: Well, I've been lucky. And I make no bones about it. My early drug abuse career gave me this interest in drug abuse.
- TB: It seems that your experiences at Walter Reed and also at SKF had a major impact on your professional development.
- CS: Now, let me talk a little bit about Smith, Kline and French. That, clearly, was one of the turning points in my own career, because prior to that time I had been interested in the brain, but I didn't know anything about pharmacology. I was fortunate to come in at the time of the major revolution; chlorpromazine was introduced onto the market in the United States at a time when American psychiatry was largely dominated by psychoanalytic thinking and the idea of biological psychiatry was rather foreign. Also, the the notion that medication might be useful was foreign to the thinking of most psychiatrists. So, Smith, Kline and French spent a year before they actually took the drug onto the market, but within a few months after they did, train loads were going out to state mental institutions all around the country. So, this was very, very exciting.
- TB: Didn't you develop several procedures while with SKF to study how chlorpromazine affects behavior?
- CS: Yes, what happened was that there had been findings that chlorpromazine would block the avoidance behavior of rats in doses that did not affect their escape latency to electric shock or other adverse ostimulants. That was all that was used. When I came to Smith, Kline and French, we developed a variety of different kinds of procedures for studying how drugs might affect behavior, including what was called the Conditioned Emotional Response where animals, who were working to obtain food, periodically would be given a warning stimulus that would last for five minutes, but at the end of that five minutes, no matter what they did, they were going to get a shock. Between the warning

signal and the shock animals would show great autonomic activity. Rats would urinate and deficate and they would stop responding for food, because they were, essentially, in a state of fear during this period of time. So, we were looking for agents that might overcome some of these autonomic changes. At the same time we were concerned that drugs like chlorpromazine might have toxic effects on cognitive processes, so we had monkeys, who were being forced to learn new things all the time in order to see whether or not chlorpromazine would interfere with new learning.

- TB: You have mentioned it before that you collaborated with Len Cook while at SKF.
- CS: Yes, Len Cook was in charge of the screening for new psychoactive medications. Dr. David Tedeschi was also there involved with screening. The laboratory that I was involved with was a laboratory that was to develop new techniques. That if they showed anything interesting, could then be put into the routine screening laboratories that they headed up. Dr. Cook was my boss and I learned a great deal from him. One of the fortunate things there was that they encouraged those of us, who didn't have a background in pharmacology, to take an extension course in pharmacology, which was run by the University of Chicago, and Dr. Kelsey of thalidomide fame was the instructor for that course. And the pharmacologists at Smith, Kline and French would then give us lectures at work, which was really marvelous, and it was a great opportunity for me to learn and I contributed by bringing my skills as a psychologist to them and they taught me a little bit about pharmacology.
- TB: Then, in the mid-1960s you published the first textbook on *Behavioral Pharmacology*. Could you tell us something about that important book? Have you considered publishing a revised, second edition?
- CS: The *Behavioral Pharmacology* textbook, which Dr. Thompson and I wrote, was widely used in psychology departments and since behavioral pharmacology suddenly burst on the field, having a textbook at that time was very helpful to many, many people. I don't know how to say this, but I still run into people who say to me, my first introduction in this area was using your textbook when I was an undergraduate at this school back in the '60s. Dr. Thompson and I we'd been together at the University of Maryland, but we separated. I went, first, to the University of Michigan and, then, to the University of Chicago and he went to the University of Minnesota. Although, we talked about revising this book, but we never did it. It was never revised, but I will tell you that the opening chapters of that book, I would write again today.
- TB: Could you tell us something about your activities in the ACNP?

- CS: Sure. The American College of Neuropsychopharmacology has been very important to me and I hope that in, at least some small ways, I've helped to contribute to its activities. I have been the Chair of the Credentials Committee on, at least, two occasions and have participated in many, many of the meetings in a variety of ways, both as member of committees, a part of the infrastructure of ACNP, as well, and probably in two thirds of the meetings that I've come to, and I've come to most every single one of them, I have made a presentation. And many students and colleagues, whom I've brought to the College, have also made presentations. So, I would say I have continued to be active in the College and look forward to continuing to be active into the future.
- TB: On this note we should conclude this interview. I would like to thank you for sharing all this information with us.
- CS: You're welcome. Thank you.

NORA D. VOLKOW

Interviewed by Charles P. O'Brien Scottsdale, Arizona, March 14, 2009

- CO: This interview is part of the ACNP oral history project and the interviewee for today, December 9, 2008, is Dr. Nora Volkow,* who is currently the Director of the National Institute on Drug Abuse (NIDA). Nora, thanks for agreeing to being an interviewee for this project. The interviews are going to be stored in the archives at UCLA and also be made into a transcript so that historians of the future will be able to have a look at this when they write books about this era. Probably, it's going to go online as well so that people will be able to go to the internet and access it. Personally, I was very surprised that people actually watched my interview when I did it some years ago and reviewed the transcript, so you can be sure that sometime in the future, there'll be scholars reading this. I don't want to put you on the spot, but, you know, it's taking your time for a good purpose, I think. So, would you begin by telling us where and when you were born and something about your background?
- NV: Yes, I was born in Mexico City on March 27, 1956. I grew up in the house of my great grandfather. Leon Trotsky, Since my grandfather had been sent to a concentration camp and my grandmother committed suicide, my father, who was left to fend for himself, ended up living with his grandfather, Trotsky, who took care of him. In 1937, after about eight years in exile, Trotsky was finally transferred to Mexico, which was the only place that gave him political asylum, and he brought my father with him. When Trotsky was assassinated in Mexico City in 1940, my father was left with Trotsky's second wife. He grew up and went to school in Mexico, got married and raised a family. We were born in the very same house where Trotsky was assassinated, so, I was brought up in a very unique environment; people would come from all over the world to see the place. On one hand, it was very interesting, because it exposed me to a very diverse group of people, but on the other hand, I was instilled, while growing up, with the concept that you're brought into this world and you have a responsibility for other human beings and that whatever your talents may be, in principle, you should be using them to make it better for others. So, that was very, very clear to me even as a child. I was brought up with that moral precept that you have a responsibility towards others. So, as I grew up, then, that certainly influenced the decisions I made throughout my career and life. I was fascinated with

^{*} Nora D Volkow was born in Mexico City, Mexico in 1956.

biology and, particularly, with the human brain, and from very early on, I knew I wanted to do research on the brain. I was very curious and particularly attracted to and intrigued by human behavior. One of the things that always interested me about human behavior was the constant conflict between an individual's acting on what he or she thinks they want to do, and their ability to really do it, and the extent to which people really have control over their actions and emotions. And yet, many times people just cannot control their behaviors, regardless of how committed they are about doing it. One of the extreme examples of this conflict, of course, is epitomized by the disease of addiction, when a person who has become addicted to a drug may say that he/ she doesn't want to take a drug, but has lost the ability to control the behavior. So, we could say that, in its extreme manifestations, addiction represents a breakdown of our ability to exercise free will. This realization was one of the first things that drove me toward the study of the effects of drugs.

- CO: So, it started very early, but I'm going to go back a little bit, because you've already got into the real meat of this interview, but I think that just to make sure that we get the standard information, let me just clarify. I gather from what you said that your mother is a Mexican woman?
- NV: No, my mother was not Mexican. She was born in Spain and grew up in the midst of the Civil War. At some point, by pure chance, she got separated from the rest of her family. When Franco took power, her family had to emigrate out of Spain and Mexico had an open immigration policy according to which foreigners could be granted political asylum. The same openness that brought Trotsky to Mexico also brought the family of my mother. I have always said, somewhat facetiously, although there is some reality in it, that I'm the product of the belligerent nature of human kind: from one side, the Russian Revolution, and from the other, the Civil War, and that's why I ended up in Mexico, because it was that country, at that time, that really was open to all political outcasts.
- CO: And, you obviously were raised in a very intellectual atmosphere?
- NV: Correct; and I think that when you're raised in a family in which your ancestors have been persecuted and destroyed, you tend not to take things for granted, you are more aware that your current well being is the result of the sacrifice of many individuals and that it's not a given and that it can be very easily disrupted or taken away.
- CO: I had the pleasure of meeting your sister when I was in Mexico City recently and your brother-in-law. Do you have any other siblings?
- NV: Yes, we are four girls. My father wanted boys and I think that he got chastised by having four very belligerent girls. I am the second one.

My older sister, is a rather well known writer, poet. One of my younger sisters, who are identical twins, is a physician doing fascinating work on HIV and the role of plasma transfusion in the dissemination of the AIDS epidemic. The other twin is an economist. So, I have three very talented sisters and of the four of us I'm the only one that left Mexico. All my sisters live in Mexico City. And, by the way, my physician sister was very impressed with you when she met you at the international AIDS meeting.

- CO: Thank you. I liked her a lot, too, and I'm hoping that I run into her again sometime, because she said that her husband was interested in the kind of things that I'm doing. And, one time you shared with me the fact that you were speaking French since age seven, so tell me about your languages, you know, in the home, and I guess you speak French, as well as Spanish, and, then at some point, you learned English, so can you tell us a little bit about that?
- NV: My father was born in Russia, but he lived as a child in Germany, France, and Turkey, so when he came to Mexico he only spoke German, French and Russian. I think that, in a curious way, the language that he considered to be his mother tongue was French, not Russian. He left Russia when he was four years old, and he has always had an admiration for the French culture. Both my parents encouraged us to learn languages from early on. In Mexico, we went to private schools, where half of the courses are taught in English starting in kindergarten. But my father, who loved the French language, sent us from age seven to learn French. Naturally, that instilled in me a fascination with languages. I like the concept of being able to switch between different languages when I give a talk. You get conditioned to a word in a given language that does not necessarily gets conditioned in the other language. So, a word that you may hear in one language may be associated to a particular emotion or memory, but when translated to another language it loses that emotional connection or "conditioning effect" that conveys an experience beyond the mere meaning of a word. Similarly, the grammatical structure of a language imposes constraints into your thinking and therefore, I like to analyze events in my brain using different languages to see how they affect my conclusions. My love for Contemporary German literature prompted me in high school to learn German. In medical school I started to study Russian and Italian but unfortunately, by then, I was too old and rapidly forgot these languages. I say this because the languages that I learned before I was eighteen I remember whereas those that I learned at eighteen or later I have forgotten.
- CO: I met a young doctor once who said he was in your high school class and he's practicing now, I think, in Boston but I don't remember his

name, and he was telling me how smart you were in high school. Can you tell me a little bit about that?

- NV: I'm trying to figure out, in high school or medical school?
- CO: I thought he said high school. Maybe, I'm wrong, but he's working in this country as a physician.
- NV: Yes, now I know who you're referring to. His name was Rick and he had the highest score in the entire school. Rick was the same age as my sister, who was also considered a genius; both of them were at the same academic level. So sibling rivalry was very good for me; having this extraordinary brilliant sister triggered my competitiveness. I think I've got the competitive gene(s), whatever that is, which pushed me to emulate my extremely bright sister. Since I am also enormously perseverant, I never gave up. So, I think that's how it happened: the combination of having a brilliant sister and my competitive and perseverant nature motivated me to always try to be the best at every step of the way. I think this explains Rick's comment.
- CO: So, why did you decide to go to medical school?
- NV: Well, I was fascinated by the human body. I liked biology and was always very interested in understanding how it works. I think that if you could go back in time and interview me as a little girl, and asked me: what would you like to be when you grow u my answer would have been to understand how the human brain works. It's just an amazing enigma that never stops fascinating me. For example, and this happens often, when I look in the mirror I think of that first time I recognized myself looking in the mirror when I may have been two or three years old, and realized that I am the same person and, yet, it's so different. Moreover, and even more bewildering, it's me the observer, using my brain to observe my own self, which is the product of my brain that I use to observe. How does all this work? That's always been something that I wanted to get into and medical school provided me the means to do that, because, what a better way to understand humans than in the process of investigating and understanding the concept of disease. I mean, sickness removes a lot of a person's defenses and you can see much more of who they are under those circumstances, of who, "we" are as individuals, but also who we are as social creatures. It was this human element both in the individual and in the social system that drove me to medicine.
- CO: When did you start to become interested in addiction?
- NV: I've always been very interested in addiction and I think one of the reasons was that my favourite uncle, the brother of my mother, was an alcoholic. I adored my uncle, he was an extraordinary generous man,

incredibly warm, and, yet, when he drank alcohol, he was transformed into another person. I could never understand the process of how a person could become so completely disrupted by drugs; at the same time, I was also distressed by the complete social rejection of the addicted individual. For it was evident to me that a person who was so generous would not suddenly act in that way in order to purposefully hurt others; that the transformation had to take place outside of his conscious control. There was another event that further influenced me, which occurred many years later when I was already a medical student. It was then that my mother confided to me, for the first time, that her father had committed suicide. She explained to me that he had been an alcoholic and unable to control his addiction so he killed himself. That made me clearly aware of the disconnect that exists in terms of our ability to empathize with individuals suffering from some diseases while rejecting those suffering from other diseases, namely those that manifest with abnormal behaviors. I think that the fact that these diseases hinge on behavioral perturbations has been interpreted to imply that, somehow, they are the individual's fault. These personal experiences shaped my professional goals in science and medicine, which is to have drug addiction understood as a disease and treated accordingly, and in the process help develop better treatments.

