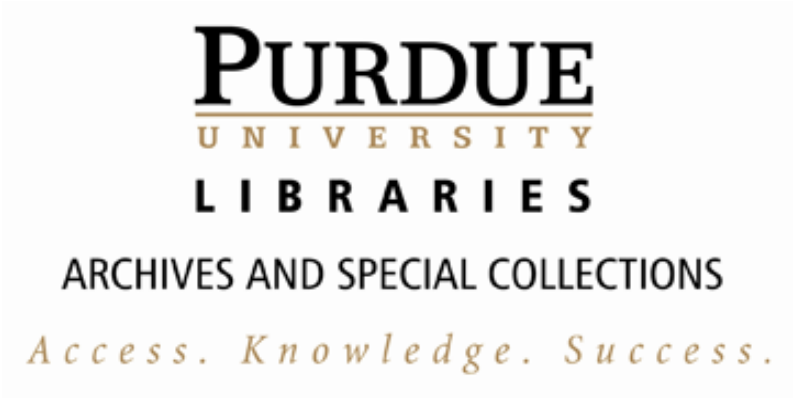
David Nichols Interview

Conducted by Katherine Markee on August 4, 2009



The following interview was conducted with David E. Nichols (DN), the Robert C. and Charlotte P. Anderson District Professor Chair in pharmacology for the Purdue University Oral History Program. It took place on Tuesday, August the 4th, 2009 in Stewart Center. The interviewer was Katherine Markee (KM), the oral history librarian.

KM: Welcome Dr. Nichols and good afternoon. Tell us a little bit about where you were born, and your parents, and siblings, and early years.

DN: I was born in Covington, Kentucky, just across the river from Cincinnati. My parents both basically came from farms, my mother from down in Kentucky, my father from eastern Kentucky. I had three brothers, and we were all raised by a fairly stern, demanding father who expected a lot from us. We were very disciplined little kids, and he instilled values of perfectionism, I guess. We always had to do things right, so he had high standards for all of us.

KM: What was high school like? Any activities or student organizations?

DN: High school was an interesting mix of people because there were people that came from the older section of Park Hills which came from very wealthy families, people from the section where we live, which was mainly populated by families who had come back after World War II and the Korean War, and then lower income families from farther out. So there was a kind of a gemisch, and although I normally would've mixed with the more wealthy people because I lived in Park Hills, I was actually on the other side of the highway so to speak. So I didn't really have a lot of social connections in high school, although I went to school with those kids all the way from first grade on up through senior high. Really, my later years in high school, some of the people noticed me because I was taking the

advanced chemistry course, and advanced physics, and was sort of the science geek. And they suddenly realized, who's this guy Dave Nichols, we've been going to school with him for all of these years, and he's been in all of our classes, and we just never realized who he was. So I -- really, the first activity that I got very involved in was when I got in the senior play. I had never done any acting, and a lot of people were in the drama club and so forth, and so I just on a lark, decided to audition for the senior play, and the director of the play was my advanced chemistry teacher, Mr. Richardson. So I read one of the parts, and I ended up with the male lead. And that was a lot of fun, and I've been to some of the high school reunions and they say oh, that was great, you were in the senior play and it was so much fun. And that was really -- my senior year was where I really started, I guess, growing socially, and becoming more outgoing and interacting more with my classmates.

KM: OK. And then what came next, where'd you go to college now? (inaudible)? Cincinnati?

DN: I started off in engineering at University of Cincinnati. My parents were not well off, shall we say. We didn't know that as kids, we thought everything was fine, but they basically scrimped and saved every penny. And so going to college was something that there really wasn't much of a plan for. And if I went to University of Cincinnati, they could pay the first quarter's tuition, and then I could co-op after that. And if I lived at home and commuted, then it would be a fairly inexpensive way to go. And my father had said, this is post-Sputnik, my father said, oh, there's a big demand for engineers, you like chemistry, so go into chemical

engineering. And not knowing any better, I went into chemical engineering, which really was not chemistry at all, but was math. And math was not something I particularly enjoyed. And I stuck it out for two years and finally said, you know, this isn't what I want to do, I want to do chemistry. And I then dropped out of engineering, and started working in industries in the Cincinnati area. I had a variety of positions in process research, and analytical labs, and development.

KM: In the Cincinnati area?

DN: Cincinnati area. A lot of industries there. Then I decided to go to night school, and keep up with school until I could save up enough money to go back to school full-time as a chem major. But in the interim, I got married, then had a baby, so that was not possible. So I finished my Bachelor's degree going to night school, so I worked a full work week, and then went to school from basically 6:00-10:15 four nights a week for five and a half years. So I pretty much was burning the candle at both ends to get through.

KM: But you made it?

DN: I made it.

KM: Yeah.

DN: I graduated with my B.S. in Chemistry in 1969.

