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?

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

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 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 quite 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, long-acting 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 short-acting 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 forty-eight hours in humans. But in rats we found that methadone has a half-life 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, with 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 long-access 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 molecular-cellular 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 point-wise 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, long-term 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 say into the recording machine, but I'll say 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 involvedpathways 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 mu 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 <u>not</u> addiction. Addiction is the compulsive, relentless drug seeking driven by "drug hunger" or craving, and resultant drug self-administration, 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.