- CO: Did you do some research in medical school?
- NV: Yes, from the very beginning. As a first year medical student I started to work in the laboratory of Julian Villarreal who was a very special person. He had trained at the University of Michigan. At that time, people were very interested in opiates and were trying to develop analgesics that would not generate physical dependence or psychological dependence, as addiction was then called. As a medical student, I worked in the afternoons in this project as a volunteer. That was the time when Kosterlitz and Akil first identified the endogenous opiates and I was trying to manipulate the opiate system by exposing animals to stressful environmental conditions.
- CO: Did you happen to go to the CPDD meeting that was in Mexico City in the early 1970's?
- NV: No, I did not go. I started medical school in 1975 and I started in the laboratory of Julian Villarreal in 1976, so it was after the CPDD meeting in Mexico.
- CO: Well, Julian was also a friend of mine. We called him Julian, but anyway, he invited me and a few other addiction scientists to Mexico City. I think it was in the late '70s, or even the early '80s, so you might have been
there, but we came and we gave a series of lectures at the university there in Mexico City and there were a lot of students..

At that time I was a medical student. I started medical school in 1975. NV: and in '79, as part of my medical education I travelled for one year to Paris, where I studied with Pierre Pichot, who was at the time the president for the World Psychiatric Association. I was very interested in his work, which focused on developing measures to quantify psychiatric symptoms reliably, particularly for clinical depression. At that time, I was intrigued by the underlying processes that make certain symptoms correlate with others in specific "symptom clusters". I did a project, which, unfortunately, never got published, where I studied the effects of treatment on the relationships between individual symptoms in these "symptom clusters" obtained from patients with depression. I wanted to assess whether the relationships persisted or if treatment preferentially improved some symptoms but not others in such a way that it uncoupled them from the original "symptom cluster". For this purpose I analyzed the symptoms from a large number of hospitalized patients with depression, for whom there was quantitative data on their symptoms before and after they completed inpatient treatment and achieved clinical recovery. The analysis showed that treatment did not affect the cluster structure and that the relationship between the symptoms remained the same before and after treatment. What the treatment did was just decrease symptom intensity. That was one of the first clinical studies I did in Psychiatry. After one year in Paris, I returned to Mexico to complete the rest of my medical education. Having lived one year in the heights of "civilization", I was ready for the opposite so I chose to spend the last year of my medical training practicing in the jungle. In the border between Mexico and Guatemala you have the remnants of the Lacandon Indians who occupy areas of the jungle where the Maya culture once existed. My father was furious at my decision and stopped talking to me for almost three months. He was concerned by my going to the middle of the jungle, where they would not normally allow women because it was perceived as too dangerous. But I had received the highest score of all the medical students in my generation, which comprised three thousand students; this allowed me to question why my selection to practice in the jungle had been rejected. My argument being that what was the advantage of having the highest academic score if I was not allowed to chose where I wanted to do my last year of training in medicine. I convinced the authorities of the university and I was authorized to do the year of "social service" in the jungle. I was interested on the reality of practicing medicine in an environment that was so completely different from mine and to experience the interactions with people whose everyday existence, while simple, was so much more precarious than my own. However, I went, with the naïve assumption that one person, if sufficiently motivated, when going into a new environment could make a big difference; but I failed. My failure was the result of the local conditions and circumstances, which I rapidly learned can sabotage the best of intentions. I was stationed in a very small community called La Arena situated between Palengue and Bonampak in the state of Chiapas. There was no electricity or paved roads and I was sleeping in the school using one large table as my bed. One of the rooms in the school also served as my clinic where I saw patients suffering from tuberculosis, gastrointestinal diseases, pregnancies, trauma, people fighting each other with machetes, and snake poisonings. However, I had access to very few medications, and those I did had, where in too small quantities to sustain the needs, which was very frustrating to me, because I realized that many of the cases could have been treated much more effectively than what I was able to do. This experience made me keenly aware of the crucial importance of clinical infrastructure to sustain a successful therapeutic community effort.

- CO: So, from that background, what made you choose to go into psychiatry?
- NV: After I finished medical school. I applied to MIT and to Harvard to do a PhD after which I was planning to do a residency in either psychiatry or neurology. Harvard rejected me and MIT accepted me to its neuropsychology program. Since I had seven months in between finishing Medical School and starting courses at MIT, I asked my father, who always encouraged any science related activity to support me while I volunteered doing research in the USA. He agreed and I decided to try my luck at New York University. I had read in a scientific American magazine an article on Positron Emission Tomography, a new imaging device that allowed for the first time to image the human brain in action and that investigators at New York University were using to study the brain of patients with schizophrenia and with Alzheimer's disease. While reading this article, I realized that the advent of imaging was going to transform clinical neuroscience. So, I went to New York University and without an appointment I asked if I could meet the Chairman of the Department of Psychiatry who at that time was Robert Cancro. This tells you a lot about my naiveté regarding academic environments but in this case the naiveté served me well because otherwise I would have not dared to show up unannounced.
- CO: Pick up on NYU, which is we're sort of at the point where you were just deciding to take a residency and I want to hear about that and

especially who was the scientist who had the most impact on you at NYU and Brookhaven.

NV: I give Bob Cancro the credit; he agreed to meet with me and after listening to me talk about my interest in doing research with brain imaging he introduced me to Jonathan Brodie, who was the psychiatrist in charge of the positron emission tomography (PET) program. The next day I started as a volunteer working with the brain imaging team. My first project was on the use of PET for the diagnosis and evaluation of glioblastomas. This project interested me since malignant cells undergo biochemical transformations I reasoned that PET would allow one to measure these biochemical transformations obviating the need of a biopsy. I proposed a new radiotracer, putrescine, which is a polyamine involved with cell division, that was intended to target cell division, which in the brain would mostly be restricted to malignant cells. Though the radiotracer was eventually developed for PET and assessed in patients with glioblastoma its usefulness was limited by the fact that its main accumulation in the tumors reflected blood brain barrier disruption rather than enhanced cell division. By then the seven month hiatus period that I had prior to my entry to MIT was coming to an end and Cancro convinced me to stay at NYU and complete a residency in psychiatry instead of going to MIT. Once in the residency program at NYU, I started working on a project that used PET to investigate the regional brain metabolic changes in schizophrenia patients. Between taking care of patients and doing on call duties at Bellevue Psychiatric Hospital I found the time to screen and evaluate potential research subjects in the project whom I would also take to Brookhaven National Laboratory to undergo their PET scans. In this respect, Cancro was very influential in my career since he provided me with the support and flexibility that I needed to do the research while being a resident. Of those who influenced me professionally Julian Villarreal was probably the one who influenced my thinking processes as a scientist the most. Why was his influence so important? He had an analytical mind that looked at things in ways that were very unique and that others could not see. He was also not afraid of setting ambitious goals or of being bold with his insights into mechanistic effects of drugs. Alfred Wolf, who was the head of the PET program at Brookhaven Laboratory was also very influential. He was a brilliant man and what impressed me the most was his recognition of the importance of transdisciplinary science. Of those who have influenced my career, I have to also single out my closest colleague and friend, Joanna Fowler. I have learned many things from her including how rewarding scientific partnerships can be,

how to integrate research from different scientific fields, and how to successfully blend friendship and scientific partnerships.

- CO: What about your interest in addiction? How did that begin?
- NV: My interest in addiction started very early on, probably at the time when I was a medical student working with Julian Villareal on opiate addiction. Then, when I finished my residency and moved to the University of Texas in Houston, where they had an amazing imaging program, I started to use imaging to investigate the effects of drugs in the human brain. However, my interest at that stage of my career with respect to the use of imaging for studying drugs of abuse- was not the desire to understand the processes that initiate addiction, which has been obsessing me for many years, but to investigate the processes by which drugs can produce psychosis. I was intrigued by the fact that some individuals who abuse stimulant drugs, such as amphetamine or, to a lesser degree, cocaine, can became acutely psychotic. As part of my interest on understanding the neurobiology of schizophrenia, I reasoned that, by comparing the brain of stimulant abusers when they were psychotic vs. when the psychosis wore off I would be able to identify neuronal changes that could inform about psychosis in general.
- CO: At some point, the concept of addiction came into it.
- NV: I first started by measuring cerebral blood flow (CBF), which I used as a marker of brain function to evaluate changes in the brain of cocaine abusers that would inform me about stimulant induced psychosis. To my surprise. I found that the brain images of cocaine abusers showed defects in perfusion reminiscent of those reported in patients that have suffered from multiple small strokes. These CBF defects were very common in the cocaine abusers and diverted my attention towards trying to understand their clinical significance. At the time when I did these studies there was no recognition that cocaine could produce cerebrovascular pathology so I encountered a lot of resistance from the medical community to accept this finding, which was later corroborated by other investigators. In these studies we used PET and ¹⁵O labeled water to measure cerebral blood flow. I did these studies in the mid '80s, when cocaine was believed to be a relatively safe drug. However, the imaging data showed otherwise. But as I say to my trainees, "do not ignore the data, the data is the data, whether it fits your hypothesis or not". The brain imaging data were portraying a picture of cocaine that did not fit the perceptions of this drug at that time. In reviewing the literature, I encountered an old paper in the New England Journal of Medicine that reported that the abuse of amphetamine resulted in vascular pathology that affected several organs; though it did not mention the brain.

It hypothesized that the pathology resulted from the vasoconstrictor effects of amphetamine and from the injection of contaminated material. So, I reasoned that cocaine being a stimulant like amphetamine, was also causing vasoconstriction and this was probably responsible for the CBF abnormalities. There was also a couple, at SUNY in Brooklyn, who had reported that cocaine induced vasoconstriction on isolated blood vessels, which also supported my interpretation that what I was seeing in the PET CBF images reflected the vasoconstrictor effects of cocaine. Because of the unexpectedness of the finding, the novelty of PET technology and the belief that cocaine was a safe drug it took me a long time to get the finding accepted and the study published. Nobody believed that cocaine was producing CBF abnormalities or that it could produce small strokes or small haemorrhages. By then, of course, I had been sidetracked from studying the effects of drugs causing psychosis to studying these toxic effects of cocaine. One of the strategies that I've always used in imaging is to have parallel gueries into at least two distinct drugs of abuse, so when I was studying the effects of cocaine I was also studying the effects of alcohol. The reason for this was both to assess the overlap between drugs and to identify the unique changes specific to a given drug. In the alcoholic patients, I was not seeing the CBF defects that I noted in the cocaine abusers. On the other hand, the effects of acute and chronic alcohol showed very distinct changes, implicating GABA neurotransmission, which led me to guestion their potential involvement in addiction and in the vulnerability to addiction. I was also very intrigued by the large variability that I was observing in the brain response to drugs among different individuals, both with respect to their behavioral responses as well as in their brain responses, and both to acute and chronic drug administration. That's how my focus shifted towards trying to understand the processes of addiction, reinforcement and addiction vulnerability.

CO: How long did you stay in Houston before you went back to New York?
NV: I stayed at UT in Houston for three years and then, Alfred Wolf convinced me to move back to Brookhaven National Laboratory. I remember the day I was in his office when he said, well, Nora, what will it take? I said, you know, I'm doing imaging work in substance abuse and I would like to be able to continue doing that. His response to this was, would you like us to synthesize labeled cocaine? My response was, you bet, I would love to have [¹¹C]cocaine. That conversation sealed my fate and I moved to BNL. The labeling of [¹¹C] cocaine was performed by Joanna Fowler and that allowed us to investigate for the first time the distribution and pharmacokinetics of cocaine in the human brain. I

recall a couple of years later a similar interaction with Alfred Wolf at the lunch table: I was describing to him that methylphenidate was pharmacologically very similar to cocaine but that nobody wanted to accept that these two drug could have similar actions in the human brain. He smirked at me and asked if I was trying to convince him to label methylphenidate, which of course I was. The labeling of [11C]methylphenidate was done by Yu-Shin Ding and it allowed us to compare the distribution and pharmacokinetics of cocaine and methylphenidate in the human brain. Because labeling with Carbon-11, doesn't affect the pharmacological effects of drugs, one carbon is substituted with another carbon, this is a very powerful pharmacological strategy to study the behavior of drugs in the human brain. It's almost like science fiction. If you love pharmacology, that's almost as good as it gets: to be able to actually look at that drug as it circulates in your body and to start looking at its pharmacodynamic and the pharmacokinetic properties. This potential is what actually attracted me to BNL, the possibility of using PET to assess the pharmacological effects of drugs in the human brain and its implications for reward and addiction.