KM: OK. And then what came next then?

DN: Then I went to graduate school in medicinal chemistry at the University of Iowa College of Pharmacy.

KM: OK. How did you happen to select them for the graduate work? Did you know someone, or one of the professors?

DN: Well, I had become interested in drugs that affected the mind. And there weren't many people working in that area. And the head of the department, Joe Cannon, was working on compounds for the military that would produce hallucinations, and would disorient the enemy troops so to speak. So I decided that would be interesting, and I went there, actually to work for him. But when I got there, there was another professor who he, and Joe Cannon had ceased activity in that area, and was working on another kind of compound that I wasn't particularly interested in, but they had another professor, Charles Barfknecht, who was still sort of dabbling in the area of hallucinogens, what we call hallucinogens now. And I got really interested when I talked with him. And I had a fellowship, so I could work with any of the faculty I wanted to, so I decided to work for him.

KM: So you continued to receive -- you finished up there then?

DN: Yes. I started in '69, and basically finished my research in the summer of '72. Graduate school, for me, was really kind of like a picnic. If you imagine that I worked full-time, had a baby, and had gone to night school for five and a half years, when I went to graduate school, all I had to do was to take a couple of classes and do research. So it was really much less of a burden than my life had been prior to that time. So I finished the project I had for a Master's degree in about my first semester. I finished up, well, more quickly than anyone else ever had there. My thesis was thicker than anyone else's ever had been before. And my professor was trying to push me out of the door before I'd even been there for three years. He came in the summer of '72 and said I should write my thesis up, and I begged him to let me stay because there was another compound I wanted

to make. So he said OK, so I stayed to the fall, and then he bugged me again, and I said well, let me try to get this one last reaction. And then he came to me about mid-semester and said look, write it up, you've got enough. So I wrote it up, defended it, and then I finished and went over and started a post-doc in the pharmacology department, the first of '73.

KM: OK.

DN: So officially, I graduated in 1973, but my work was all done, really in 1972.

KM: OK. Now your family were with you at that time? Was your wife, was she in school too?

DN: Yes, I had a wife and -- my wife started working part time, and then she actually got a degree in physiological psychology, that was my first wife, and we had a son that we took with us, and then we had a second son that was born in 1973.

KM: OK. So you had your family then with you?

DN: Yes.

KM: OK. What was your career path then prior to coming to Purdue? Did you come to Purdue right after?

DN: I came right after.

KM: OK.

DN: I did a post-doc in pharmacology, and they had a faculty member here who had left, had gone on sabbatical, and decided not to come back and they --

KM: Here, meaning Purdue?

DN: At Purdue in Med Chem, and they had decided to replace him. They had interviewed senior candidates, but none of them looked very acceptable, so what

they did was split his senior position into two junior positions, and I interviewed for one of those positions. And they wanted someone who had a very biological perspective to their chemistry, and so with my chemistry BS, my Med Chem Ph.D., my pharmacology post-doc, I fit right in, and really was conversant with the biology end of things.

KM: OK. So then that brings us to Purdue. Let's talk a little bit about that, about the teaching when you were here, and then move into some of the research that you started, or continued on that you'd already begun.

DN: Well, when I first came, I taught organic chemistry, and actually, I got the teaching award when I was teaching organic chemistry, which is fairly difficult to do, because the pharmacy students typically don't like organic chemistry very well. And I taught that for a few years, and then we had the other candidate that was hired about the same time I was slightly, Mark Cushman, he was teaching in medicinal chemistry, and he really wanted to teach in organic, so after a couple of years, we switched, and he started teaching organic, and I started teaching medicinal. The research that I started with was actually a continuation of what I did for my graduate work. When I was a graduate student Charles Barfknecht had dabbled a little bit with some analogs of mescaline metabolites, it was a psychoactive drug, but really had not gotten into the field. So when I worked for him, I really developed that whole field myself, that I published, you know, 12 or 13 papers as a graduate student in that field. So when I left, it was really an area that I had developed, although he had been formally my mentor, but he wasn't

going to stay in the area, so when I came to Purdue, I just kept on doing that, and that was the first grant I got funded.

KM: What was funding like in those days?

DN: It was a lot easier to get. Of course, the grants were smaller, but you -- they were more willing to take a risk. The first grant I wrote had a lot of speculative hypotheses in it, because not much was really known about the structures of these molecules and what their relationship was to their activity. So I could propose some things that today, would just, I mean, they would throw them out of the review section because they want -- now, they want things that are almost a guarantee. But there were still difficult to get, you had to write well, they had to be well-documented, you had to have -- the chemistry schemes had to be documented. They couldn't find any obvious flaws. But you were allowed to speculate a little bit more about what might work, and what might not work in terms of the overall gist of the project. And I had funding up until last year, so that's been from about '76 until 2008, I had continuous funding from the National Institute on Drug Abuse to study the relationship between the structures of hallucinogenic molecules and their biological activity.

