Dr. Nora Volkow has served as Director of the National Institutes of Health's National Institute on Drug Abuse since 2003. She has been a leading figure in research on addiction as a chronic brain disease and has widely promoted that conclusion in professional and public venues. Her research work and leadership at NIDA have generated wide professional acknowledgement and numerous awards. The interview below with Dr. Volkow was conducted by Dr. Charles O'Brien.

DR. CHARLES P. O'BRIEN: This interview is part of the ACNP oral history project and the interviewee for today, December 9, 2008, is Dr. Nora Volkow,[*] who is currently the Director of the National Institute on Drug Abuse (NIDA). Nora, thanks for agreeing to being an interviewee for this project. The interviews are going to be stored in the archives at UCLA and also be made into a transcript so that historians of the future will be able to have a look at this when they write books about this era. Probably, it's going to go online as well so that people will be able to go to the internet and access it. Personally, I was very surprised that people actually watched my interview when I did it some years ago and reviewed the transcript, so you can be sure that sometime in the future, there'll be scholars reading this. I don't want to put you on the spot, but, you know, it's taking your time for a good purpose, I think. So, would you begin by telling us where and when you were born and something about your background?

DR. NORA D. VOLKOW: Yes, I was born in Mexico City on March 27, 1956. I grew up in the house of my great grandfather, Leon Trotsky. Since my grandfather had been sent to a concentration camp and my grandmother committed suicide, my father, who was left to fend for himself, ended up living with his grandfather, Trotsky, who took care of him. In 1937, after about eight years in exile, Trotsky was finally transferred to Mexico, which was the only place that gave him political asylum, and he brought my father with him. When Trotsky was assassinated in Mexico City in 1940, my father was left with Trotsky's second wife. He grew up and went to school in Mexico, got married and raised a family. We were born in the very same house where Trotsky was assassinated, so, I was brought up in a very unique environment; people would come from all over the world to see the place. On one hand, it was very interesting, because it exposed me to a very diverse group of people, but on the other hand, I was instilled, while growing up, with the concept that you're brought into this world and you have a responsibility for other human beings and that whatever your talents may be, in principle, you should be using them to make it better for others. So, that was very, very clear to me even as a child. I was brought up with that moral precept that you have a responsibility towards others. So, as I grew up, then, that certainly influenced the decisions I made throughout my career and life. I was fascinated with biology and, particularly, with the human brain, and from very early on, I knew I wanted to do research on the brain. I was very curious and particularly attracted to and intrigued by human behavior. One of the things that always interested me about human behavior was the constant conflict between an individual's acting on what he or she thinks they want to do, and their ability to really do it, and the extent to which people really have control over their actions and emotions. And yet, many times people just cannot control their behaviors, regardless of how committed they are about doing it. One of the extreme examples of this conflict, of

[*] Nora D Volkow was born in Mexico City, Mexico in 1956.

course, is epitomized by the disease of addiction, when a person who has become addicted to a drug may say that he/she doesn't want to take a drug, but has lost the ability to control the behavior. So, we could say that, in its extreme manifestations, addiction represents a breakdown of our ability to exercise free will. This realization was one of the first things that drove me toward the study of the effects of drugs.

DR. CHARLES P. O'BRIEN: So, it started very early, but I'm going to go back a little bit, because you've already got into the real meat of this interview, but I think that just to make sure that we get the standard information, let me just clarify. I gather from what you said that your mother is a Mexican woman?

DR. NORA D. VOLKOW: No, my mother was not Mexican. She was born in Spain and grew up in the midst of the Civil War. At some point, by pure chance, she got separated from the rest of her family. When Franco took power, her family had to emigrate out of Spain and Mexico had an open immigration policy according to which foreigners could be granted political asylum. The same openness that brought Trotsky to Mexico also brought the family of my mother. I have always said, somewhat facetiously, although there is some reality in it, that I'm the product of the belligerent nature of human kind: from one side, the Russian Revolution, and from the other, the Civil War, and that's why I ended up in Mexico, because it was that country, at that time, that really was open to all political outcasts.

DR. CHARLES P. O'BRIEN: And, you obviously were raised in a very intellectual atmosphere?

DR. NORA D. VOLKOW: Correct; and I think that when you're raised in a family in which your ancestors have been persecuted and destroyed, you tend not to take things for granted, you are more aware that your current well being is the result of the sacrifice of many individuals and that it's not a given and that it can be very easily disrupted or taken away.