- CO: And, that's been a terrific location for you, because it's been so efficient, allowing you to turn out so many seminal papers, with the facilities that Brookhaven has there. It's just been wonderful.
- NV: Yes, and I think what makes Brookhaven so great, clearly, it's actually not the facility but its people. If you go to Brookhaven National Laboratory and visit the PET laboratories they are old buildings and they don't have the latest in equipment. It's the brains of the scientists that make it unique.
- CO: Is Wolf still there?
- NV: Al Wolf died about thirteen or fourteen years ago. After his death Joanna became the leader of the PET program at BNL. She has been an extraordinary colleague who has built up the PET group, promoted training of new investigators and encouraged collaborations. Joanna has been terrific.
- CO: This is a really tough question. This is one of the things that they want to get on here. What do you consider to be your most important scientific contribution, so far, because you have many more to come in the future, but so far?
- NV: That's an interesting question to consider, albeit hard to answer. I think that probably one of the most important ones, if I had to choose one, is the concept that a key region in addiction is the frontal cortex. Now, everyone recognizes that the orbital frontal cortex and the cingular gyrus are crucial in addiction. However, this was not the case when I

first documented abnormalities in the orbitofrontal cortex and cingulate gyrus of cocaine abusers, which I then reported were associated with the reduction in dopamine-D, receptors in striatum that are seen in addicted subjects. The first time I reported on these prefrontal abnormalities in drug abusers again it was guestioned because at that time, a lot of the work had concentrated in the area of the nucleus accumbens. and the limbic brain. But again, I go back to my motto of "the data is the data, is the data". The fact that I could blindly distinguish between a brain metabolic image of an addicted person who had recently taken a drug of abuse and that of a non-addicted person on the basis of the enhanced activity in the orbital frontal cortex in the former, was very compelling. It was a very consistent signature that was difficult to ignore or miss. At that time, I was also intrigued by the overlap between my findings and those reported by Baxter on metabolic changes in patients with obsessive compulsive disorders that also showed enhanced activity in orbital frontal cortex, cingulate gyrus as well as caudate. And then, through association, I questioned in my brain what those two disorders had in common? It was immediately evident: the compulsive and the obsessive quality of the behaviors in both disorders, which I reasoned reflected disruptions in overlapping prefrontal circuits. Again, the field rejected this new perspective on the neurobiology of addiction first, because I was implicating the frontal cortex as opposed to classical limbic areas such as nucleus accumbens, and second from the misconception that I was implying that addiction was an obsessive compulsive disorder. However, I wasn't implying that these were similar disorders but rather that these two disorders shared neurobiological substrates in the brain as part of broader mechanisms that resulted in distinct pathologies. I was basically thinking of shared territories. There are so many ways in which the brain can become impaired. So, to me, that is probably the finding that I considered to be the most important, because it transferred the whole focus of addiction from the limbic brain into other brain regions, prefrontal brain regions. The recognition of the importance of the orbital frontal cortex and the cingulate gyrus has been crucial in advancing our understanding of the process of addiction. Since then, many other investigators have also delineated that there are other circuits involved, like the insula for interoception and self awareness, the memory circuits including hippocampus, amygdala, which actually have to do with your work at U Penn. This has shifted our views to not just focus on one particular brain region but to explore multiple neuronal circuits that become disrupted in addiction.

CO: How hard was it for you to agree to accept the NIDA directorship?

- NV: It was hard. I remember discussing it with you. You called me and said, Nora, you should consider it and I said, Chuck, why don't you consider it and I remember you said to me, no, I have too many good things going on in the laboratory; this is not a good time for me. I don't know if you recall that conversation.
- CO: I felt guilty about it, figuring that it would have a bad impact on your career, but it's been just the opposite.
- NV: Being director of NIDA does require a big investment of time, but it's an investment that's worth it; otherwise, you should not do it, because it's so demanding that either you really want to do it or you should just stay out of it. That's it. The moment that I feel I don't have the same passion for the job I will stop, because it's too important of a job not to give it your very best. I also called Herbert Kleber for advise and I said to him that I felt it was not the right time for me and he responded, Nora, there's never a right time, that's when he was called to be the deputy director for ONDCP, he initially had felt similarly; that it was a great opportunity but that it was not the right time. I spoke with many colleagues, friends and relatives; I wasn't convinced. It was a very difficult time for me, there were days where in the morning I would be convinced that I should take the job and then later during the day I would find myself thinking there is absolutely no way that I can leave my research work. Chuck, you have to realize that my identity as a scientist is crystal clear. In my brain, it's automatic, so the notion of giving up who I was, was very difficult, and, so, most people were encouraging me and there were a couple of people that weren't and I think that they knew me in a way that was very fundamentally me. One of them was my friend and colleague Burt Angrist, I remember his words: Nora, I've known you since you were a resident; you thrive on science; what are you going to do as an administrator? During my interview with Dr Elias Zerhouni, who was the director at NIH recruiting me, I felt guilty for wasting his time since I had internally come to the conclusion that I was not going to take the job. But Elias Zerhouni is a very perseverant individual who, I think, rarely gives up, so he finally asks me one day when he comes to visit BNL, what will it take for me to take the job? I told him that the issue that would make the difference is if I could continue doing research and working with my colleagues at BNL. He looks at me and states I think we can arrange that. And, he did and that's how I took the job at NIDA and how I've been able to continue my research work as an intramural investigator in the NIAAA whose laboratory is located at BNL. It has also allowed me to keep my relationships with my colleagues at Brookhaven National Laboratory, which are very important to me.

- CO: And somehow, you've managed to squeeze it all in, the demands of the NIDA directorship and the research into your really busy schedule.
- NV: Yes, and, you know, there are two things that happen when you get into a situation like that. I mean, I don't take jobs that I don't think I can do well, very well, and, I'm also very competitive, so I want to do the best that can be done and that goes in both areas, so it's actually recognizing that is something that I have to do. So in these five and a half years of my life, I've worked harder than I've ever worked before, and I've always been criticized for being pretty compulsive as a worker, but I stretched it and I stretched it because I think it's worth it. It's not even something that I actually think about. I am aware that I'm very lucky being married to someone who is also very hard working and supportive, someone that has never guestioned me for working excessive hours and that has helped me enormously. Also, I do not have children, which also avoids the conflict that most women scientists with children must struggle with. This may be seen as a selfish way of organizing one's life but my passion for science has driven my choices in life. I think that's how I've been able to manage being NIDA director and maintaining my research work. For me, it's almost a survival strategy to be able to do science and be creative at that level, while doing this job at NIDA.
- CO: So, here you are on the cutting edge of a very important field. What do you see as the future of addiction research?
- NV: There are many areas that are ripe for significant progress in the future of addiction research. I think that in the next few years we're going to see acceleration in the rate of discoveries. In fact, we are already starting to see extraordinary opportunities, driven in part by advances in imaging technology, genetic knowledge and access to open data bases and computation resources. For example, by using imaging technology, we are beginning to better understand how the brain is affected by drugs of abuse and how its disruption results in the behaviors we see in addicted individuals. In the process, we are also learning about how the human brain works. Genetic studies are starting to identify families of genes involved in drug responses and in addiction, and, in the near future, epigenetic research will allow us to understand how drugs affect the expression patterns of these genes in the brain. Now, findings from genetic research can help us to come up with better treatments, in your case, for example, by predicting which patients are more likely to respond to naltrexone. Wide genome association studies are helping us identify genes involved in addiction that the field had not previously considered that important, such is the case for the nicotine receptor subunits, α -3, α -5, and β -4. These findings give us clues about

where to focus research that can ultimately shape the development of new treatments. For example, there is only one compound listed as ligand for the α -3-receptor, probably because in the past there was no evidence that this receptor was involved in the rewarding effects of nicotine. Now, the findings from genetic research introduce the possibility that compounds that target this receptor may have therapeutic benefit in nicotine addiction. Coupling genetic studies with imaging research will allow us to better understand how genetic variants associated with vulnerability to addiction, affect the development, morphology and function of the human brain and how drug exposures, stress and other environmental factors, including social systems, can affect them in turn. Let me give you another example, the monoamine oxidase A gene, which has a variable nucleotide terminal repeat (VNTR) that is likely to influence transcription levels, has been associated with an aggressive phenotype. However, if you actually measure the concentration of monoamine oxidase A in the brain, which you can do with PET technology, there's no difference in the concentration as a function of the genotype. This suggests therefore that whatever influence the MAO-A VNTR has on the aggressive phenotype it is likely to reflect its effects during early developmental stages, not during adulthood, since at that stage we can find no differences in enzyme concentration as a function of genotype. Since the MAO-A gene is involved in brain development and architecture it is therefore likely that its association with aggressiveness reflects this role. Indeed, it is likely that many of the genes that are associated with neuropsychiatric disease contribute to these disorders by affecting developmental brain trajectories. The use of imaging in conjunction with genetics will start to reveal how vulnerability factors affect brain functions, which can then lead us to a better understanding of addiction. Ultimately, we want to understand why is it that someone can become addicted?

The question is frequently asked of why drugs are rewarding. It is accepted that they are rewarding because they activate systems, including the reward system that are crucial for survival. However, few have asked the question about a potential physiological role to the state of addiction, a state where you become so obsessed that nothing else matters, where you're actually willing to forego things that are crucial for survival in order to get the drug. How does nature allow for the emergence of this state if it's not already hard wired for a physiological purpose? I believe that the mental state of compulsion and obsessiveness is a state that can occur at unique stages in our lives and that is also important for the survival of the species. For example, when a mother has a child or during romantic love, on both these situation there is a hypermotivational state that overrides other reinforcers and that allows the individual to do behaviors that, otherwise, would not succeed.

As we learn how genes affect neuronal circuits implicated in addictions it will give us a new way of trying to strengthen those circuits when they become disrupted by drugs. So, that's where I see the field, the integration of knowledge from genetic studies into understanding brain development and neurobiology, and how these are affected by drugs.

- CO: I hear what is exciting you now, and we're just about out of time, but I just wonder is there anything else that you think is important, considering who is going to be reading this or looking at this sometime in the future, is there anything that you want to sort of say for posterity at this point before we end it?
- NV: I assume that if these tapes are going to be seen by people who are scientifically inclined, I would not have much to say. But, if they are going to be read by individuals without scientific leanings, I'd like to send the message that science is an extraordinary career, probably one of the most exciting human endeavours. It is utterly fascinating to be able to use your brain to try and understand the world in ways that others have not seen before. But, at the same time, it advances knowledge that actually, in turn, can help improve the life of other people, so in a very real way, is the best of both worlds.
- CO: That's a good note to end on and I'm sure that it will be seen by nonscientists, because, you know, the person who has already seen some of these tapes has just written a history book on it and, so, I'm sure, help future historians and maybe some people who are considering a career in science. Thank you very much, Nora.
- NV: Chuck, thanks a lot.

LEONG E. WAY

Interviewed by Lynn E. DeLisi Hollywood, Florida, December 12, 2006

- LD: Just to begin, let me just tell you that I'm a member of the History Committee. My name is Lynn DeLisi. I'm a psychiatrist, a biological psychiatrist and I'm a Fellow of the ACNP. I am very interested in the history of the ACNP and, so, I've been asked to interview you. Maybe the best way to start would be if you could state your name and your current position where you are and, then, we'll proceed from that.
- EW: I go, professionally, by E. Leong Way,* but most of my friends know me as Eddie Way. I'm professor emeritus of pharmacology at the University of California at San Francisco. I was there for over 50 years and served as Chairman, from 1972 to '78.
- LD: OK. Well, that gives us an ending to the story that I'd like to begin with your earlier life and experiences. And if you could just begin with, maybe, a description of yourself, how you got into this field and what drove you into it in the beginning.
- EW: How I made my living from drugs? How I became a pharmacologist?
- LD: Well, how you got into the field and where you are today?
- EW: Well, I started as chemistry major in Berkeley, but after a couple of years there, I decided that dancing atoms and electrons are not the kind of chemistry I was interested in; even though there were a lot of Nobel Laureates in physics and chemistry on campus at the time.
- LD: What year was that? What period of time?
- EW: Well, that was in the 1930s. I enrolled in 1934 and spent two years there. But then, I decided that I was more interested in drugs, so I transferred in 1936 to the School of Pharmacy on the San Francisco campus. I received a BS in Pharmacy, which was awarded in Berkeley, because, at the time, San Francisco was still not an independent campus. After I got my degree, I practiced Pharmacy for one year. It was interesting and somewhat satisfying, but it wasn't the academic and intellectual challenge I wanted. Fortunately, a graduate program in the School of Pharmacy was initiated and I became its first student to acquire an MS in 1940 and a PhD in 1942 in Pharmaceutical Chemistry. For my dissertation, I synthesized 80 compounds, which were derivatives of organic arsenic. I tried to make organic arsenic compounds in the hope that they would find clinical applications. At the time the organic arsenic cal, arsphenamine 606, was used mainly for treatment of trypanosomes infections and syphilis. And, sulfanilamide had just been introduced

^{*} Leong E. Way was born in Watsonville, California in 1916

as an antibacterial agent for gonococcus, streptococcus and staphylococcus. I made about 80 arseno-sulfa combinations but I wasn't able to study them in the pharmaceutical chemistry department. However, there was a famous pharmacologist, Chauncey Leake on campus, and so I started to do research with him.

- LD: When was this?
- EW: 1942. Unfortunately, or fortunately, Chauncey resigned from his position as Chairman at UCSF in 1942 to become Vice President and Chairman of Pharmacology at the University of Texas in Galveston. When he left, I could not continue my studies, so I accepted a job at Merck. It was during the war and I was assigned to study the stability of vitamins.
- LD: Are we talking about World War II?
- EW: Yes.
- LD: How did the war affect you in your career?
- EW: Well, Merck employees were deferred from active duty for doing essential work. Although I got a deferral for studying vitamin stability, I didn't think doing that was very essential, and after four months I accepted an offer to become an instructor in pharmacology at George Washington University Medical School in Washington, DC where medical students were being trained to join the Armed Forces, either in the Army or in the Navy. I found that not only more interesting but also more satisfying. I stayed at GW for five years. I finished my studies on the biologic activity of my arsenic compounds. I found they weren't much good in their action on trypanosomes. After these negative findings I shifted my research to studying narcotic drugs. I was sort of gently nudged into the field. At that time, meperidine, Demerol, the first synthetic opiate-like analgesic was introduced. Meperidine, at the time known as isonipecaine, was designed to be a substitute smooth muscle relaxant for atropine but was serendipitously discovered to be analgesic. I asked Dr. Roth, the chairman of the department who had hired me, what we know about the vagal inhibitory properties of meperidine. He said, "Why don't you study it on frogs, Doctor"? I tried to put him off but the week following Dr. Roth said, "Your frogs have arrived for your research, Doctor". I got the message, and that's how I got hooked on narcotics for good. When P. K. Smith succeeded Roth as chairman in 1946, he suggested I do drug metabolism studies because the field was better suited to my background and training. P.K. was interested in acetyl salicylic acid, good old aspirin, and supported me to study the biodisposition of p-amino-salicylic-acid. So, that's how drug metabolism became my main research field. I received a NIH grant that I held for about twenty years, studying the biodisposition of opiate drugs,

morphine, codeine, heroin, meperidine, methadone, and 1-acetylmenthadone, LAAM.