KM: OK, OK.

DN: And because that was a subject that no one else was really interested in commercially, I was kind of in a bind. If I'd gone into anti-cancer drugs, or almost any other kind of drug, I would've found collaborators who were doing research in the biochemistry, or the pharmacology of these drugs, and I could've collaborated. Because of the area that I chose to work in, there really was no one

to collaborate with. So what I had to do is basically create my own pharmacology to go along with the medicinal chemistry. So I started working with smooth muscle from guinea pigs and rats, and then we worked with cats, and mice, and rats, and over the years built up a repertoire of pharmacology to the point where actually I became, well my chair is the Anderson Chair in Pharmacology. So I'm recognized as much as a pharmacologist as I am as a medicinal chemist. And I don't know where -- maybe more nowadays, even more of a pharmacologist. But that was out of necessity, I had to create the pharmacology program to test my own compounds. So I still do that, I still have a program where we do pharmacology, in vitro, and animal pharmacology that couples with the synthesis and design aspects of it.

KM: OK, OK. And you were working with the -- you said, one thing I read, to understand the role of your brain, the neurotransmitters, and normal behavior as your...

DN: Right. So there's the monoamine neurotransmitters in the brain are norephinephrine, dopamine and serotonin. And all of those transmitters are very important for the action of psychoactive drugs. There are others, scetylcholine as well as some others, but dopamine, for example, is the principal transmitter that's involved in the stimulant and rewarding effects of drugs like cocaine, and methamphetamine, and I've done some work in that area. Serotonin is principally the transmitter system that's involved in the action of hallucinogens, or psychedelics, whatever term you want to use. And norepinephrine, we really don't know a lot about its role in behavior, but it clearly plays a role. So I basically

have looked at the drugs in terms of how they affect those systems, dopamine and serotonin; do they increase activity, decrease the activity, do they block the receptors, or do they cause the release of the transmitter? And all of those affect behavior, the way people feel, the way they perceive, and so what is the role of those transmitter systems in behavior?

KM: All right. And what about -- are you doing clinical studies as well?

DN: No, the clinical studies that I'm involved in really don't occur in my lab, although I've been involved in planning and implementing, especially through the Heffter Institute, and to a certain extent with Darpharma, but I don't run any clinical studies.

KM: Right, OK, OK. And also the entactogens, you coined that to describe the unique psychopharmacological effects of MDMA, would you comment about that?

DN: Yeah.

KM: Because that's been cited a couple of times in some of the research that I checked.

DN: Yeah, MDMA is an interesting psychoactive drug that really came on the scene in the early, I'll say 1980's. And I knew a lot of the psychiatrists who had used it in an unapproved way prior to its being scheduled. So when MDMA first sort of came on the scene, it was not a controlled substance. And physicians were allowed to prescribe things in the course of their own practice if they made them, or if they were plant extracts they made, so physicians had a lot of latitude. So there were a lot of physicians, particularly in California, who had heard about this substance, and had made it, and had gotten samples, and were using it to treat

their patients in psychotherapy, and various types of therapy. So I was invited to a meeting at Esalen in 1984 where they had all of the people who had done anything with this substance, and they knew that the Drug Enforcement Administration was about to try to schedule it and make it a controlled substance, and they were trying to think of ways to prevent that from happening because they were convinced that this was a valuable tool for therapists and psychiatrists. And I was invited as a scientist because we had looked at some of the effects on brain monoamines, and done a little bit of the work. So when I talked to the people that were there who had actually used it, the stories were fairly impressive. I mean, there were therapists who said, you know, I had this woman in therapy for 10 years, and I never could reach into whatever her problem was, and I gave her a dose of MDMA and all of a sudden, she's telling me that she was abused as a child, and all of this stuff was coming out, and suddenly, everything made sense, and so I made years of progress in just literally an hour. I thought wow, you know, if this is true, there may be some potential here. But because the drug had become so wildly popular, and was being used at raves, and you know, was going to be scheduled, I realized it could never be developed as a commercial medicine. So what I thought was well, let's see if there's a way we could develop something that would do the same thing but wouldn't have its genesis in the street market. And the first thing I realized was that politically, it had been cursed by being called "just another hallucinogen". And from what I knew of the pharmacology, I wasn't convinced it was just another hallucinogen. We did a couple of studies, and we published them where we pointed out that