DR. CHARLES P. O'BRIEN: I had the pleasure of meeting your sister when I was in Mexico City recently and your brother-in-law. Do you have any other siblings?

DR. NORA D. VOLKOW: Yes, we are four girls. My father wanted boys and I think that he got chastised by having four very belligerent girls. I am the second one. My older sister, is a rather well known writer, poet. One of my younger sisters, who are identical twins, is a physician doing fascinating work on HIV and the role of plasma transfusion in the dissemination of the AIDS epidemic. The other twin is an economist. So, I have three very talented sisters and of the four of us I'm the only one that left Mexico. All my sisters live in Mexico City. And, by the way, my physician sister was very impressed with you when she met you at the international AIDS meeting.

DR. CHARLES P. O'BRIEN: Thank you. I liked her a lot, too, and I'm hoping that I run into her again sometime, because she said that her husband was interested in the kind of things that I'm doing. And, one time you shared with me the fact that you were

speaking French since age seven, so tell me about your languages, you know, in the home, and I guess you speak French, as well as Spanish, and, then at some point, you learned English, so can you tell us a little bit about that?

DR. NORA D. VOLKOW: My father was born in Russia, but he lived as a child in Germany, France, and Turkey, so when he came to Mexico he only spoke German, French and Russian. I think that, in a curious way, the language that he considered to be his mother tongue was French, not Russian. He left Russia when he was four years old, and he has always had an admiration for the French culture. Both my parents encouraged us to learn languages from early on. In Mexico, we went to private schools, where half of the courses are taught in English starting in kindergarten. But my father, who loved the French language, sent us from age seven to learn French. Naturally, that instilled in me a fascination with languages. I like the concept of being able to switch between different languages when I give a talk. You get conditioned to a word in a given language that does not necessarily gets conditioned in the other language. So, a word that you may hear in one language may be associated to a particular emotion or memory, but when translated to another language it loses that emotional connection or "conditioning effect" that conveys an experience beyond the mere meaning of a word. Similarly, the grammatical structure of a language imposes constraints into your thinking and therefore, I like to analyze events in my brain using different languages to see how they affect my conclusions. My love for Contemporary German literature prompted me in high school to earn German. In medical school I started to study Russian and Italian but unfortunately, by then, I was too old and rapidly forgot these languages. I say this because the languages that I learned before I was eighteen I remember whereas those that I learned at eighteen or later I have forgotten.

DR. CHARLES P. O'BRIEN: I met a young doctor once who said he was in your high school class and he's practicing now, I think, in Boston but I don't remember his name, and he was telling me how smart you were in high school. Can you tell me a little bit about that?

DR. NORA D. VOLKOW: I'm trying to figure out, in high school or medical school?

DR. CHARLES P. O'BRIEN: I thought he said high school. Maybe, I'm wrong, but he's working in this country as a physician.

DR. NORA D. VOLKOW: Yes, now I know who you're referring to. His name was Rick and he had the highest score in the entire school. Rick was the same age as my sister, who was also considered a genius; both of them were at the same academic level. So sibling rivalry was very good for me; having this extraordinary brilliant sister triggered my competitiveness. I think I've got the competitive gene(s), whatever that is, which pushed me to emulate my extremely bright sister. Since I am also enormously perseverant, I never gave up. So, I think that's how it happened: the combination of having a brilliant sister and my competitive and perseverant nature motivated me to always try to be the best at every step of the way. I think this explains Rick's comment.

DR. CHARLES P. O'BRIEN: So, why did you decide to go to medical school?

DR. NORA D. VOLKOW: Well, I was fascinated by the human body. I liked biology and was always very interested in understanding how it works. I think that if you could go back in time and interview me as a little girl, and asked me: what would you like to be when you grow u my answer would have been to understand how the human brain works. It's just an amazing enigma that never stops fascinating me. For example, and this happens often, when I look in the mirror I think of that first time I recognized myself looking in the mirror when I may have been two or three years old, and realized that I am the same person and, yet, it's so different. Moreover, and even more bewildering, it's me the observer, using my brain to observe my own self, which is the product of my brain that I use to observe. How does all this work? That's always been something that I wanted to get into and medical school provided me the means to do that, because, what a better way to understand humans than in the process of investigating and understanding the concept of disease. I mean, sickness removes a lot of a person's defenses and you can see much more of who they are under those circumstances, of who, "we" are as individuals, but also who we are as social creatures. It was this human element both in the individual and in the social system that drove me to medicine.