- LD: So this was the field you were working in and what you were doing. Could you tell us what you would consider your best accomplishments in research?
- EW: After completing a review and a monograph on the biodisposition of morphine and its surrogates, I shifted my research to studying the two biologic properties of the opiates that develop after repeated administration: tolerance and physical dependence.
- LD: What were your most exciting findings in this area of research?
- EW: Providing the pharmacologic evidence that the two parameters, tolerance and physical dependence, have a common underlying biochemical basis. Clinically, tolerance and physical dependence appear to be related because when addicts develop tolerance to opiates such as morphine or heroin they also become physically dependent on the compound as evinced by a severe withdrawal syndrome shortly after drug taking is discontinued. However, some investigators have maintained that tolerance and physical dependence are not related. Tolerance and dependence have been used as qualitative terms without quantification and, in order to relate tolerance and physical dependence to a single parameter, it was first necessary to develop experimental methodology to measure tolerance and physical dependence of morphine in the laboratory quantitatively. We developed procedures for measuring tolerance and physical dependence in mice and rats that helped open the field for scientific evaluation. Our first paper and last papers in the area were to be most satisfying. In the first paper, we reported on methods in mice to measure tolerance and physical dependence. Over the years we provided considerable circumstantial evidence that certain neurotransmitters could modify tolerance and would also alter dependence development. And finally we were able to show by in vitro methods that tolerance and physical dependence have a common underlying basis related to neurotransmitter release. I began the studies after I visited Professor Huidobro-Toro in Chili. He had developed a morphine pellet to make mice dependent on morphine that eliminated having to inject mice repeatedly with morphine very day. By implanting a single compressed pellet underneath the skin, mice became highly dependent on morphine as evidenced by the precipitation of a severe abstinence syndrome after an injection of nalorphine, a morphine antagonist. The dependent mice became very excited and ran off the table. I decided that would be a great way to study opiate tolerance and dependence. However, Professor Huidobro's handmade pellet was laborious to

make. So I went to our pharmacist, Bob Gibson, who developed a product that could be machine manufactured, and, provide a steady release of morphine. We could easily implant thirty or forty of our pellets in our animals on Friday, go off dancing, playing golf on the weekend. and return on Monday for the evaluation of our tolerant and dependent animals. To quantify tolerance, we used an analgesic response, actually an antinociceptive effect, known as the tail flick response. A mouse would flick its' tail away after a heat stimulus, and after the administration of an opiate, its reaction time would be delayed. After repeated doses of morphine, tolerance could be quantified by a shift of the dose response curve of morphine to the right, and the degree of shift gave a quantitative estimate of the degree of tolerance. Physical dependence was displayed by withdrawal signs, such as weight loss and defecation, after removing the pellet but we could quantify the physical dependence easier by measuring the dose of the opiate antagonist naloxone, to precipitate jumping. Antagonist precipitated withdrawal was reported earlier by Abe Wikler, Harris Isbell and Frank Fraser. We found the more dependent the mice became; the less naloxone became needed to precipitate the withdrawal jumping. So, having a quantitative measure of tolerance and physical dependence we demonstrated that the degree of tolerance, as shown by the increase in dose of morphine to elicit antinociception, was paralleled by a decrease in the amount of naloxone to precipitate withdrawal jumping.

- LD: Why did it take you over 20 years to demonstrate that tolerance and physical dependence have a common underlying biochemical basis?
- EW: We found much circumstantial evidence early that neurotransmitters, serotonin (5-hydroxytryptamine), norepinephrine, dopamine, and acetylcholine could be involved in tolerance and physical dependence, but this still didn't prove that tolerance and withdrawal have a common underlying biochemical basis, and it took about another twenty years, and shifting from in vivo to in vitro techniques, to show it. In the meantime, some investigators continued to maintain that tolerance and dependence were not related. They argued that the tolerance response in one system could be reduced without altering a dependence response in another system. We pointed out that such considerations are comparing apples to oranges because tolerance to various opiates effects on various systems or organs have different times of onset and degree; tolerance to the analgesic effect comes on very early and is of a high degree, whereas tolerance to pupillary constriction appears later and is of a lesser degree. To show a relationship between tolerance and physical dependence, it is necessary to measure a common

parameter in both syndromes. Investigators in the UK, especially Hans Kosterlitz, used the Guinea pig ileum to study opiate action. Earlier Paton had shown that after an electric stimulus of the ileum a twitch response occurs that is inhibited by the administration of an opiate. The model provides a surprisingly good predictor for analgesic potency experimentally and clinically. Also, the rank order of potency yielded surprisingly good correlation with dependence liabilities in monkeys in Mo Seevers' lab at Michigan. So, using the guinea pig ileum one can predict the addictive liability of opioid substances. The decrease in twitch response elicited by morphine in this system is due to inhibition of acetylcholine release but found it difficult to measure. So we then decided to use the vas deference of the mouse for measuring withdrawal. The mouse vas deferens has also a twitch response to electric stimulus that is inhibited by opiates, but the neurotransmitter inhibited in this system is due to norepinephrine. Thus, with the employment of this test, we finally demonstrated that norepinephrine release is the common underlying biochemical basis for tolerance and physical dependence. As tolerance developed more morphine was required to inhibit norephrine release and after washing out the morphine there was substantial increase in norepinephrine release. That was the last original publication from our laboratory.

- LD: When was this?
- EW: In 1990.
- LD: In 1990?
- EW: Yes and our first report, was published in 1968 or 1969.
- LD: What made you stop working in this area of research?
- EW: Well, I retired in 1987, and didn't have any more research space.
- LD: Why did you retire?
- EW: There is mandatory retirement at age 70 but I was able to fudge almost two years.
- LD: How were you able to cheat them?
- EW: Well, retirement ends on June 30th and I was only 69 then but because my birthday is on July 10th, so that got me almost one additional year. Then the research grant administrators unwittingly had approved the support for my research for five years and did not realize they obligated two additional years past my mandatory retirement.
- LD: This was at UCSF?
- EW: At UCSF.
- LD: And, they had mandatory retirement? I thought that there was not supposed to be any prejudice against age.
- EW: At that time, there was.

- LD: So, what have you been doing since?
- EW: Well, I got an offer to go to Japan to establish a neuropharmacology department. My friend, Eikichi Hosoya, who was research director at Tsumara, probably the largest herbal company in the world, wanted to validate herbal medicine with Western technology. So, the way to do that in Japan is to set up and subsidize a department at an academic institution.
- LD: So, you went over there?
- EW: I went over there as a Professor and Chairman of the Department of Neuropharmacology at Gunma University. As it turned out, I was a figurehead; just hired for show. Hosoya wanted a former colleague of his at the company to be the Chairman, but the Japanese academicians opposed a person coming directly from the drug industry to be head of an academic department. To circumvent this I was hired as professor and chairman for one year and after I left another person would inherit the chair. I wasn't aware of this. I wasn't very keen about going to Japan, but at the same time I wanted to be nice to my friend. So when he invited me I told him, "Well, I have a disabled daughter, so my wife would not be able to accompany me to bring her to Japan, and I wouldn't know what to do with my weekends. I like to golf and dance. Get me membership in a dance club and a golf club and I would consider coming." I thought he wouldn't be able to meet my terms. He replied I can get you a dance club membership, but not a golf club membership because that's very expensive. However, he came back to me two weeks later and said, OK. As it turned out, Tsumura made money on me. The golf club membership cost the company about a hundred thousand dollars. However, buying a golf club membership in Japan is like buying stocks and, by the time I quit, the economy was still at its peak and the price of my membership had ballooned three fold. Too bad I couldn't keep the membership. It belonged to the company and not to me.
- LD: Were you there just for a year.
- EW: One year.
- LD: I suppose you played a lot of golf and went dancing and, then, you returned to California?
- EW: I was allowed to come home once a month, too.
- LL: Were you born in America?
- EW: Yes.
- LD: Were you born in California?
- EW: In Watsonville, a town not far south from San Francisco.
- LD: Wasn't there a wave of immigration from China that started in the early 1900's?

- EW: No, it really started after the 1849 Gold Rush in California. Chinese immigrants were welcomed and admitted to build the railroads. But when the job was finished the immigrants were no longer welcomed and excluded in 1882. By the time my father brought my mother over in 1912 discrimination laws were still in effect against the Chinese, and, they were not revoked until 1943 and further liberalized in 1948. If you were not a US citizen, you could not bring a wife over or have property in the US. My father claimed he was a citizen by right of birth and the government had no proof to dispute his claim because in 1906, there was a catastrophic earthquake in San Francisco. Since it destroyed government records many Chinese could claim citizenship by birthright. My dad was enabled to go back to China and marry my mother and bring her over in 1912. And, they had 8 kids who all attended college This is a great country for opportunity and social justice even though there are downsides they become corrected if unbearably slow for many of those suffering.
- LD: After a year in Japan, what did you do?
- EW: Well, the director of NIDA, Bob Schuster, invited me to go there as a senior post-doctoral fellow. So, I went there for a year but I didn't contribute very much. I gave some advice to which not much attention was paid. But I learned to appreciate government employees much more while there.
- LD: How did you become an expert in herbal pharmacology? Did you become an expert of it while in Japan?
- EW: I became an "expert" in herbal pharmacology by default much before that, in the late 1950s. I did not know much herbal pharmacology before 1958. The Communists took over Mainland China in 1948 and closed the door to the West especially the US. We heard of some major advances in China in the first six or seven years. The American government was very much interested in the progress. NAS and the AAAS sponsored a symposium on The Sciences in Communist China that was later published in 1960, and I was invited to speak and publish the chapter on Pharmacology.
- LD: Ah, so, we're back now in years to1958.
- EW: Well, I'm telling you how I became an expert in herbal pharmacology without doing any research in it. Is this OK?
- LD: Yes.
- EW: After I consented to write the chapter in Pharmacology I was inundated with literature related to herbal pharmacology in China. Herbal pharmacology received great attention after Chairman Mao made the pronouncement that herbal medicine in China is a great treasure that

should be developed and elevated. Tremendous efforts were made to validate herbal remedies. Pharmaceutical chemists trained in the West were adopting advanced methods to isolate the active constituents of herbs, and pharmacologists were evaluating their pharmacologic properties. Western-trained physicians were told to learn traditional medicine and traditional practitioners to learn Western medicine. There was a huge shortage of health practitioners in China in those days, especially in the rural areas, and hastily trained local practitioners "the barefoot doctors" program was invented. It was the time of political reform movements with slogans such as the "big leap forward", "let a hundred flowers bloom" and, when scientists who were urged to criticize what was wrong got into trouble, they "confessed" and the academicians were downgraded and put into to labor camps in the countryside. I learned about this when I went to Hong Kong on my sabbatical in 1962 and 1963 to do research on Hong Kong addicts. While there I wanted to follow up on the earlier program in herbal pharmacology in China after the 1950s but now found virtually no literature because scientific activity had stopped. I learned this from my assistant, B. N. Mo. Benny, who had been a surgeon in China who had managed to get out of China with his wife. He had difficulty finding work in Hong Kong but finally became a lab assistant in the physiology department. Now how did I digress to politics?

- LD: Actually, I was wondering if we could get back to more recent years.
- EW: My chapter on *Pharmacology* in the 1960 book *Sciences in Communist China* qualified me to be appointed in 1974 to the NAS delegation to evaluate the status of herbal pharmacology in China. Well, that's how I got to be an expert in herbal pharmacology. After Nixon sent Kissinger over to China to talk with Zhou Enlai, they agreed to exchange scientific knowledge between the USA and PRC. The first delegation dealt with exchange of information in medicine, and the objective of the second was to learn about the herbal pharmacology program. The head of the latter delegation was Louis Lasagna, a prominent clinical pharmacologist who was a member of the ACNP. So, I sent Lou a reprint of my publication and managed to get on the committee. There were very few pharmacologists in the US in those years with any knowledge about Chinese herbal remedies.
- LD: So you had been pretty much involved in herbal pharmacology.
- EW: After the chapter on Pharmacology I was invited by the noted scientist and author, Joseph Needham, to write a volume on herbal pharmacology for his series *Science and Civilization in China* for Cambridge University Press. Like a dumb fool, I was flattered and accepted. I thought it would

be relatively easy; I would read some Chinese scientific publication on herbal pharmacology and adapt them using Western terminology. As a preliminary I wrote a couple of articles providing a perspective along such lines and a suitable preface for my book that was published in 1996. As I dug deeper in my subject I learned that more than a thousand years ago the Chinese had noted six types of drug interactions that correspond to certain Western terms as agonist, antagonist, partial agonist, additive action and potentiation. But, unfortunately I have not been able to find any data to support any of these notions.

