# Background to the Celebration of Herbert D. Kleber (1904 -2018)

**by**

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By the mid-1990s the pioneering generation in neuropsychopharmacology was fading away. To preserve their legacy the late Oakley Ray (1931-2007), at the time Secretary of the American College of Neuropsychopharmacology (ACNP), generated funds from Solway Pharmaceuticals for the founding of the ACNP-Solway Archives in Neuropsychopharmacology. Ray also arranged for the videotaping of interviews (mainly by their peers) with the pioneers, mostly at annual meetings, to be stored in the archives. Herbert Kleber was interviewed by Andrea Tone, a medical historian at the Annual Meeting of the College held in San Juan, Puerto Rico, on December 7, 2003 (Ban 2011a; Kleber 2011a).

The endeavor that was to become known as the "oral history project" is based on 235 videotaped interviews conducted by 66 interviewers with 213 interviewees which, on the basis of their content, were divided and edited into a 10-volume series produced by Thomas A. Ban, in collaboration with nine colleagues who were to become volume editors. One of them, Herbert Kleber, was responsible for the editing of Volume Six, dedicated to Addiction (Kleber 2011b).

The series was published by the ACNP with the title "An Oral History of Neuropsychopharmacology Peer Interviews The First Fifty Years" and released at the 50th Anniversary Meeting of the College in 2011 (Ban 2011b).

Herbert Daniel Kleber was born January 19, 1934, in Pittsburgh, Pennsylvania. His family's father's side was from Vilnius, Lithuania, and the Mother's side was from Germany. Both families came to the United State during the first decade of the 20th century.

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(PHS) at the US PHS facility in Lexington, Kentucky, the home of the Addiction Research Center with Bill Martin, Abe Wikler, and Harris Isbell. During this time he became

concerned about the very high "post Lexington" relapse rate of patients with addiction and developed a double-blind research protocol with the help of Bill Martin, Director of the Center, to study the effects of lysergic acid diethylamide (LSD) in group therapy in the treatment of volunteer addicts, using Dexedrine as the active placebo. The project was never completed because LSD was recalled by Sandoz, the manufacturer when it became, during those years, a "street drug" (Kleber 2011c).

Being at Lexington launched his life-long career in carrying out research, treatment and policy in the field of addiction.

Kleber returned to Yale in 1966 and spent the next 23 years there to become full professor in 1975.

In 1968, he received his first grant from the National Institute of Mental Health which established the Drug Dependence Unit (DDU) at Yale that was to become one of the first true multi-modality treatment and research endeavors. He became involved in his Unit with methadone maintenance, research with naltrexone and in attempts to develop medications for cocaine and marijuana dependence. (Kleber 2011c).

In the late 1970s, in collaboration with Mark Gold and D.E. Redmond, Kleber discovered that administration of clonidine, an α–adrenergic agonist, could ameliorate opiate withdrawal symptoms (Gold, Redmond and Kleber 1978). It was the first non-opiate substance to ameliorate many of the opiate withdrawal symptoms. Pursuing his research with clonidine further, about seven years later in 1985, in collaboration with Mark Topazian and Joseph Gaspari, he demonstrated that co-administration of clonidine and naltrexone significantly shortened the opioid withdrawal syndrome without significantly increasing discomfort (Kleber, Topazian and Gaspari 1985). During the first decade of the 21st century Kleber, in collaboration with Frances Levin, was one of the first to show that dronabinol, a synthetic levoisomer of tetrahydrocannabinol, could mitigate the symptoms of marijuana withdrawal (Levin and Kleber 2008).

In 1989 he was invited to Washington 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.

After he left Washington in November 1991, Kleber and his new wife at the time, the late Marian Fischman, a renowned cocaine expert and Professor at Johns Hopkins, went to Columbia Medical School in New York, where he started the Division on Substance Abuse (DSA) in 1992, with a program similar to the program he had in his DDU at Yale, and they set up human behavioral laboratories, similar to the one she had at Hopkins, with each laboratory focused on a different area of addiction research. Among these laboratories, the "cocaine laboratory" was especially productive.

In 1992 activities in the field of addiction at Columbia in the DSA were complemented with activities in the Center for Addiction and Substance Abuse (CASA) that Kleber and Joseph Califano, Secretary of Health during H.W. Bush's presidency formed. It was to become a Center for Addiction and Substance Abuse policy.

From 1992 to 2001 Kleber with his associates was carrying out research on cocaine, opioids and marijuana. They were first to demonstrate physiologic withdrawal manifestations with marijuana that could be successfully treated with dronabinol.

In a historical perspective probably the most important contribution of Herbert Kleber was that in his DSA at Yale and DSA at Columbia, he developed a cadre of researchers who were to become involved in studying addiction.

Hebert P. Kleber died while traveling in Europe on October 5, 2018, in Santorini, Greece.

An edited version of Andrea Tone's interview of Herbert Kleber conducted in San Juan, Puerto Rico, on December 7, 2003, is presented below (Kleber2011a).

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 fraternity and I 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 five or six 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.

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…

HK: …toward people going into psychiatry. Jefferson prided itself on its 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 [Federation of American Societies for Experimental Biology] 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 quickly, 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-blind 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 family 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 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 <u>unencumbered</u> 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 six to one. 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 just 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 doing 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 a year in grants and we had another $3 or $4 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, require 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 quiescent 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 believe 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 12$^{th}$ 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 endo-cannabinoid 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 three 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 over 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.

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