DR. CHARLES P. O'BRIEN: When did you start to become interested in addiction?

DR. NORA D. VOLKOW: I've always been very interested in addiction and I think one of the reasons was that my favourite uncle, the brother of my mother, was an alcoholic. I adored my uncle, he was an extraordinary generous man, incredibly warm, and, yet, when he drank alcohol, he was transformed into another person. I could never understand the process of how a person could become so completely disrupted by drugs; at the same time, I was also distressed by the complete social rejection of the addicted individual. For it was evident to me that a person who was so generous would not suddenly act in that way in order to purposefully hurt others; that the transformation had to take place outside of his conscious control. There was another event that further influenced me, which occurred many years later when I was already a medical student. It was then that my mother confided to me, for the first time, that her father had committed suicide. She explained to me that he had been an alcoholic and unable to control his addiction so he killed himself. That made me clearly aware of the disconnect that exists in terms of our ability to empathize with individuals suffering from some diseases while rejecting those suffering from other diseases, namely those that manifest with abnormal behaviors. I think that the fact that these diseases hinge on behavioral perturbations has been interpreted to imply that, somehow, they are the individual's fault. These personal experiences shaped my professional goals in science and medicine, which is to have drug addiction understood as a disease and treated accordingly, and in the process help develop better treatments.

DR. CHARLES P. O'BRIEN: Did you do some research in medical school?

DR. NORA D. VOLKOW: Yes, from the very beginning. As a first year medical student I started to work in the laboratory of Julian Villarreal who was a very special

person. He had trained at the University of Michigan. At that time, people were very interested in opiates and were trying to develop analgesics that would not generate physical dependence or psychological dependence, as addiction was then called. As a medical student, I worked in the afternoons in this project as a volunteer. That was the time when Kosterlitz and Akil first identified the endogenous opiates and I was trying to manipulate the opiate system by exposing animals to stressful environmental conditions.

DR. CHARLES P. O'BRIEN: Did you happen to go to the CPDD meeting that was in Mexico City in the early 1970's?

DR. NORA D. VOLKOW: No, I did not go. I started medical school in 1975 and I started in the laboratory of Julian Villarreal in 1976, so it was after the CPDD meeting in Mexico.

DR. CHARLES P. O'BRIEN: Well, Julian was also a friend of mine. We called him Julian, but anyway, he invited me and a few other addiction scientists to Mexico City. I think it was in the late '70s, or even the early '80s, so you might have been there, but we came and we gave a series of lectures at the university there in Mexico City and there were a lot of students..

DR. NORA D. VOLKOW: At that time I was a medical student. I started medical school in 1975, and in '79, as part of my medical education I travelled for one year to Paris, where I studied with Pierre Pichot, who was at the time the president for the World Psychiatric Association. I was very interested in his work, which focused on developing measures to quantify psychiatric symptoms reliably, particularly for clinical depression. At that time, I was intrigued by the underlying processes that make certain symptoms correlate with others in specific "symptom clusters". I did a project, which, unfortunately, never got published, where I studied the effects of treatment on the relationships between individual symptoms in these "symptom clusters" obtained from patients with depression. I wanted to assess whether the relationships persisted or if treatment preferentially improved some symptoms but not others in such a way that it uncoupled them from the original "symptom cluster". For this purpose I analyzed the symptoms from a large number of hospitalized patients with depression, for whom there was quantitative data on their symptoms before and after they completed inpatient treatment and achieved clinical recovery. The analysis showed that treatment did not affect the cluster structure and that the relationship between the symptoms remained the same before and after treatment. What the treatment did was just decrease symptom intensity. That was one of the first clinical studies I did in Psychiatry. After one year in Paris, I returned to Mexico to complete the rest of my medical education. Having lived one year in the heights of "civilization", I was ready for the opposite so I chose to spend the last year of my medical training practicing in the jungle. In the border between Mexico and Guatemala you have the remnants of the Lacandon Indians who occupy areas of the jungle where the Maya culture once existed. My father was furious at my decision and stopped talking to me for almost three months. He was concerned by my going to the middle of the jungle, where they would not normally allow women because it was perceived as too dangerous. But I had received the highest score of all the medical students in my generation, which