- LD: Are you still actively writing on herbal pharmacology?
- EW: After I published *Perspective* in 1996, I realized that it would be difficult to write a scholarly treatise on the subject but perhaps I might write a semi popular presentation in which I wouldn't have to support with original data.
- LD: Do you have any thought on where the future is going to take us in science?
- EW: A lot depends on the global economy. China has emerged as a major power and it's pretty obvious that scientific programs will be influenced by economics and politics. The current social capitalism has enabled in recent years extraordinary advances in science whereas in the US the free enterprise system is beginning to have problems. Yes, capitalism has been most successful in helping the welfare of people, since the industrial revolution, but I think it's beginning to hurt us unless we change having a system focused on profit and dependent on an ever increasing population which spawns greedy corrupt CEOs. When you have a system dependent on profit and focuses on profit, health care and education costs increase but so do corrupt CEOs. Bill Gates and Warren Buffet are notable exceptions and are doing a lot of things that the government can't.
- LD: This is economics and world politics. I'm just wondering what you think about research in the future?
- EW: Research on drugs is also is going to be more globally supported increasingly by dependency on technology in the private sector.
- LD: More global research.
- EW: Beside the NIH there are several private foundations like the Pharmaceutical Manufacturers Research Foundation and the Howard Hughes Foundation promoting more global research on drugs. My brother and I have now started one to promote US-China relations using education to help develop leaders. The free enterprise system has been very important in promoting such goals but a system based on profit has its limitations and I don't know how long such a system can last.

China has a recorded history of about 4,000 years with four or five great empires lasting 300 to 400 years. The Industrial Revolution spawned capitalism so for less than 200 years with US the leader for most of the past century. So, how much longer will the free enterprise system prevail with constant increasing cost of living and the gap between the rich and poor widening?

- LD: Since this is an interview for the ACNP, I was wondering when you became a member of the ACNP?
- EW: In 1969 and I'm a Life Fellow Emeritus.
- LD: Were you one of the founding members?
- EW: No, ACNP started in 1961. I already belonged at that time to two pharmacology societies. I was founding member of those two organizations: the International Narcotic Research Conference (INRC) the "C" used to stand for club but we have grown and the College on Problems of Drug Dependence (CPDD).
- LL: Is there anything you'd like to tell me that we've missed, or something you'd like to tell people regarding the future?
- EW: More knowledge and experience applied with common sense results in wisdom. That's why I say that Bill Gates and Warren Buffet have the wisdom to serve people. Bill Clinton is doing more now than at the time when he was President, because he's now doing it globally.
- LD: Jimmy Carter, also.
- EW: Yes.
- LD: Well, thank you very much. I think this was very helpful for the ACNP and for the future.
- EW: Thank you.

MATTHEW J. WAYNER

Interviewed by Paul R. Sanberg Waikoloa, Hawaii, December 12, 1997

- PS: I will be interviewing Dr. Matthew J. Wayner* for the ACNP history taskforce. I will be asking a series of questions to find out about his approach to neuropsychopharmacology and the history he has had and where he sees the future. So, I will go down this list and start talking.
- MW: OK
- PS: What sort of training did you have and when did you, began your career?
- MW: I began my research career and interest in psychoactive compounds when I was an undergrad at Dartmouth College in 1948 and worked with Theodore Karwoski in the Experimental Psychology Teaching Lab. During a sabbatical leave in New Mexico he became interested in mescaline; obtained from the Peyote cactus that Native Americans chewed and ate during religious and healing ceremonies; that they reported induced blue and blue green visual hallucinations during their dances. We were interested in the possibility that the mescaline was enhancing the blue Purkinje after image during the visual stimulation associated with the dancing. Our results were not conclusive but other data that we collected resulted in my second publication in 1951.

The curriculum at Dartmouth included mainly science, math, and Navy courses. During the summer following my junior year, I worked with Professor Lorrin Riggs at Brown University. We recorded human electroretinograms by using an electrode embedded in a contact lens in fluid contact with the cornea. For the first time human luminosity curves were measured objectively. These results appeared in my first publication in 1949.

After graduating from Dartmouth, with an MS degree from Tufts and a PhD. from the University of Illinois, I began my academic career in 1953 as an Assistant Professor at Syracuse University. Eventually I became a Research Consultant in Psychiatry at the Syracuse Veterans Hospital and a Certified Psychologist in the State of New York.

- PS: You did publish as an undergrad. I think that is real important. It is a real predictor that the earlier people publish, the more productive they are later in their careers.
- MW: That is an important point and it would be interesting to obtain more data in support of it. I am a firm believer in providing opportunities in my own laboratory for undergraduates; and I have done that throughout my entire career.

^{*} Matthew J. Wayner was born in 1927.

- PS: Who are the scientists that had the most impact on your career?
- MW: Theodore Karwoski at Dartmouth from 1947 to 1949; Lorrin Riggs at Brown University in the summer of 1948; John Kennedy, at Tufts University in 1950. He was Head of the Psychology Dept. He was also interested in Sensory Processes. We did some research on Human EEGs and visual stimulation. I had some spare time, so I began to build a robot with Bob Hennesy, a technician in the department. The robot became my MS thesis entitled An Electronic Bug for Demonstrating Basic Sensory Processes. It was featured in the Boston Globe newspaper in 1950. It was probably one of the first robots that displayed sensory discrimination in following a white line on the floor and simple learning. Larry I. O'Kelly was my mentor at the University of Illinois where I received my PhD. He introduced me to Verner Wulff and Ladd Prosser in the Zoology Department. Together we did some electrophysiology on the cat spinal cord. Verner left to take the Chair in Zoology at Syracuse and Professor Prosser became my advisor in Physiology. I began my dissertation research on the development of the rat spinal cord preparation because rats were inexpensive and there was a larger database on behavioral data on rats than on other animal. .Two years later my wife Therese and I were returning from having visited our families in New Bedford, Mass and we stopped in Syracuse, NY where we visited Verner Wulff. Syracuse University was establishing a new Psychology Department and Robert Pace the new Chair offered me an Assistant Professorship. Within a few months I accepted and arrived in Syracuse to begin the Fall Semester in 1953. Based on my doctoral dissertation I was awarded my first NIH Grant on November 6, 1954, the same day our first child Elizabeth Ann was born.
- PS: When did you start getting interested in psychotherapeutic drugs?
- MW: In the late 1950's reserpine was a popular hypotensive agent and tranquillizer. It also became somewhat controversial as to whether or not it induced depression. We decided to measure the effects of reserpine on learning in the rat. We also used electroconvulsive shock to possibly enhance reserpine's effects. We published these results in 1959. Other psychotherapeutic drugs that we tested were mescaline and imipramine in 1976. My interest in marijuana goes back to my undergraduate days when Professor Karwoski wanted to do some experiments with it. Obviously we discussed some possibilities that were never tested. In 1973 we measured the effects of Δ -9-THC in the rat and showed that very small doses enhanced adjunctive behavior. We reported similar effects with d-amphetamine in 1973; and methylphenidate and caffeine in 1979. In 1978 and 1979 we also published the

results of a collaborative study with colleagues in Taiwan on morphine and naloxone. During this same period we were also studying the role of serotonin in consummatory behavior; e.g. the effects of 24-hour food deprivation on 5-HT turnover in the lateral hypothalamic area, and the effects of PCPA, PCA, imipramine, fluoxetine, etc. The effects of PCA and PCPA effects on ethanol consumption were also studied. A major study of phenobarbital and several other barbiturates interactions with ethanol, including effects on taste aversion, were carried out from 1975 to 1981.

My main research interests ever since I began working on my doctoral dissertation have been on the part of the brain that is referred to as the lateral hypothalamic area (LHA) and the drug of abuse has been alcohol. Alcohol is relatively easy to ferment from honey and fruit; and its availability and human use goes back at least 6000 years. Any society that discovers alcohol or any other psychoactive compound found in nature; mescaline from the Peyote buds for example, tends to use it; and finds it difficult, if not impossible to give up.

Most of my academic preparation at the University of Illinois was in physiology; and my doctoral dissertation was on the Effects of Dehydration and Hydration on Spinal Reflex Activity in the Rat. I was the one who developed the first spinal cord preparation in the rat. We needed to look at the ultimate output of the brain to really understand behavior: the final common motor pathway. So I became very much oriented in terms of neurophysiology and electrophysiology to better understand why an animal drinks and humans drink alcohol.

A major difficulty in developing a reasonable explanation of the behavioral addictive process has been a lack of an inexpensive animal model to demonstrate the characteristics of human alcoholism. Another major difficulty has been to discover a means by which animal aversions to ethanol solutions can be overcome and voluntary consumption increased; a critical requirement has been that sufficient ethanol intakes must be maintained, in the presence of equally palatable fluids, to sustain the necessary high blood alcohol levels to produce physical dependence.

I will try to be brief and summarize the four areas of interest in which I made my contributions and how they contribute to a better understanding of not only behavioral addiction and especially to alcohol and alcoholism but to any other addictions such as overeating and obesity. These areas are:

1. Adjunctive Behavior: John Falk and I overlapped as grad students studying for PhD's. John Falk selected the term adjunctive to

describe the general category into which one could place all the various types of excessive and bizarre behaviors found in both rats and humans and published an article in 1971 entitled The Nature and Determinants of Adjunctive Behavior. Adjunctive behavior also occurs in children. For example, adjunctive aggressive behavior can be dangerous especially when children are grouped together. Eventually John discovered a very interesting type of behavior that he named scheduled induced polydipsia more commonly referred to as scheduled induced drinking. When John told me about his discovery, we discussed a number of experiments that needed to be done and I asked him to make some lesions in the rat LHA. Doing that, he confirmed that bilateral lesions eliminated drinking as expected. We confirmed John's results and began our own studies on schedule induced drinking showing that the water intake was not important and animals would lick nitrogen from the drinking tube. We were the first to show how to produce schedule induced eating when the reinforcement was water and not food. Falk was also the first to develop an animal model for human alcoholism in 1980 using schedule induced drinking that met all the requirements; except that the animals were trained under conditions of reduced body weight. We developed at alternative model that did not require reduced body weight. The modification that we developed changed the probabilities of occurrence of operants in the animal's response repertoire. This was important because for the most part in humans we do not know what is reinforcing. Jacque Le Magnen many years ago observed that when rats were exposed to ethanol solutions they tended to avoid them until the sources were removed and then returned on a schedule of every one or two days. He referred to it "as post gap alcohol drinking". He discovered the importance of "intermittent sensory stimulation in adjunctive behavior". We did a thorough study of this phenomenon and showed that it was the taste stimulation that was important.

2. Salt Arousal of Drinking: Salt arousal of drinking is way of tricking the neurons in the LHA that Yutaka and I found to be sensitive to sodium ions. The NaCl can be administered subcutaneously, intrapetotoneally, intravenously in normal wakeful rats with implanted cannulae in the brain ventricles or carotid artery. We have studied this so-called artificial drinking very thoroughly. In normal wakeful rats small amounts of salt administered through the carotid induce copious drinking in the living cage with a drinking spout present. When a rat is placed in a test chamber for the first time with a drinking spout present and is administered the same amount of salt and you keep distracting its attention, even if it sees the box and touches it with a paw, it does not drink. However once it licks the tube it begins to drink. Under these conditions it will also lick the drinking tube for nitrogen gas. The peripheral sensory feed back stimulation associated with licking that is the immediate reinforcement, and maintains the drinking as a consequence of the licking.

- 3. Spinal Reflex Excitability Changes Associated With Salt Arousal of Drinking: My work on the rat spinal cord from 1963 to 66, shows clearly that during the salt arousal of drinking the reflex pathways that innervate skeletal muscles of the hind legs increase in excitability and follow a specific time course, increasing and then decreasing to baseline. The duration of the period, following the delivery of the food reinforcement, when the adjunctive drinking occurs, follows a similar time course; as we had shown in 1976. There is no doubt that this is the critical time period following the reinforcement; and only then will the environmental stimuli be effective when they feed back into the LHA and evoke the adjunctive behavior; in this case producing licking and then drinking as a consequence.
- 4. Brain Electrical Stimulation: Several parts of the rat brain when stimulated through implanted electrodes will produce self-stimulation. The LHA is the part of the rat brain with the highest rate of electrical self-stimulation. It is also possible to stimulate some of these areas and evoke motor behaviors of the rat. With extended periods of stimulation for example in the LHA it is possible to evoke different types of complex behaviors such as water drinking whenever stimulated. Water drinking can be switched to eating food or to gnawing on a beef bone or to other behaviors in the rat's response repertoire by extensive stimulation in the presence of the alternative object. The LHA contains glucose sensitive neurons in addition to the Na salt sensitive ones. When the LHA is initially electrically stimulated the general increase in responsiveness is obvious and similar to that observed in the development of adjunctive behavior. It is clear now that salt arousal of drinking, adjunctive behavior and the switching of electrically stimulated behaviors in the LHA can all be explained by the same physiological mechanism.
- PS: But, what do you believe is your biggest contribution to this field?
- MW: In terms of Neuropsychopharmacology, my research that was focused on LHA- Hippocampal Interactions in Alcohol Effects on Memory. One of the best-known effects of alcohol on the brain is the anterograde amnesia for short-term memory commonly referred to as "black outs".