MDMA was not just another hallucinogen. It had chemical structural features that excluded it completely from that class, it was something different. So the issue was what does it do, how is it different? And I thought politically, it would be good if there was a name that distinguished it from the hallucinogens or psychedelics so you could say it's this other thing. And we tried to -- I tried to think of a word that would sort of capture what the psychiatrist had told me it was doing. So I talked to people who knew some etymology and thought about lots of different names, and finally came up with Entactogen, because “en” connoted inside, and tact, came from the latin tactus, and gen was the Greek to generate, so it was generating a sort of touching within. And there was actually debate because at that time, the other term was Empathogen that was being used, and I said well, it doesn’t sound to me like they just produced empathy, and if you say Empathogen, you hear the pathogen, and it sounds kind of like it's nasty. So I actually had a debate with a guy named Ralph Metzner about which was a better term. In Europe, Entactogen is most widely used in scientific circles. In the US, it's sort of a mixed bag, the counter culture tends to use Empathogen, the people who do the science work use Entactogen, because Entactogen is sort of a more respectable term. That was kind of fun, and the Oxford International Dictionary people called me and said well, we're putting Entactogen in the dictionary, and you coined it, can you tell us about it, so it was kind fun to think oh, I invented a word. I think there may still be some potential there, but we got into a program where we tried to see if we could reproduce the effects. And what it is is a situation where you have a substance that does a lot of different things, and

when you change its structure, everything doesn't change in parallel. Things change in disproportionate ways, and so it's almost a unique drug, just like people are unique. And we never were able to really create anything that we thought was comparable in medical utility. We did a lot of interesting work on determining what were the structural relationships that involve the individual pieces of the activity. I had a student who did a lot of work on the neurotoxicity that that drug produces at high doses, at least in rodents, and it was related to how the drug actually works, but sort of gave up on that field, and I had funding to work on MDMA and related compounds for -- that was the third grant I had running concurrently for about 12-13 years. And I finally just gave up when it was clear that the only thing that the government agencies were interested in funding was study on the neurotoxic properties, the negative aspects. If you wanted to try....

KM: Their focus has shifted.

DN: Yeah, the focus -- if you wanted to understand how it worked in terms of the psychopharmacology, and how it might be useful, there was no interest in that. And I was getting the message on that on the last grant, I'd sent it in, and they basically were beating me up for "why aren't you studying the toxic effects," blah, blah, blah, and I said that's it, I'm not interested in why the drug is toxic, I'm interested in how it works.

KM: Right.

DN: So that was -- I had three grants at that time. That was one of them.

KM: You have any contact with -- (inaudible) with the FDA at all, over time? Or not? Do you ever -- you've never done any consulting for the FDA, with the FDA at all?

DN: Not with the FDA, no.

KM: Yeah. What were some of your consulting activities?

DN: Most of the consulting that I've done, and especially recently has been on intellectual property issues. The first consulting that I really did in a large way was for Eli Lilly on a drug called Prozac. And what happens is when the drug companies have a big blockbuster that makes three or four billion a year, it doesn't have to be that, but typically, that's what they've gone after. The generic companies try to find flaws in the patent, so that they can attack the patent, have the patent invalidated, and then they can market their generic versions. And they do that...

KM: Rather than waiting until it expires?

DN: Yeah, they do it to all of the big drugs now, every single one of them. And I didn't actually testify in that case; I was an expert that worked with the Lilly attorneys to help them craft a case, and develop questions for other experts from the generic side. But then when the same thing happened with Zyprexa, which is a drug that treats schizophrenia, and they retained me for that, and I actually testified in the United States, in Canada, and in the UK, and worked with their attorneys in Germany, and in the Netherlands on the same case, because it was being attacked a lot of different places. Successfully, they've defended that patent so far. And some other ones are related too, Seroquel, which is another drug that

treats schizophrenia, and Abilify, which is another drug that treats schizophrenia. And these are all cases where the generics have said well, anybody who is in the field at the time, who was skilled in the art would've known this was an obvious drug to make, and so it really wasn't new knowledge, shouldn't have been patented. And they're really ridiculous arguments, but you still have to fight them back, and...

KM: Oh yeah. You have to defend it all the way.

DN: Yeah.

KM: You're right, yeah. Talking about teaching, talk about what you worked with the IU School of Medicine here on campus or the research at the West Lafayette campus. Are you still doing that? And what courses are you teaching?

DN: Yes. I teach in courses, there's a pharmacology course for the second year students in the second semester, and I teach the psychotropic drugs. So these are the anti-depressants, the anti-psychotic drugs, mood elevators, drugs to treat anxiety. So they're all -- I teach the drugs basically that affect mood and behavior, which is sort of allied with my interest.

KM: Yeah. Just a second year then. We talked a little bit about money, let's talk about some of the -- can you make some comments about some of the patents that you've gotten, and successfully, the challenges that you're faced when trying to apply for those.