comprised three thousand students; this allowed me to question why my selection to practice in the jungle had been rejected. My argument being that what was the advantage of having the highest academic score if I was not allowed to chose where I wanted to do my last year of training in medicine. I convinced the authorities of the university and I was authorized to do the year of "social service" in the jungle. I was interested on the reality of practicing medicine in an environment that was so completely different from mine and to experience the interactions with people whose everyday existence, while simple, was so much more precarious than my own. However, I went, with the naïve assumption that one person, if sufficiently motivated, when going into a new environment could make a big difference; but I failed. My failure was the result of the local conditions and circumstances, which I rapidly learned can sabotage the best of intentions. I was stationed in a very small community called La Arena situated between Palenque and Bonampak in the state of Chiapas. There was no electricity or paved roads and I was sleeping in the school using one large table as my bed. One of the rooms in the school also served as my clinic where I saw patients suffering from tuberculosis, gastrointestinal diseases, pregnancies, trauma, people fighting each other with machetes, and snake poisonings. However, I had access to very few medications, and those I did had, where in too small quantities to sustain the needs, which was very frustrating to me, because I realized that many of the cases could have been treated much more effectively than what I was able to do. This experience made me keenly aware of the crucial importance of clinical infrastructure to sustain a successful therapeutic community effort.

DR. CHARLES P. O'BRIEN: So, from that background, what made you choose to go into psychiatry?

DR. NORA D. VOLKOW: After I finished medical school, I applied to MIT and to Harvard to do a PhD after which I was planning to do a residency in either psychiatry or neurology. Harvard rejected me and MIT accepted me to its neuropsychology program. Since I had seven months in between finishing Medical School and starting courses at MIT, I asked my father, who always encouraged any science related activity to support me while I volunteered doing research in the USA. He agreed and I decided to try my luck at New York University. I had read in a scientific American magazine an article on Positron Emission Tomography, a new imaging device that allowed for the first time to image the human brain in action and that investigators at New York University were using to study the brain of patients with schizophrenia and with Alzheimer's disease. While reading this article, I realized that the advent of imaging was going to transform clinical neuroscience. So, I went to New York University and without an appointment I asked if I could meet the Chairman of the Department of Psychiatry who at that time was Robert Cancro. This tells you a lot about my naiveté regarding academic environments but in this case the naiveté served me well because otherwise I would have not dared to show up unannounced.

DR. CHARLES P. O'BRIEN: Pick up on NYU, which is we're sort of at the point where you were just deciding to take a residency and I want to hear about that and especially who was the scientist who had the most impact on you at NYU and Brookhaven.

DR. NORA D. VOLKOW: I give Bob Cancro the credit; he agreed to meet with me and after listening to me talk about my interest in doing research with brain imaging he introduced me to Jonathan Brodie, who was the psychiatrist in charge of the positron emission tomography (PET) program. The next day I started as a volunteer working with the brain imaging team. My first project was on the use of PET for the diagnosis and evaluation of glioblastomas. This project interested me since malignant cells undergo biochemical transformations I reasoned that PET would allow one to measure these biochemical transformations obviating the need of a biopsy. I proposed a new radiotracer, putrescine, which is a polyamine involved with cell division, that was intended to target cell division, which in the brain would mostly be restricted to malignant cells. Though the radiotracer was eventually developed for PET and assessed in patients with glioblastoma its usefulness was limited by the fact that its main accumulation in the tumors reflected blood brain barrier disruption rather than enhanced cell division. By then the seven month hiatus period that I had prior to my entry to MIT was coming to an end and Cancro convinced me to stay at NYU and complete a residency in psychiatry instead of going to MIT. Once in the residency program at NYU, I started working on a project that used PET to investigate the regional brain metabolic changes in schizophrenia patients. Between taking care of patients and doing on call duties at Bellevue Psychiatric Hospital I found the time to screen and evaluate potential research subjects in the project whom I would also take to Brookhaven National Laboratory to undergo their PET scans. In this respect, Cancro was very influential in my career since he provided me with the support and flexibility that I needed to do the research while being a resident. Of those who influenced me professionally Julian Villarreal was probably the one who influenced my thinking processes as a scientist the most. Why was his influence so important? He had an analytical mind that looked at things in ways that were very unique and that others could not see. He was also not afraid of setting ambitious goals or of being bold with his insights into mechanistic effects of drugs. Alfred Wolf, who was the head of the PET program at Brookhaven Laboratory was also very influential. He was a brilliant man and what impressed me the most was his recognition of the importance of transdisciplinary science. Of those who have influenced my career, I have to also single out my closest colleague and friend, Joanna Fowler. I have learned many things from her including how rewarding scientific partnerships can be, how to integrate research from different scientific fields, and how to successfully blend friendship and scientific partnerships.