In the late 1960s, from 1967 to 1969 we began publishing some of the circuits that Yutaka Oomura and I were studying in both labs to record from individual neurons in the LHA. The report on glucose and osmosensitive neurons of the rat hypothalamus appeared in *Nature* in1969. The effects of ethylalcohol administered microiontophoretically onto lateral hypothalamic neurons appeared in1971. Because angiotensin when applied to the brain ventricles induces intensive drinking in the rat, we wanted to test it in the LHA. In 1973 we reported that LHA neurons as well as hippocampal dentate granule cells were responsive to angiotensin II (Ang II). It wasn't until 1990 when John Denny a post doc in our lab called our attention to the fact that the functions of angiotensin hippocampal receptors were unknown. At that time Deborah Armstrong had just completed a study on the effects of trimethyltin on evoked potentials in mouse hippocampal slices and was setting up to measure long term potentiation (LTP) in hippocampal dentate granule cells. I knew from our early studies that granule cells in the dentate gyrus were sensitive to Ang II. So we decided to determine the effects of ethanol, diazepam, and Ang II on LTP in dentate granule cells. In the first experiments Ang II was applied directly onto the granule cells and inhibited the induction of LTP. We decided to do a thorough neuropharmacology study on these inhibitory effects of Ang II in granule cells. Dose effect experiments were done in vivo and in vitro hippocampal slices in 1991 and 1993. We modified the technique so that we could administer the Ang II in very small amounts at the tip of the recording electrode. The time course of the inhibition is very interesting from at least 40 minutes to one and a half hour. The inhibitory effect is mediated by the Ang II AT1 receptor because it can be blocked by pretreatment with losartan a specific AT1 receptor antagonist. The results of the next study published in 1995, demonstrated that Ang II inhibited 24 hour memory in one trial step through avoidance experiment and the inhibition could be blocked by pretreatment with losartan. Next, in 1997, we showed that ethanol impairs both working and reference memory in an 8-arm radial maze, and that the impairment of both working and reference memory could be prevented by pretreating the animals with losartan. In another series of experiments we demonstrated that the alcohol, administered by gavage in our behavioral studies was acting in the LHA and was not having a direct effect on the granule cells. We perfused the LHA and did a dose effect experiment showing that the threshold for the inhibitory effect of granule cell inhibition of LTP was 1 to 2 mM and probably less at the individual LHA GABA-A interneuron. Where do these Ang II containing presynaptic axons originate? When we applied horseradish peroxidase (HRP), an anterograde tracer to the dendritic layer of the dentate, using a new staining technique that one of us developed, we found LHA neurons that contained both HRP and angiotensin. We also found that electrical stimulation of the LHA inhibits granule cell LTP, and that the inhibition can be blocked by pretreatment with losartan indicating direct neural connections to the granule cells. Therefore we have shown without any doubt that these cells in the LHA that are extremely sensitive to alcohol, project to the hippocampal dentate granule cells and produce anterograde amnesia for short-term memory.

As to my other major contribution to the field, as an Editor-in-Chief, of the four journals that I founded and also published, I can say it was time consuming. As you know, *Physiology and Behavior* was the first journal and the first issue was published in 1966. The other three appeared in rapid succession over the next several years: *Pharmacology, Biochemistry and Behavior, Brain Research Bulletin, and Neuroscience and Biobehavioal Reviews.* The first three began to being published monthly almost immediately and the review journal is now published bimonthly. I had a sincere interest in publishing and editing journals that emphasized physiology, pharmacology, biochemistry, neuroanatomy, etc but the information had to be relevant to behavior.

- PS: It is an interesting answer when you talked about your biggest contribution, you really focused on what you are doing now, but I think you are being too humble there. I think the fact that you are not only Editorin-Chief, but you started those journals, you really moved the field in a certain way. Wouldn't you agree?
- MW: Well yes. What you are saying is correct and others agree. Yesterday morning at breakfast a colleague was sitting at the next table having breakfast. He raised the issue of Journal publishing today with every-thing online. He said, "When you started *Physiology and Behavior* it turned out to be very important because people were starting to sort of ignore behavior, but your journals called attention to the importance of behavior bridgig the gap between biochemistry, pharmacology and physiology and now that we are beginning to see the importance of behavior again as the result of new technology, e.g., knockout mice etc, I think those journals you created and also edited for many years kept people focused on behavior." So Paul, do you agree with that?
- PS: Oh yes, absolutely
- MW: It sort of fits in with what you were saying.
- PS: I think they are some of the first innovative neuroscience journals. Well, a few more questions. How did you, manage to keep in the field the

various jobs and academic position and are you happy the way things turned out. Was it hard in your day to do that?

MW: My answer is very simple "With difficulty". "It was not easy". Also you must depend upon the good people who work closely with you. In an academic environment doing research, you are not under the same kind of pressure that you are under if you are managing a journal. All manuscripts must be reviewed, a journal must come out on time, and you cannot neglect any one even when you are editing four. Because of the International Cooperative Grants that I had with Japan, Taiwan, Mexico and Visiting Professorships that I had in Florida, Japan, Arizona, and Australia we had to develop an effective communication system. We used IBM dictating equipment and magnetic tapes mailed back and forth, telephone, and copies and tapes mailed ahead in anticipation of where I would be next, so I could select the reviewers etc. Julie Berger, Dawn Barton, then Chris Scannel, and now Marianne Van Wagner were the backbone, the muscle, and brain of the system. My wife, Therese, was the CEO and CFO of our two companies Ankho International and Fayettewille Typesetting. Russ Peterson, Al Florczyk, Warren Klare provided technical support as well as having worked in the lab as technicians. I had excellent students many of whom received their doctoral degrees in my lab and became productive academicians or worked in industry, or have positions with the federal government.

We also published another journal, *Art in Psychotheapy* that I acquired from Pergamon as well as four other acquired journals: *Journal of Neurotoxicology and Teratology, Neurobiology of Aging, Peptides, and Alcohol.* Then, our companies ultimately were sold to Pergamon in 1986. Later on Pergamon was bought by Elsevier. All of these other five journals are still doing very well.

In doing research you need a certain amount of free time to think, ideas need to incubate for a time. Unfortunately as you get older, and even though you are more experienced in your profession, it seems as if you have less time to do that. You must be experiencing this now. Also because of the increase in the number of scientists and the proliferation of new information; there is more to read and less time to do it.

- PS: So. Are you happy with the way things have turned out?
- MW: Well I am very happy in that respect. I am most impressed by, not only my own accomplishments over the last 50 years, but the technical achievements of many people in science in general. What we can do today in comparison to what we were able to accomplish 50 years ago is just phenomenal. For less than \$5000 today you can buy a complete

desktop computer, printer etc. system that surpasses all the capacity that was available in all of the computers in the world in 1953.

- PS: So, what do you see developing, here we are in the 36th annual meeting, what do you see developing in the next five to ten years?
- MW: Well there is a tendency to simplify things. It would be great if there were a single drug that could cure a mental illness in everyone that had the symptoms of it. New drugs are usually claimed to be very specific but as time goes by they become less specific and more side effects become noticeable. The concepts of brain centers and brain nuclei based on electrical stimulation and cell staining can no longer adequately explain localization of brain functions. Then there was search for single neurotransmitter explanations. We found the neurotransmitter that was involved in how alcohol produces its anterograde amnesia for short-term memory. There are probably other factors involved that will be discovered in the future. The great English mathematician and physicist Professor Dirac said some time ago "Everything is getting more complex but a clearer picture is emerging". Maybe now that Neuropsychopharmacology is getting more complex it indicates that we are maturing as a science and new important discoveries lie ahead.
- PS: We got through their questions. I guess we can end by asking you, is there anything you want to say for this archive?
- MW: Well, I have enjoyed being a member of ACNP. I believe it is one of the best Societies to which I belong. I enjoy the meetings and they have been an important source of information enabling me to keep up to date in my teaching. I like the informality of a small but still high quality meeting.
- PS: Do you remember the year you became a member, or first came to a meeting?
- MW: No. My first meeting was in Puerto Rico but I do not remember when. I did attend several meetings before becoming a member. I believe that was a requirement. A candidate had to show a proven interest in the Society. The College needs to maintain those types of requirements for membership. Do you agree with that or not?
- PS: Oh yes, absolutely.
- PS: OK, any last words?
- MW: Well, let's all keep doing research.
- PS: OK.
- MW: It makes life interesting.
- PS: All right.

JAMES H. WOODS

Interviewed by David Healy Las Croabas, Puerto Rico, December 16, 1998

- DH: Wednesday 16th December, 1998 it is 8:35 at the ACNP Annual Meeting in Puerto Rico and on behalf of ACNP I am interviewing James Woods.* James, can we begin with where you were born and when?
- JW: I was born in Louisa, Kentucky in 1937. We stayed in Kentucky for quite some time and then moved to a farm in Ohio and I started school in Ohio and later went to graduate school at the University of Virginia. I went then to the University Michigan, and I have been there ever since.
- DH: You did a BSc in Psychology. Was this, what got you interested in drug abuse or did you have any interest before you did the degree?
- JW: I took a very general interest in Psychology, and I was always interested in the experimental aspects of it. All of my graduate work was just in general experimental Psychology. I actually did a PhD thesis on Learning Theory and didn't do any work in Pharmacology until I went to the University of Michigan. I learned most of the Pharmacology on the bench doing experiments and going to lectures when I had a chance. So it was informal training in Pharmacology.
- DH: Let's go back. Your PhD was on Learning Theory. Which aspect?
- JW: I tested some aspects of a popular theory at that time that was put forward by Kenneth Spence at the University of Iowa on relationships of drives and incentives. It was materially of no interest whatsoever to me and hasn't been for a long time. It served to give me my calling card and not much else.
- DH: So, in a sense, things really began when you went up to Michigan and began to do the informal training in pharmacology.
- JW: The reason why I got interested in Michigan is that they were doing some of the first work in addiction models in primates and had just started to do drug self administration work in rhesus monkeys, and that fascinated me. That was a procedure where I thought that I could use some of the things that I knew and apply them to drugs in interesting ways. I had the opinion that I could at least explain to someone, apart from my colleagues, the relevance of that kind of work when I had a difficult time even to explaining to myself the relevance of the work that I had done for my thesis.
- DH: At that point in time drug self-administration had just begun. Who were the people who kicked it off?

^{*} James Woods was born in Louisa, Kentucky in 1937.

- JW: There were two Pharmacology groups, both in Michigan, and both of them intimately related to the Department that I joined. One fellow who did the work on rats. Jim Weeks, and the fellows who were doing work in rhesus monkeys, the Chair of the Department, Maurice Seavers and some colleagues of his. Seavers hired an experimental psychologist, Bob Schuster, and I took a job with Bob Schuster. Then about three years after I joined. Schuster went to Chicago to work with Jerry Jaffe, and I took over the Lab and continued work with the Chair of the Department. He had a long-standing interest in narcotics and the abuse liability assessment of narcotics, and he was instrumental in keeping a committee going that was, at that time, associated with the National Academy of Science. It was specifically charged to find new pain relieving agents that didn't have addictive potential. They had set up an organization to assess compounds for abuse liability using a very standard set of assessments that included abuse liability assessments in humans. The human abuse liability evaluation was done at that time in Lexington at the Addiction Research Center.
- DH: That was with people like Abe Wikler?
- JW: Abe Wikler, Bill Martin, Harris Isbell and most of the generation of physicians that have been important in the field went through the ARC "farm" as well. People like Jaffe and Herb Kleber. Don Jasinski was one of the junior staff members; all very important people in the field.
- DH: Let me go back and pick up two issues. When you moved into the Pharmacology Department, I guess you were on your way to becoming a behavioural pharmacologist. Would that be right?
- JW: Yes, that's fair.
- DH: How did the overall field of behavioural pharmacology look to you at that point? There were a few different groups around the places. Within the kind of Chicago area people like Howard Hunt and Joe Brady were still there I guess.
- JW: Yes. I'm not sure if he was or not. I remember Brady but I don't know if I've ever met Howard Hunt actually. It was a very interesting time actually because there was what would be considered very traditional pharmacological approaches to addiction which dealt mostly with pharmacological variables and factors that were associated with physical dependence and didn't deal with anything in which there wasn't a strong withdrawal syndrome.

There was also a batch of people who were very interested in operant conditioning and studying the effects of drugs on conditioned behaviour, and different patterns of conditioned behaviour, and showing that drug effects were dramatically different depending upon what

kinds of conditioning were examined. The key people in that area were Peter Dews, Bill Morse, and Roger Kelleher at Harvard and the enormous number of people who they trained at that time who have been continued to be influential in the field. There were also a large number of people that Brady had trained as well, at Walter Reid, and the University of Maryland. Bob Schuster was a trainee of Joe Brady. So there was a strong mix of experimental psychologists with interests in operant conditioning, and they were trying to get to know intellectually more about pharmacology and learn some other things about addiction. When they melded self administration with drugs, and it turned out that most of the drugs that people abused, animals self-administered, it became a quite natural joint interest because pharmacologists had to pay attention to what folk in experimental psychology were telling them about the phenomenon that they were seeing. Some of the more dramatic findings had to do with the fact that animals that self administered drugs, self administered them in patterns of severe intoxication and showed many of the kinds of things that had been hard to capture in other experimental models associated with addiction. So it was a very interesting time.