DN: Yeah, the first patent I got was actually as a graduate student. These hallucinogens, one class of them are called hallucinogenic amphetamines. They're really sort of amphetamine that has things stuck on it. And to really

understand how they work, you need to know what these separate isomers do. And so these drugs occur in what's called a racemic mixture. This is like you have a left and a right hand, they're both hands, but they're right and left mirror images. You have the same thing in biological molecules, organic molecules. And so with the amphetamines, you essentially have a right and a left handed one. And the left handed one is the one that actually has the biological activity. But the right, sort of the other one, has different effects. And they were always studied before as a mixture of the two, and so it complicated. And I just stumbled, sort of on a way, I don't want to say stumbled, but stumbled on a way to do that as a graduate student, which we then patented. And then actually the National Institute on Drug Abuse provides those isomers to researchers free of charge, and they use the method that I developed, as far as I know, the last time I checked, they did. We actually tried to see if we could get some royalties a few years ago, and they got all upset because they didn't realize it was a patented method. And then they realized that oh, they never charged anybody and they never made any money, so there were no royalties. That was the first one. But then most of my patents have been in the dopamine D1 agonist area, and that's an area I started working on when I came to Purdue actually, but it was working with drugs to treat shock, and then it developed into a focus on the dopamine receptors in the brain.

KM: What kind of shock would they be treating?

DN: Well, when you're in an accident, if you have a lot of...

KM: Like a trauma shock?

DN: A lot of hemorrhage.

KM: OK.

DN: Your blood pressure drops, and one of the things that happens is the blood vessels in your kidneys constrict to try to decrease the volume of the vascular bed to raise the blood pressure. And when they constrict, they restrict the flow of blood through the kidneys. And of course, that's the blood that brings the glucose and the oxygen to the kidneys. So what you would have is renal failure, secondary to hemorrhagic shock. And there was a fellow at the University of Chicago named Leon Goldberg who was trying to find new drugs to use to treat people in shock to prevent kidney failure. And I actually got a small grant from him in the late '70s after I got here to work on those kinds of drugs. And that receptor in the kidney turns out to be almost identical to the brain dopamine D1 receptor that I subsequently focused my efforts on. So that's sort of how I got into it. And interestingly, when I was a graduate student at the University of Iowa, the fellow that I worked for, Charlie Barfkwecht only had three or four graduate students. The department head -- Joe Cannon had about a dozen or so graduate students, and they were all working in the dopamine field. And so it was my habit to find out what everybody was doing in the whole department. So I knew what all of Joe's students were doing, I knew their research, and I knew their backgrounds, and why they were doing it. So when I came to Purdue, I knew the dopamine field as well as I knew my own serotonin field. So when I connected with an associate of Leon Goldberg, I said yeah, I know the dopamine field really well. And so that sort of led me to continue what -- although I hadn't formally

done it as a graduate student, was a sort of secondary interest that I had maintained and knew a lot about.

KM: Yeah, sounds good. Let's talk a little bit about the Heffter Institute.

DN: The Heffter Institute.

KM: And how that came about, and your role in it.

DN: I was convinced at a certain point that these drugs, hallucinogens, might be very useful in psychiatric practice. I hadn't seen good controlled clinical trials, but it was clear from some anecdotal reports that people had some pretty amazing things that had happened when they'd taken these substances. So I thought you know, what we need are good clinical trials. All of the work -- after LSD was discovered, there were thousands of papers published, thousands of clinical trials where psychiatrists raved they could do this, they could treat autism, they could treat schizophrenia, I mean, everything under the sun. But the trials were not controlled and well done. And I realized you really had to do good clinical trials to see whether they had any value at all. And so I used to go to scientific meetings and we'd be having a beer in the hotel restaurant and we'd be talking about this, and I'd say somebody needs to do research on these things, see, you know, is there anything there. I mean, there was such a big splash, and then it just sort of was shut off. And they'd say oh, you can't do it, you can't do research on these things. And I said well, you can, you just can't get the government to fund it. You need somebody, you need private money, you need to get private funding, and you can do it, there's no reason you couldn’t do it. Oh no, no, no. And I told that story over, and over, and over, and I said well, in the beginning, and I told the

story, I said you know, all you'd need would be an endowment of like a million dollars and you could set up an institute to study these things. Well, as the story went on, and the years went on, pretty soon, it was two million, and four million, and five million, and it got to be ten million. And I don't know, sometime around 1990, I was sitting telling the story for the umpteenth time, and I said you know, I'm going to be 75 years old, retired, sitting in a rocking chair telling the same story. And I hadn't done it because I didn't have an MD: you can't do clinical studies without an MD. So I called a bunch of my friends who were psychiatrists who had MD's, and said hey, let's do this. And they all got very excited and enthusiastic. And so in '93, we incorporated the Heffter Institute.

KM: OK. Did you get some funding?