DR. CHARLES P. O'BRIEN: What about your interest in addiction? How did that begin?

DR. NORA D. VOLKOW: My interest in addiction started very early on, probably at the time when I was a medical student working with Julian Villareal on opiate addiction. Then, when I finished my residency and moved to the University of Texas in Houston, where they had an amazing imaging program, I started to use imaging to investigate the effects of drugs in the human brain. However, my interest at that stage of my career with respect to the use of imaging for studying drugs of abuse- was not the desire to understand the processes that initiate addiction, which has been obsessing me for many

years, but to investigate the processes by which drugs can produce psychosis. I was intrigued by the fact that some individuals who abuse stimulant drugs, such as amphetamine or, to a lesser degree, cocaine, can became acutely psychotic. As part of my interest on understanding the neurobiology of schizophrenia, I reasoned that, by comparing the brain of stimulant abusers when they were psychotic vs. when the psychosis wore off I would be able to identify neuronal changes that could inform about psychosis in general.

DR. CHARLES P. O'BRIEN: At some point, the concept of addiction came into it.

DR. NORA D. VOLKOW: I first started by measuring cerebral blood flow (CBF), which I used as a marker of brain function to evaluate changes in the brain of cocaine abusers that would inform me about stimulant induced psychosis. To my surprise, I found that the brain images of cocaine abusers showed defects in perfusion reminiscent of those reported in patients that have suffered from multiple small strokes. These CBF defects were very common in the cocaine abusers and diverted my attention towards trying to understand their clinical significance. At the time when I did these studies there was no recognition that cocaine could produce cerebrovascular pathology so I encountered a lot of resistance from the medical community to accept this finding, which was later corroborated by other investigators. In these studies we used PET and ^{15}O labeled water to measure cerebral blood flow. I did these studies in the mid '80s, when cocaine was believed to be a relatively safe drug. However, the imaging data showed otherwise. But as I say to my trainees, "do not ignore the data, the data is the data, whether it fits your hypothesis or not". The brain imaging data were portraying a picture of cocaine that did not fit the perceptions of this drug at that time. In reviewing the literature, I encountered an old paper in the *New England Journal of Medicine* that reported that the abuse of amphetamine resulted in vascular pathology that affected several organs; though it did not mention the brain. It hypothesized that the pathology resulted from the vasoconstrictor effects of amphetamine and from the injection of contaminated material. So, I reasoned that cocaine being a stimulant like amphetamine, was also causing vasoconstriction and this was probably responsible for the CBF abnormalities. There was also a couple, at SUNY in Brooklyn, who had reported that cocaine induced vasoconstriction on isolated blood vessels, which also supported my interpretation that what I was seeing in the PET CBF images reflected the vasoconstrictor effects of cocaine. Because of the unexpectedness of the finding, the novelty of PET technology and the belief that cocaine was a safe drug it took me a long time to get the finding accepted and the study published. Nobody believed that cocaine was producing CBF abnormalities or that it could produce small strokes or small haemorrhages. By then, of course, I had been sidetracked from studying the effects of drugs causing psychosis to studying these toxic effects of cocaine. One of the strategies that I've always used in imaging is to have parallel queries into at least two distinct drugs of abuse, so when I was studying the effects of cocaine I was also studying the effects of alcohol. The reason for this was both to assess the overlap between drugs and to identify the unique changes specific to a given drug. In the alcoholic patients, I was not seeing the CBF defects that I noted in the cocaine abusers. On the other hand, the effects of acute and chronic alcohol showed very distinct changes, implicating GABA neurotransmission, which led me to

question their potential involvement in addiction and in the vulnerability to addiction. I was also very intrigued by the large variability that I was observing in the brain response to drugs among different individuals, both with respect to their behavioral responses as well as in their brain responses, and both to acute and chronic drug administration. That's how my focus shifted towards trying to understand the processes of addiction, reinforcement and addiction vulnerability.

DR. CHARLES P. O'BRIEN: How long did you stay in Houston before you went back to New York?