- DH: How much input to all-these there has been from the work by James Olds and people like that with the intracranial stuff?
- JW: Very little actually. Let's see, how to construct that right. Olds had a lab that was about two buildings from where we were doing our work and I had a friend who was a graduate student in Psychology at Michigan who took me over because Olds was probably one of the most famous of physiological psychologists going at that time, and Olds had interests in drugs. His wife also studied drug effects on self-stimulation and actually collaborated with some of the people from the Pharmacology Department for a while, but nothing terribly interesting came of that work. Olds also worked fairly hard on trying to get drugs through a cannula directly into the brain without very much success. He certainly was administering drugs centrally and trying to figure out something about the circuitry associated with self-stimulation by doing so. It wasn't too long after that a lot of people got very interested in dopamine, norepinephrine, and self-stimulation and then that came to be a very strong controlling interest in drug self-administration later on and it continues to be a strong guiding conceptual focus for a lot of work now. But, it didn't really grow-out of the Olds's work; the conceptual focus came more from self-administration.
- DH: What happened to Jim Olds? He kind of faded out of the scene.

- JW: He did. He went to Caltech and died prematurely. It was a shame. It was a really exciting time for him when he was at Michigan and when he went on to Caltech. He was a very bright man and very interesting. But he didn't have whatever it was that takes you in a functionally important way.
- DH: Did self-administration become the interest of your little group, or was the entire field interested?
- JW: Yes and no. There was a very strong continuing influence of operant conditioning traditions within the field. People who became more interested in the neurochemistry of drug self-administration I would say had a more traditional physiological psychology background than either a pharmacological or behavioural pharmacology background. A continuing traditional pharmacology approach is what I champion perhaps because of where I live. I've always thought that this kind of work should try to embrace and push forward principles of pharmacology in important ways. But I think those three kinds of intellectual influence, i.e., conditioning, addiction, and pharmacology, have been important and continue to be.
- DH: When you say that what you pushed was the relevance of all this to pharmacology and the light shed on pharmacological principles, what did you mean?
- JW: Receptor theory more than anything else. Receptor theory and pharmacological principles associated with dependence and tolerance, the traditional kind of things that have been linked to addiction. And then to try to link those to important psychological constructs, which we're still struggling with, with people arguing about what cravings are and what specifities of what roles dependence actually have in addiction. Those kinds of things are continuing riddles for the field.
- DH: When you began to do your early work, receptor theory was a very theoretical thing even within mainstream pharmacology. They still hadn't isolated the receptors or developed radiolabels. Sure they had to exist but you know until they were actually seen it was hard to believe in them for sure. So when did that really begin to play a part in the whole thing?
- JW: There were not many questioning that at least in the field of narcotics. I was in Washington for meeting and got on a plane with Gardner Quarton who at that time was running the Mental Health Research Institute that was part of our Department of Psychiatry, currently being run by Huda Akil and Stan Watson. Gardner and I sat down together and he told me that Sol Snyder had just identified the opiate receptor, and I said "Jesus, Gardner, we've known about opiate receptors for a long time, what's the excitement". But, this was something that you could look

at in a neural membrane, and there were many reasons in the pharmacology world to know that they were there. And it was an incredibly important spur for the field because at the time that Snyder and other people developed those techniques to find recognition sites for opiates it spurred other people to try to put forward other propositions that could be as interesting. Certainly the whole field of endogenous opiates after the recognition sites were discovered played an important role. And if nothing else, this certainly guided a lot of very important work in the science of neuropeptides. It raised all kinds of interesting questions in relation to endogenous dysfunction that could be related to addiction.

- DH: Take me through that.
- JW: I can't because it's still an open issue.
- DH: Sure it is.
- JW: There is of course a lot of continuing argument about that. The intellectual influences at that time were very strong and there were a couple of very important things that played into it at least for me and for a fair number of people in the field who were doing animal work. When we studied strong drugs of addiction like cocaine and opiates of various kinds, intravenous alcohol, barbiturates, all monkeys displayed the major patterns of behaviour that we saw so there simply wasn't a significant influence of individual difference among the monkeys that we were studying. So we had a very natural response to that, which was that these things are important.

At the same time the people at the Addiction Research Centre had markedly different ideas about that and really believed that the patients who they saw, who were fully developed addicts, with recurring social problems, were definitely psychopaths, sociopaths, and were significantly different to begin with from others. Bill Martin had very strong ideas about that and he was an excellent theoretician and physician with perhaps not as strong a psychiatric background as someone like Abe Wikler, for example, but he had very interesting ideas about it and was a continuing intellectual champion of those factors as they may be related to addiction and the perpetuation of addiction in people. If anything our increasing information about the epidemiology of addiction and the patterns of natural history of addicts has brought us more toward the view that our monkey models are wrong in some ways and then in other ways absolutely on the mark. An interesting stage that we are at now essentially is trying to match animal models to natural history courses that we can segregate in a population and then test in animals in a more a valid way than we have in the past. The early animal
self-administration work showed us that we actually had the crux of the problem. The nature of the effects was so dramatically clear that probably the way that we were misled was that we had hit the nail on the head in terms of actually demonstrating all phenomena that we wanted to. We had such strong pharmacological control of the drug and the behaviour that we were interested in, that all other influences pailed in consideration. That's important for some things, but not important from the point of view of trying to reconstruct a causal chain of events where there are clearly multiple causes of addictions in probably most human cases.

- DH: Back at the end of 1960s when you are at the point where you've begun to get the animals to self-administer the various different drugs, and you've got Wikler and his group over in Lexington who had begun with describing withdrawal effects first and this was all about the consequences rather than anything else, you've got Bill Martin beginning to say really these are odd guys to begin with, you introduced a third bit, the actual drug, the liabilities that go with the drug. How did they receive that? Did they say yes, sure or did they say no?
- JW: Everything started to be melded in a functionally good way, to my way of thinking. Let me give you some examples. At the time the World Health Organisation was arguing about definitions, which they spent a whole lot of time doing, and there were arguments about whether these terms "habituation", "addiction", etc., are well based. At the time they just threw out all the old terminology and substituted pharmacologically-based terms so there was all of a sudden cocaine dependence, cocaine addiction, morphine dependence and everything was pharmacologically tied to different kinds of drugs.
- DH: All that happened when, 1964, '65, '66? It was early 1969 when they came out with the idea of drug dependence.
- JW: That was a big turn of events for the ways that a lot of people thought about things at that time and it was very strongly pharmacologically based and it probably led to a great deal of changes in the way that the DSM criteria have been modified over the years as well.
- DH: It seems to me that I can see that they made this big move forward from saying that people who are addicts aren't just addicts because they're scared of withdrawal but the nature of the drug has something to do with it. To introduce the term drug dependence introduces a terribly ambiguous kind of concept because what you get then may be me saying to a person Look I'm going to put you on steroids of some sort, and in a sense you may become dependent on them. In fact when you think about it you become dependent on virtually every drug we use

in that body systems bounce back but that's a different thing to abuse liability of a drug isn't it? Do you think the term in a sense potentially causes as many problems as it solves?

- JW: Just about everything that we do creates problems in one way or another in that respect. I've become almost anti word. It got us into problems in the sense that drugs per se alone can't carry the concept, they simply can't. There is a return to older terminology to try to get at some of the things that we haven't studied like craving or wondering what that essence of addiction is and things of that sort. There's been a refocusing of attention towards those things since we know so much more about a lot of things than we did at the time that this started. I think there is a general interest in trying to get at what some people believe are more basic issues.
- DH: To come back, you're there and you've got the animals self-administering opiates happily. What did it look like the implications for clinical practice might be? This very powerful drug influence, were there any obvious indications as to what could be done to modify this one way or the other? Did it look like this behaviour was inextinguishable once it was established?
- JW: One of the things that have continued to be very important is a behavior analytic way of treating the problems. We don't have pharmacotherapies for some things as is the case for cocaine now for example, and even when we do there are approaches that can be advanced more strongly in clean conceptual ways, by treating drugs as reinforcers and using a good behavioural management approach to the problems through that kind of conceptual focus. There are good voucher types of programs with cocaine that take a very nice kind of approach from a contingency management point of view. These are things that I always mention in lecture because they are interesting intellectually to me. There are community reinforcement approaches to handling alcoholism. They were put forward by some of the early students of Skinner who I've always thought have been very interesting and these were the intellectual forerunners of the people who have been doing the most interesting work with voucher systems managing cocaine problems.
- DH: What was actually involved? What were the community approaches to alcoholism? What were the proposals?
- JW: The fellow who did this was a fellow by the name of Nate Azrin. He took revolving door alcoholics and restructured their lives. He went after every aspect of their lives that he thought was important and did two things. He tried to set up a contingency so that they could not interact with any of the significant social others if they were intoxicated. So if,

for example, John came home drunk, his wife couldn't let him in the house if that was the appropriate thing to do under the circumstance. If people didn't have significant social others because of alcohol related problems, he set up synthetic families for them, alternate ways for them to get social support, social reinforcers, to set up ways that they could recreate without drinking. The whole emphasis was entirely to provide alternative reinforcers that did not involve alcohol and to punish behaviour that was associated with alcohol taking. The approach is a very general one, works on animals and works on people generally and it doesn't make any difference what their reinforcers are. People have had success applying it with cocaine problem behaviours. Even though Azrin was dramatically successful in handling alcohol problems, the issues associated with benefit and cost he wasn't interested in and he didn't pursue them. What he was interested in was simply showing there wasn't such a strong problem associated with the addiction that he couldn't lick it with his behavioural approaches. They showed that convincingly, and it hasn't been pursued as much I think as it should have been from the point of view of a conceptual approach that should be looked at very seriously all the way through the various phases at which we treat the problem.

- DH: You mention the voucher scheme. This is the one from Vermont?
- JW: I don't know enough about it to tell you how it did start. I know a little bit about the intellectual history of the guys who did it but not a great deal about how they actually got their game going. There are three of them that are involved with this: Steve Higgins, Warren Bickel, and John Hughes. Steve Higgins is the person who has probably done the most work with respect to cocaine vouchers. John Hughes started at the University of Minnesota with Travis Thompson and went I think to Vermont and then hired Steve and Warren; they were working at Hopkins as post-docs. They have always had slightly different interests but they co-operated on a whole bunch of things. The scheme does work. Earlier we were talking about who the cliques are and whether there is a broad influence among people. There is a very strong continuing intellectual influence of people who are really interested in behaviour and very interested in drugs, interested only in those two things and the relationship of things having to do with operant work and drugs and all three of those fellows are very good proponents of that point of view and they have done a fine job of pushing it.
- DH: Let me bring you back to the 1970s. You've got the animals opiate selfadministering, what comes next? In my mind, the issue about possible

dependence to the benzodiazepines begins to rear its head maybe in the late '70s or had you guys begun to get on to it before that?

- JW: It was clear that most depressants were self-administered and you could find strong barbiturate physical dependence in the animal preparations.
- DH: Physical dependence as opposed to abuse liability?
- JW: The early studies were simply to show that the animals would take something like pentobarbital or a shorter acting barbiturate and would stay intoxicated virtually around the clock. So the most interesting aspects of them had to do with how much they took and how continuously they were intoxicated. Benzodiazepines weren't studied probably to any great extent until the early 80s if my memory serves me correctly. There started to be an interesting difference in benzodiazepine self administration right from the very beginning because they were never as commandingly reinforcing to the animals as were shorter acting barbiturates. In some cases it was difficult to even show that some benzos were reinforcing, and if they were, they were very weak reinforcers. So that became an interesting issue right off the bat and an interesting issue with respect to abuse liability. This paralleled when people started becoming interested in dependence on therapeutic doses of the benzodiazepines and I think there has been a continuing interest both in abuse potential studies in benzodiazepines and how that's related to reinforcing effects and the issue of who is likely to continue long-term self administration of them and who isn't and all that kind of thing.
- DH: Can I pick you up on this? I get this hunch that what's happening is you're there with the models saying well these drugs are not too bad and on the other side there's this mounting public hysteria almost that these drugs are the most dangerous thing that ever happened. Is that the way things went?
- JW: Certainly benzodiazepines have had a very complicated history in terms of how the public has responded to them. In the late 1960s, early '70s there was a strong response from some kinds of critics that they were being used more by women, that the costs were too high - the costs being too high continue to be things that people are concerned about – and that they were being terribly over-prescribed. And some of those themes continued certainly on into the 1980s, emphasised in different ways and by different people. But it doesn't seem to me that some of the conditions have changed very much over that period of time.
- DH: In a sense what your saying is that during the 1960s 1970s the big issues were the overuse, the cost and the fact that they were being used for problems of living, almost for socio-political purposes to keep certain groups of people quiet, but the issue of there being seen as

agents as dangerous in terms of their abuse liabilities as the opiates weren't there. Then, all of a sudden then in the 1980s the thing being the whole story begins to play in terms of we're making these people addicts? How did you see all that? The animal work has to play the part because what you seem to be saying is that in the animal models compared to the opiates these drugs shouldn't have been making these people addicts? In a sense they weren't were they?