DN: It's all been private. I mean, in the beginning, we had a fellow named Bob Wallace, who was I think, the 9th employee of Microsoft, and he supported us to the tune of $100-150,000 a year for many years before he died. And that allowed us to sort of become established. And now we sort of -- we're a virtual institute so we kind of go hand to mouth. We'll encourage people if they have a grant -- if they have a proposal for a research project, we'll send it out and get it peer reviewed, make suggestions on how they can improve it, how they can make it better. We have some small studies that we fund at a very basic level. We serve as sort of the focal point, as a not for profit to work with them and if people want to fund the study, then they can give us money, and then we'll support those studies. We've actually published quite a few papers from investigators who got funding from the Heffter Institute. On our website, hefter.org, there's a whole list

of research publications. We also have a laboratory at the University of Zurich where Franz Vollenweider is. There's actually a Heffter Clinical Research Center there, and he uses that money to leverage a larger amount of money from the Swiss National Science Foundation. He's sort of the world's top clinical researcher now. And he's doing some really amazing clinical stuff with pet imaging and EEG, etc., correlating brain states with brain chemistry. So it's really nice to see that. It's not where I wish it was, we don't have that big benefactor who's come in and given us the endowment to lead us from...

KM: It's located in New Mexico, is that right?

DN: New Mexico is where it was incorporated, and the medical director, George Greer runs a lot of the day to day, he lives out there.

KM: OK. And then the other thing, you have a publication that you issued to that, the Heffter Review?

DN: The Heffter Review of Research, we had two of those that were pretty nice, and we thought about doing a third one a couple of years ago, and everybody said well, do we fund research, or do we fund the bulletin? And people said well, everything's online, if we want to do it, let's just do an online thing. And it's a shortage of manpower and funds, we haven't done the third one. Those are nice little reviews that were written in a kind of scientific American style by people like myself and others in the field for the common person. And people generally, they were well received, but there's only so many hours in a day, and yeah....

KM: Well and a set of priorities too, right, exactly. And then the other one was that Darpharma that you have?

DN: Darpharma.

KM: Yeah, tell us a little bit about that.

DN: That was a collaboration with a fellow named Richard Mailman who was at the University of North Carolina-Chapel Hill, and the D1 agonist, we published a study in 1991 showing that a dopamine D1 agonist was as good as the best therapy in Parkinson's Disease. And we had tried to license it first to a company called Interneuron, and they had simply used it to boost their stock prices, as far as I could tell, they could never commercialize it. And then they dropped the ball. Then I had a second compound, and that was with dihydrexidine, the first one. By the second compound, I called dinapsoline, and Bristol-Meyers Squibb worked with that for a while, and licensed it from Purdue briefly, and they kind of goofed up one of the tests, where they were at a decision point, a go no-go, and misinterpreted one of the tests. And so they dropped the license. And so Richard went to England and was working in the laboratory, the guy who had done this test, and he found out that in fact the compound worked really well, they had just misinterpreted their early results. So he called me and said let's start our own company, I'm tired of working, and we'd also worked with another German company briefly that almost signed a license and then backed out because they had changed leadership. So there had been three companies that had come in, played with the D1 field, and then had sort of backed out. So he decided to start a company, and I said Richard, I don’t know if I have the time for this. He said, oh, just be on the advisory board, I'll do all of the work, yada, yada, yada. So he sort of tried, he didn’t know what he was doing, I didn’t know what he was doing,

we hired a CEO who didn't know what he was doing, and we hired other people who didn't know what they were doing, and the company limped along for several years. We did get a CEO named Praba Fernandes, who was really good at the very end, and tried to resurrect things, but there had been so much, sort of bad publicity. I mean, if you go in and see an investor, you get one chance to make your schpiel, and the fellow we had who was making those presentations was really botching them up. And then once Praba came in, she couldn't get back, she couldn't get back, they said, "We've already heard about the company, we're not interested anymore." She did the best she could, but it was finally merged out into another company, which became defunct and basically nothing happened.

KM: (inaudible)

DN: I really am still convinced that if we can get one of these drugs out there, that they will work in Parkinson's patients where nothing else works, because of the way they work, they will work long past the time when most therapies stop working. What's happening now is there's a lot more interest in the effects on working memory and cognition. There was a researcher at Yale named Patricia Goldman-Rakie, who died in a tragic accident a few years ago, but she showed that D1 agonists can improve working memory and cognition in monkeys. And so the belief out there now is that in schizophrenia, these deficits in working memory and cognition are the big problems that can't be treated, and so there's a lot of interest now in going back and commercializing some of these drugs; some of the D1 agonists I developed to use in treating schizophrenia. Probably within the next year, we'll see whether those efforts are successful.

KM: What are the drugs and things that you've worked on, and the growing, with the senior people in geriatrics, and a lot of them like the Parkinson's, and the dementia, and things of that sort, Alzheimer's, there's quite a challenge. And try to work -- and hopefully that some of these drugs, some names that you mentioned, the name you hear advertised, you know, some of the materials. It's a real -- it's a big challenge, and now with people living longer, and the memory thing is one thing that is of concern to a lot of people.