DR. NORA D. VOLKOW: I stayed at UT in Houston for three years and then, Alfred Wolf convinced me to move back to Brookhaven National Laboratory. I remember the day I was in his office when he said, well, Nora, what will it take? I said, you know, I'm doing imaging work in substance abuse and I would like to be able to continue doing that. His response to this was, would you like us to synthesize labeled cocaine? My response was, you bet, I would love to have [^{11}C]cocaine. That conversation sealed my fate and I moved to BNL. The labeling of [^{11}C] cocaine was performed by Joanna Fowler and that allowed us to investigate for the first time the distribution and pharmacokinetics of cocaine in the human brain. I recall a couple of years later a similar interaction with Alfred Wolf at the lunch table: I was describing to him that methylphenidate was pharmacologically very similar to cocaine but that nobody wanted to accept that these two drug could have similar actions in the human brain. He smirked at me and asked if I was trying to convince him to label methylphenidate, which of course I was. The labeling of [^{11}C]methylphenidate was done by Yu-Shin Ding and it allowed us to compare the distribution and pharmacokinetics of cocaine and methylphenidate in the human brain. Because labeling with Carbon-11, doesn't affect the pharmacological effects of drugs, one carbon is substituted with another carbon, this is a very powerful pharmacological strategy to study the behavior of drugs in the human brain. It's almost like science fiction. If you love pharmacology, that's almost as good as it gets: to be able to actually look at that drug as it circulates in your body and to start looking at its pharmacodynamic and the pharmacokinetic properties. This potential is what actually attracted me to BNL, the possibility of using PET to assess the pharmacological effects of drugs in the human brain and its implications for reward and addiction.

DR. CHARLES P. O'BRIEN: And, that's been a terrific location for you, because it's been so efficient, allowing you to turn out so many seminal papers, with the facilities that Brookhaven has there. It's just been wonderful.

DR. NORA D. VOLKOW: Yes, and I think what makes Brookhaven so great, clearly, it's actually not the facility but its people. If you go to Brookhaven National Laboratory and visit the PET laboratories they are old buildings and they don't have the latest in equipment. It's the brains of the scientists that make it unique.

DR. CHARLES P. O'BRIEN: Is Wolf still there?
DR. NORA D. VOLKOW: Al Wolf died about thirteen or fourteen years ago. After his death Joanna became the leader of the PET program at BNL. She has been an

extraordinary colleague who has built up the PET group, promoted training of new investigators and encouraged collaborations. Joanna has been terrific.

DR. CHARLES P. O'BRIEN: This is a really tough question. This is one of the things that they want to get on here. What do you consider to be your most important scientific contribution, so far, because you have many more to come in the future, but so far?

DR. NORA D. VOLKOW: That's an interesting question to consider, albeit hard to answer. I think that probably one of the most important ones, if I had to choose one, is the concept that a key region in addiction is the frontal cortex. Now, everyone recognizes that the orbital frontal cortex and the cingular gyrus are crucial in addiction. However, this was not the case when I first documented abnormalities in the orbitofrontal cortex and cingulate gyrus of cocaine abusers, which I then reported were associated with the reduction in dopamine-D_2 receptors in striatum that are seen in addicted subjects. The first time I reported on these prefrontal abnormalities in drug abusers again it was questioned because at that time, a lot of the work had concentrated in the area of the nucleus accumbens and the limbic brain. But again, I go back to my motto of "the data is the data, is the data". The fact that I could blindly distinguish between a brain metabolic image of an addicted person who had recently taken a drug of abuse and that of a non-addicted person on the basis of the enhanced activity in the orbital frontal cortex in the former, was very compelling. It was a very consistent signature that was difficult to ignore or miss. At that time, I was also intrigued by the overlap between my findings and those reported by Baxter on metabolic changes in patients with obsessive compulsive disorders that also showed enhanced activity in orbital frontal cortex, cingulate gyrus as well as caudate. And then, through association, I questioned in my brain what those two disorders had in common? It was immediately evident: the compulsive and the obsessive quality of the behaviors in both disorders, which I reasoned reflected disruptions in overlapping prefrontal circuits. Again, the field rejected this new perspective on the neurobiology of addiction first, because I was implicating the frontal cortex as opposed to classical limbic areas such as nucleus accumbens, and second from the misconception that I was implying that addiction was an obsessive compulsive disorder. However, I wasn't implying that these were similar disorders but rather that these two disorders shared neurobiological substrates in the brain as part of broader mechanisms that resulted in distinct pathologies. I was basically thinking of shared territories. There are so many ways in which the brain can become impaired. So, to me, that is probably the finding that I considered to be the most important, because it transferred the whole focus of addiction from the limbic brain into other brain regions, prefrontal brain regions. The recognition of the importance of the orbital frontal cortex and the cingulate gyrus has been crucial in advancing our understanding of the process of addiction. Since then, many other investigators have also delineated that there are other circuits involved, like the insula for interoception and self awareness, the memory circuits including hippocampus, amygdala, which actually have to do with your work at U Penn. This has shifted our views to not just focus on one particular brain region but to explore multiple neuronal circuits that become disrupted in addiction.