- JW: No. I think there is congruence actually between what the animals are telling us and what happens to the people. Speaking simply from an epidemiological point of view, there are a few people who take benzodiazepines as a pattern of poly-drug abuse; most of the time benzodiazepines play a secondary or tertiary role in terms of what the main driving drug is of the poly-drug abuse. Those people from an epidemiological point of view are very small in number and social importance. If you take a batch of monkeys and expose them to benzodiazepines, the drugs that have the strongest abuse liability are the ones that are short acting and have very rapid onset of effects. The reinforcing effects don't really strongly push animals to take them and self-administer enough to get them to the point of were they actually produce strong dependence of the physiologic kind. So I have always thought that our crude animal models mimic the clinical situation in some respects. I don't think that physical dependence of the benzodiazepine type actually represents any more of a significant problem than physical dependence of any kind for a drug that's chronically administered. People who are taking benzodiazepines for a long period of time and who are getting therapeutic effects shouldn't be in any way classified as addicts.
- DH: But they have been haven't they? Did you ever get pulled into this big public debate?
- JW: Yes. I've talked about it.
- DH: In a sense the message you have during the '80s can't have been the message the critics wanted to hear. Remember the pharmaceutical companies were going to say, oh gosh, you know, this is good, this is what we want to hear but the band wagon of public opinion wanted to be told these drugs were nasty and medical people were awful to be giving them.
- JW: Yes, that's certainly true and there were certainly a significant influence of that kind. It seems to me that within the ACNP and within a small set of people who have done some of the most interesting research there've always been people on the right track who've been proponents of benzodiazepine use and it seems that they are pro-therapeutic drugs, and I have always thought that that voice for benzodiazepines

and for drugs that have been used for anxiety always had a difficult row to hoe. There are probably multiple influences related to that, one being that there is still a strong component of people who believe that those who suffer from anxiety have weak wills or have some sort of environmentally produced moral weakness.

- DH: And the answer is for them to pull themselves together.
- JW: That's right. Just say don't have the problem. Those kinds of attitude problems exist probably all over mental health issues one way or another.
- DH: Can I just take you on to one more group of drugs you worked on. You got into phencyclidine, PCP work. Was this out of interest in PCP or was it because PCP actually became a big public health problem in the US in the late '80s?
- JW: Well for me it was an interest in just expanding what we knew about behavioural pharmacology of drugs and it was something I got interested in. I continue to have an interest in teaching myself by doing research on things that I work on. It's a great teaching device. For me getting interested in things related to PCP didn't have very much to do with drug abuse related problems as much as it was that they were extremely interesting behavioural drugs. They altered behaviour in very interesting ways. It turned out that it was an exciting time in the pharmacology of PCP because one of the first meetings that we went to on this had a nice link to excitatory amino acids and to a coming together of a different set of people again. The excitatory amino acid field had been driven by an interesting set of medicinal chemists and electrophysiologists, Jeff Watkins, first of all, and McLennon, at Vancouver. They were probably 30 to 40 people who had taken the field for two decades, kept it to themselves and developed it beautifully conceptually and then relating phencyclidine to excitatory amino acids was a very important thing. It was done by David Lodge and the field blossomed both from what could be done that was interesting. It was a delightful time. One thing that was extremely fun for me was going to some of these meetings. If you didn't talk about channels, if you were interested in more general integrative things, people thought you were really wasting their important chemicals. I actually had somebody tell me that at a cocktail party at one of the first meetings I went to. But by the same token I was strengthened by Jeff Watkins telling me that if he was starting in the field again he would do the kind of work I was doing.
- DH: Jeff was unique though with his nose for the scientific issues and things like that and working pretty consistently.

- JW: Delightful guy, magnificent chemist. Good medicinal chemists are incredibly important for this whole field and when you find one that's very interested in significant problems as they were, they are an exciting set of people who tend to be getting interested in one or two areas of pharmacology and really push it.
- DH: Did you link back at all then to people who have been involved in PCP work in the US, people like Ed Domino.
- JW: Yes. Well, he's a colleague. I talk to him about it all. I would check with him on things that I did. He'd easily tell me when I was off the mark and sometimes when I was on. I talk to him about everything.
- DH: Does PCP have the abuse liability of the opiates? In the UK, in the late '80s, Ed gave a wonderful lecture on PCP and all this group of compounds and said look you know we don't really think it causes craving so we are not sure why all these people are having it at the moment.
- JW: That's an interesting question. There are probably things that we can't really conceptualise well yet. There are very few people who actually show prolonged patterns of use, yet when you get animals involved with them they take them excessively. Perhaps we have too strong pharmacological control. There is an example now that I am interested in sort of belatedly, which is ecstasy, which is very much the same way. Monkeys take ecstasy on a chronic basis and people don't. They tend to take it and run out fairly quickly. Those are things that we don't know very much about that we should know more about and we don't have animal models of it. There are a lot of things that we have to study more.
- DH: There is another very important behavioural pharmacology technique, drug discrimination that's come on the scene at this stage. When did you begin to get involved with this?
- JW: I got interested in drugs discrimination techniques because they seemed to provide nice links to receptors and that's what really interested me. That was shown very nicely in the mid-70s by Frances Colpaert and Steve Holtzman with narcotics. And I got interested in it in that way to try to characterise different kinds of narcotics the techniques are really great for that sort of work. I continue to use them for that reason, and it seems to me to be one of the nicer kinds of procedures that behavioural pharmacologists have used in very intelligent ways, in all kind of areas in CNS pharmacology.
- DH: Could you take me through it?
- JW: It's hard to think of a class of drugs that hasn't been studied with drug discrimination techniques where the technique hasn't been useful in making distinction of interest. For instance, you can pick out

receptor type differences very nicely with them. You can characterise antagonists well. You can differentiate competitive and non-competitive antagonists. Where the techniques are difficult and where a lot of people thought that they would be more useful is in trying to figure out what subjective effects are related to discriminable effects and one of the kinds of conceptual missteps that many people have made has to do with the fact that if an animal is trained to discriminate morphine, it has been assumed that the discrimination must be the euphorigenic effects as opposed to any other discriminable effects that morphine might have. People continue to fall into that trap. That's difficult to draw an inference about but nevertheless people find it tempting.

- DH: Even if we take benzodiazepines or the antidepressants or whatever, even if you say to the subject we don't want you to go for the subjective effects in the sense of any euphoria of any sort we want you to focus just on whether there are differences between this drug and the other and if you can pick them out maybe its because of GI effects or whatever, surely that would be an extremely important thing to be able to show reliably.
- JW: Sure it is, but you just can't use these techniques for it. You can start to approach it perhaps with human subjects, but trying to adapt those to animals is extremely difficult if not impossible.
- DH: You got involved with the Committee for Problems of Drug Dependence.
- JW: A Committee that became a College recently. The Committee was first associated with the National Academy through the National Research Council then became an independent non profit corporation; changed its name to The College, and it has become a sort of the drug abuse equivalent of the ACNP professionally. The Committee, when it was started, had the primary focus of developing abuse-free, pain relieving narcotics. It set up a Drug Evaluation Committee which essentially acted as a Scientific Evaluative Group using mostly behavioural measures of pharmacological action to draw inferences about abuse liability. And they use as well the concept of pharmacological equivalence in the sense that if morphine does it and you have another drug that also does what morphine does, then drug X is going to produce morphine's effects. With that Committee set up, the drug evaluative part of the Committee grew over the course of the Committee's existence within the Academy and has continued to function.
- DH: Can you put a time frame on this Committee?
- JW: The Committee started, I think, in 1929. I don't remember the exact time that it was dissociated from the Academy but when it was it was the longest standing Committee that the Academy had ever had. In the

late '60s and early '70s the pharmacology of dependence was largely studied with withdrawal procedures in dogs or primates and then with the advent of self-administration procedures, those procedures were added. Stimulants then were easy to study so the drug evaluation component of the Committee on Problems of Drug Dependence was expanded so that depressants and narcotics that had been their mainstay were also continued but stimulants were also studied. In assessing abuse liability they took compounds from anyone. Eitherthe Drug Enforcement Administration, the FDA, academic medicinal chemists, or pharmaceutical companies can submit compounds blindly to the Committee, and getting a report back that tries to draw an inference about abuse liability. It's been an extremely important Public Health Service that the Committee, and then College have supported over the years. It was something that my boss at Michigan helped start and supported and then I took over the role in the late '70s and ran the Committee, just the Michigan component of it, and then other people were involved from Pharmacology and Psychiatry Departments and other institutions as well.

The Committee has changed a great deal over that time too and its function has become different. It was first there for the very specific purpose and objective of finding non-abusable narcotics and then they started to devote more and more attention to other kinds of things. It took on roles of assigning drugs to the Controlled Substance Act, and had some important role in that respect - they made recommendations to the FDA that were taken up. Then FDA set up its own Committees to do those things without the advice of the Committee. They have served as advisers to regulatory agencies in more informal ways and that was probably a very important component of their function in the '70s and '80s. Now the organization has changed its function to become more a professional membership organization in the way that ACNP is, though they continue to be very interested in regulatory functions either through people who are on the Board or some specialised committees that pay more attention to those sorts of things. It's become a very diverse professional organization from its narrow beginnings.

DH: Let me take you back to a group of issues perhaps to close on. You are there on the plane on your way to Washington in 1973 or thereabouts and you're told Sol Snyder has just isolated the opiate receptor – he's been able to radiolabel it so we can see it. You say so what we've known that it was there for all time, what is the big deal? But maybe the big deal is capturing public opinion. People really have a thing that they can hang their hat on, a thing we can see. It's real. These are maybe real problems. It seems to me that more than any other branch of psychopharmacology addiction research has a huge public relations issues. It's very important to get the scientific breakthroughs that the public will understand, out into the public mind in the right way. In *Time* or *Newsweek* about a year ago there was this very eye grabbing front cover of a fish going after another fish and there's a hook etc., saying "now we really understand it, its now we are on the verge of really understanding it all". Could you take me through these issues a bit just how this work played? Addicts are the lowest of the low in the public mind so we really have to work to get the funds to treat the problem, etc.

- JW: I've always felt that its always been a very charged public health issue and over time there has been hue and cry about the drug abuse epidemic in the late-1960s and then various things get played up in the press perhaps in some good ways some bad ways and I'm not sure if it's any different than other things, though it certainly captures the public imagination perhaps more than other problems. The public interest sometimes runs in terms of the politics but the politics do not necessarily run well with the science of it and those are the kind of things that are sometimes the most difficult to deal with. I can remember times when people would ask how, can you spend all the money that can possibly be dumped into the scientific community, and sometimes I've actually thought there's been more money spent than there should be. It's going to be a continuing problem. It's going to get all kinds of different glances from the public and its something for which we have to have the best kind of scientific framework that we can provide to deal with in an intellectually honest way. There will be various mistakes that we will all make in trying to deal with it given that it is a very complicated problem.
- DH: There is an issue that I left out earlier. Back with PCP, which doesn't cause much in terms of craving, there is also the Joe Brady view that a lot of people take these drugs because of the behavioural toxicity they cause. What do you think of that in the light of the PCP models that you have? For example you've been working on the issue of craving, but too there are still an awful lot of people out there saying I'm not absolutely sure that there is anything such thing as craving. The other view is that if you take drugs like LSD which don't cause much in the line of craving but you go out of your mind, you've got a distorted world and maybe people want this altered state of consciousness as a driver to drug taking. PCP is interesting from that of point of view. Yes it pro-

duces the altered state of consciousness. Did any of this cause you to think again about what the critical pharmacological factors are?

- JW: I think if you think about these things in a pharmacological point of view it's a great riddle. It's an extremely interesting riddle. We are really at a very crude state of understanding with respect to that. To pick out something that is common among them may be a mistake because there probably are as many differences in the ways that they function even though they may have a common reinforcing function, there are so many differences among them that it would be extremely hard to try to nail a common element even though some people have emphasised a dopaminergic function as a common link. Maybe that's not the most interesting common link that we can find and I don't know that emphasising a toxicologic consequence as something that might be common would be helpful. I like the differences among them as much as the similarities at this point in terms of the fascination with the riddle.
- DH: I guess that's the answer to scientists but in terms of how these things play in the public mind; they want a simple answer don't they?
- JW: Sure.
- DH: I think that that is a perfect ending point,

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The American College of Neuropsychopharmacology (ACNP), founded in 1961, is a professional organization of leading scientists. The core purpose of the College is to contribute to alleviating human suffering by advancing the dissemination of knowledge related to the biology of the brain as well as the biology, prevention, and treatment of brain disorders; by promoting emergence of pioneering young scientists as leaders within our College and within their fields of science; and by facilitating the collaboration among relevant organizations and agencies.

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In This Volume

In the first five volumes of this series the focus was on different methodologies used in the study of psychotropic drugs; in Volume Six the attention shifts to the employment of these methodologies in the study of "addiction", a class of psychiatric disease. While in prior volumes interviewees reflected on their contributions to behavioral pharmacology, pharmaco-EEG, neuropharmacology, psychopharmacology and neuropsychopharmacology, in this volume interviewees talk about their contributions to elucidating the biological underpinning of addiction, and to the development of pharmacological treatments for addictions. The transcripts of Volume Six document the replacement of norepinephrine by dopamine as the molecular substrate of reinforcement; the identification of opiate receptors in the brain; the extension of the site of brain structures involved with addiction from the limbic lobe to the frontal cortex; and the supplementation of behavioral methodologies with brain imaging and molecular genetic techniques in addiction research. Dedicated to the memory of Daniel X. Freedman, President ACNP, 1970, Volume Six is edited by Herbert D. Kleber one of the leaders of addiction psychiatry. Kleber was instrumental in introducing clonidine in the treatment of opiate and dronabinol in the treatment of marijuana withdrawal.