DN: Well, I'm 64 now, so if I go up to someone, and I say you know what, I forget people's names, and they say oh, I do too. And right now...

KM: We have junior moments. I do that, we all do that, it's OK.

DN: The FDA approves drugs for pathological conditions. If you have Alzheimer's, everybody's scrambling to come up with something to treat Alzheimer's, but if you just have normal lapses in memory, there's no drug for that. But everybody that I know says you know, if there was a drug that could give me back that memory, I would buy it, and it would make a lot of money.

KM: Because it bothers people when they're way up. You have talked to people and so have I, it just...

DN: What's his name, I should know this person's name, I'm going to be embarrassed, I'm going to fake it until I can remember what their name is. I think there's a market there. I think like a lot of these drugs, they may call it a lifestyle drug, but it's really not, it's not a lifestyle drug if you have a memory deficit, things you can quantify and then you say well, they'll come up with some category for age-related cognitive decline. I mean, that's already a category, but they'll then

quantify it. So if you have it at this level, then it would justify treatment. I think what'll happen is they'll find one of these drugs that improves cognition and memory for some pathological condition, like schizophrenia or Alzheimer's, and then they'll try it on someone, or it'll get off-label, and they'll go to someone who doesn't have that, and if it improves cognition, then what you'll see is a proliferation and you'll get to that point, but it'll take a while.

KM: Sure. How do you think your field has changed since you had gotten into it?

DN: Oh, it's completely different.

KM: OK. And your role has certainly impacted that?

DN: Well, one would hope so. But in the beginning, what I did was really more of a gut feeling like what you should make, and how good you were depended on how good your instincts were about the molecules to make and how well you understood the targets. And now it's computationally driven, and biopharmaceuticals, and they're mining big databases, because finding new drugs is so difficult, finding a drug now means first identifying what the target is, and then validating the target, and then finding drugs that only activate that target and don't produce toxic effects of any kind in anyone. And they're so stringent in terms of the requirements for new drugs.

KM: What has caused that, why it's so difficult?

DN: Well, I think it's because our society is so litigious, we have so many attorneys. You develop a drug for the majority of people. If you think of people being on a normal curve, you develop a drug for the majority of people. If you think of people being in the normal curve, you develop a drug for that person who's in the

middle, and you go one or two standard deviations away, but you have these people out in the end that are hyper responders, people that die after they get a dose of penicillin, even today. Or people that have a severe reaction to aspirin, or whatever. You come out with some drug for treating some condition, and 25 million people take and it works fine, and two or three people die of some kind of a liver problem. All of a sudden, the drug is suspect. And it's probably unrealistic to find a drug that doesn't do anything at all like that that's adverse.

KM: Because people have different makeup, and it can affect...

DN: Yeah, completely different.

KM: You could be one of a million, and you just happened to be the one that it had the adverse effect on.

DN: Or if it's your 17 year old son who's treated with this new drug and he dies, and you sue the company. So everybody's afraid to get in there because of the ramifications.

KM: Absolutely.

DN: A lot of controversy over the price of drugs today, but if they really do shut down the US drug discovery process by taxing it, or regulation, whatever, and there are some ways they could probably trim up and become more efficient, but if they really shut it down, we're the country that leads in the discovery of new drugs now. So you'd sort of see the pipeline really dry up. That's what's going on in major pharma, they're all merging because the pipelines are dry. They don't know how to discover the drugs, they don't know how to find the targets, and how to validate them, and how to find a drug that will hit that target. Computer-based

drug design, I mean, we're doing that in my lab now, but models of receptors that we've got, computer generated models, and we take drugs, and we see if they fit in, and how they fit, and can we correlate how they fit with something else.

KM: Does that make it something a little bit easier that's a help?

DN: Well, no. It gives you a deeper level of understanding.

KM: OK.

DN: Whereas before we could talk about well, the drug binds in some way to the receptor. Well now we can say well, the drug fits in between these alphahelices, and the nitrogen binds to this aspartate in helix three, and the hydroxy binds to serine 242 in helix five. And so you now have a deeper understanding of how they're binding, and maybe how the activation process is occurring. But I wouldn't say it's really gotten us to a point where we can actually use that to design new drugs.

KM: But it's another help along the way?

DN: Yeah.

KM: Right.

DN: Sort of the ideal is what's called structure-based drug design. If you actually have the molecular structure of the target, you know the target you want, you have the structure of it, and you know what it takes to activate it. In theory, you could develop software programs that would dock different molecules, and you could dock molecules, and it would fit and be complementary, but nobody's really there.

KM: Yeah, that's a shame, OK. Let's talk about the psychoactive substance research collection. And for researchers, this is currently in the Purdue Archives Special

Collections that the (inaudible) cards. Just talk a little briefly about that, how that came about.