DR. CHARLES P. O'BRIEN: How hard was it for you to agree to accept the NIDA directorship?

DR. NORA D. VOLKOW: It was hard. I remember discussing it with you. You called me and said, Nora, you should consider it and I said, Chuck, why don't you consider it and I remember you said to me, no, I have too many good things going on in the laboratory; this is not a good time for me. I don't know if you recall that conversation.

DR. CHARLES P. O'BRIEN: I felt guilty about it, figuring that it would have a bad impact on your career, but it's been just the opposite.

DR. NORA D. VOLKOW: Being director of NIDA does require a big investment of time, but it's an investment that's worth it; otherwise, you should not do it, because it's so demanding that either you really want to do it or you should just stay out of it. That's it. The moment that I feel I don't have the same passion for the job I will stop, because it's too important of a job not to give it your very best. I also called Herbert Kleber for advise and I said to him that I felt it was not the right time for me and he responded, Nora, there's never a right time, that's when he was called to be the deputy director for ONDCP, he initially had felt similarly; that it was a great opportunity but that it was not the right time. I spoke with many colleagues, friends and relatives; I wasn't convinced. It was a very difficult time for me, there were days where in the morning I would be convinced that I should take the job and then later during the day I would find myself thinking there is absolutely no way that I can leave my research work. Chuck, you have to realize that my identity as a scientist is crystal clear. In my brain, it's automatic, so the notion of giving up who I was, was very difficult, and, so, most people were encouraging me and there were a couple of people that weren't and I think that they knew me in a way that was very fundamentally me. One of them was my friend and colleague Burt Angrist, I remember his words: Nora, I've known you since you were a resident; you thrive on science; what are you going to do as an administrator? During my interview with Dr Elias Zerhouni, who was the director at NIH recruiting me, I felt guilty for wasting his time since I had internally come to the conclusion that I was not going to take the job. But Elias Zerhouni is a very perseverant individual who, I think, rarely gives up, so he finally asks me one day when he comes to visit BNL, what will it take for me to take the job? I told him that the issue that would make the difference is if I could continue doing research and working with my colleagues at BNL. He looks at me and states I think we can arrange that. And, he did and that's how I took the job at NIDA and how I've been able to continue my research work as an intramural investigator in the NIAAA whose laboratory is located at BNL. It has also allowed me to keep my relationships with my colleagues at Brookhaven National Laboratory, which are very important to me.
DR. CHARLES P. O'BRIEN: And somehow, you've managed to squeeze it all in, the demands of the NIDA directorship and the research into your really busy schedule.
DR. NORA D. VOLKOW: Yes, and, you know, there are two things that happen when you get into a situation like that. I mean, I don't take jobs that I don't think I can do well, very well, and, I'm also very competitive, so I want to do the best that can be done and that goes in both areas, so it's actually recognizing that is something that I have to do. So in these five and a half years of my life, I've worked harder than I've ever worked before, and I've always been criticized for being pretty compulsive as a worker, but I stretched it and I stretched it because I think it's worth it. It's not even something that I actually

think about. I am aware that I'm very lucky being married to someone who is also very hard working and supportive, someone that has never questioned me for working excessive hours and that has helped me enormously. Also, I do not have children, which also avoids the conflict that most women scientists with children must struggle with. This may be seen as a selfish way of organizing one's life but my passion for science has driven my choices in life. I think that's how I've been able to manage being NIDA director and maintaining my research work. For me, it's almost a survival strategy to be able to do science and be creative at that level, while doing this job at NIDA.

DR. CHARLES P. O'BRIEN: So, here you are on the cutting edge of a very important field. What do you see as the future of addiction research?

DR. NORA D. VOLKOW: There are many areas that are ripe for significant progress in the future of addiction research. I think that in the next few years we're going to see acceleration in the rate of discoveries. In fact, we are already starting to see extraordinary opportunities, driven in part by advances in imaging technology, genetic knowledge and access to open data bases and computation resources. For example, by using imaging technology, we are beginning to better understand how the brain is affected by drugs of abuse and how its disruption results in the behaviors we see in addicted individuals. In the process, we are also learning about how the human brain works. Genetic studies are starting to identify families of genes involved in drug responses and in addiction, and, in the near future, epigenetic research will allow us to understand how drugs affect the expression patterns of these genes in the brain. Now, findings from genetic research can help us to come up with better treatments, in your case, for example, by predicting which patients are more likely to respond to naltrexone. Wide genome association studies are helping us identify genes involved in addiction that the field had not previously considered that important, such is the case for the nicotine receptor subunits, α-3, α-5, and β-4. These findings give us clues about where to focus research that can ultimately shape the development of new treatments. For example, there is only one compound listed as ligand for the α-3-receptor, probably because in the past there was no evidence that this receptor was involved in the rewarding effects of nicotine. Now, the findings from genetic research introduce the possibility that compounds that target this receptor may have therapeutic benefit in nicotine addiction. Coupling genetic studies with imaging research will allow us to better understand how genetic variants associated with vulnerability to addiction, affect the development, morphology and function of the human brain and how drug exposures, stress and other environmental factors, including social systems, can affect them in turn. Let me give you another example, the monoamine oxidase A gene, which has a variable nucleotide terminal repeat (VNTR) that is likely to influence transcription levels, has been associated with an aggressive phenotype. However, if you actually measure the concentration of monoamine oxidase A in the brain, which you can do with PET technology, there's no difference in the concentration as a function of the genotype. This suggests therefore that whatever influence the MAO-A VNTR has on the aggressive phenotype it is likely to reflect its effects during early developmental stages, not during adulthood, since at that stage we can find no differences in enzyme concentration as a function of genotype. Since the MAO-A gene is involved in brain development and

architecture it is therefore likely that its association with aggressiveness reflects this role. Indeed, it is likely that many of the genes that are associated with neuropsychiatric disease contribute to these disorders by affecting developmental brain trajectories. The use of imaging in conjunction with genetics will start to reveal how vulnerability factors affect brain functions, which can then lead us to a better understanding of addiction. Ultimately, we want to understand why is it that someone can become addicted?

The question is frequently asked of why drugs are rewarding. It is accepted that they are rewarding because they activate systems, including the reward system that are crucial for survival. However, few have asked the question about a potential physiological role to the state of addiction, a state where you become so obsessed that nothing else matters, where you're actually willing to forego things that are crucial for survival in order to get the drug. How does nature allow for the emergence of this state if it's not already hard wired for a physiological purpose? I believe that the mental state of compulsion and obsessiveness is a state that can occur at unique stages in our lives and that is also important for the survival of the species. For example, when a mother has a child or during romantic love, on both these situation there is a hypermotivational state that overrides other reinforcers and that allows the individual to do behaviors that, otherwise, would not succeed.

As we learn how genes affect neuronal circuits implicated in addictions it will give us a new way of trying to strengthen those circuits when they become disrupted by drugs. So, that's where I see the field, the integration of knowledge from genetic studies into understanding brain development and neurobiology, and how these are affected by drugs.

DR. CHARLES P. O'BRIEN: I hear what is exciting you now, and we're just about out of time, but I just wonder is there anything else that you think is important, considering who is going to be reading this or looking at this sometime in the future, is there anything that you want to sort of say for posterity at this point before we end it?

DR. NORA D. VOLKOW: I assume that if these tapes are going to be seen by people who are scientifically inclined, I would not have much to say. But, if they are going to be read by individuals without scientific leanings, I'd like to send the message that science is an extraordinary career, probably one of the most exciting human endeavours. It is utterly fascinating to be able to use your brain to try and understand the world in ways that others have not seen before. But, at the same time, it advances knowledge that actually, in turn, can help improve the life of other people, so in a very real way, is the best of both worlds.

DR. CHARLES P. O'BRIEN: That's a good note to end on and I'm sure that it will be seen by non-scientists, because, you know, the person who has already seen some of these tapes has just written a history book on it and, so, I'm sure, help future historians and maybe some people who are considering a career in science. Thank you very much, Nora.

DR. NORA D. VOLKOW: Chuck, thanks a lot.