DN: That was a project of Betsy Gordon. She actually was on the board of the Heffter Research Institute, and realized that there was no source where researchers could go to get all of this information that had been published about work that had been done on hallucinogens over the years. It was fragmented, there were -- it was primary literature here and there, and people had private libraries and so forth. And I guess it was her dream to put it all in one place so that researchers could study it. And I think in a sense, she's visionary, because up until almost the present time, there hasn't been much awareness that these substances were really that important, other than in the counterculture. But I think people are starting to see now that these things may be very important interesting research tools. And for example, when you think about the question of consciousness, what is consciousness, what does it mean to be conscious? What is consciousness, is it a process, does it occur in some part of the brain? 10 or 15 years ago, you couldn't study that, there was no money, no funding for that, it was sort of a taboo subject. And now, you have cognitive research, cognitive neuroscience, you have researchers studying what is consciousness. And if you were living hundreds of years ago and you were a philosopher, it was a perfectly respectable profession to speculate on, Plato, what is consciousness? And you can't make any money as a philosopher today. But I think human beings still have this need to understand who they are, and how they fit into the scheme of things, and where do we come from, and where are we going. Those are

questions that always interested me, and I think interested most people if they think about it. Most people are just so busy with their everyday lives, that they don't really think about it. And in pharmacology, if you want to study a system, the way you study it is to perturb it. So if you want to study how the heart works, you find drugs that affect different receptors, or mechanisms that regulate heart rate, and you put them in, see what they do, and that helps you to understand how the heart works, or the blood pressure system, or the kidney, whatever. So if you want to understand how consciousness works, you're going to have to perturb consciousness. So these drugs are the best tools for perturbing consciousness. So I think they will, over time, as we become more mature as a society, and realize these are really important questions, and you can kind of put aside the drug abuse hysteria and everything from the '60s and say well, you know, they're really interesting compounds. People have asked me, and I have a standard answer for this now, it took me a while to formulate, but people asked me, "why do you study LSD, what's interesting about it?" And so my standard response now is I say well, think about the things that can change your life. You fall in love, you get married, have children, a parent dies, a sibling dies, a child dies, you get a divorce, or you take LSD. And they'll stop...what? And I say, that actually is true though. How is it that a substance can diffuse into your brain, stay there for three or four hours, diffuse back out, and you may never see the world exactly the same way again? How is it possible that a chemical substance can do that? And that's a really interesting question.

KM: You would think so.

DN: And people say wow, that's right. And the thing that surprises me is that more people are not trying to understand that. What actually happens, because it relates to who we are, and consciousness and perception.

KM: Are there many people going into the field, I mean, similar to what you're doing?

DN: There are a lot of people who would like to, and I get letters all the time, and I've had people write to me, how do I get into the field, what do...

KM: What do I need to get?

DN: Yeah, there's just no funding. What I tell most people today, a lot of them are chemistry majors and they say oh, I want to do what you do. And I said you know, there's no interest in the chemistry of these things anymore. The really interesting questions are in the pharmacology and the neuroscience, how do they work in the brain? What do they do, and how do they affect perception conscious? That's really neuroscience, neuropharmacology, it's not chemistry. So I tell those people, I say get an MD degree, or get a Ph.D. in biochemistry or neuroscience, and then get an MD or something, focus on the biology of it. And that's such a long road to hoe, that not many people do it. There's a lot of interest, and I think a lot of young people will still experiment with these substances again. Very interesting, studying this -- a lot of people now who are in their 50's or 60's who are in neuroscience, and especially in serotonin research, I gave a talk at the Serotonin Club meeting years ago, an after dinner talk. And I looked around the room, and there's 50 or 60 people there, all focused on serotonin research. And I said, “I would hazard to guess that the majority of people in this room are interested in serotonin because A, they either

experimented with psychedelics, B, they knew a friend or someone who experimented with psychedelics, or C, they read about them, were so impressed by the descriptions that they thought this was interesting to go into." And all of the heads nodding you know, I don't know who's doing what. I have a friend who went into psychiatry because he said he was taking LSD, and he was finishing his B.S. and he didn't -- or his Bachelor's degree, and he didn't know what he was going to do with the rest of his life. And he was taking LSD, and this big neon light lit up and it said go into psychiatry. And he's a psychiatrist today, and he's enjoyed it.

KM: It worked.

DN: Yeah.

KM: [laughter] Oh, let's talk a little bit about your awards, start with the distinguished chair that you received, and how did that come about? Was it somewhat of a surprise, it's a nice recognition.

DN: Yeah.

KM: Do you know the name of the chair, are they living?

DN: Yes.

KM: Oh, OK.

DN: Well, their father and mother, Robert and Charlotte have passed away. He was a pharmacy school graduate, I believe in the class of 1931, toxicologist at Eli Lilly for all of those years. And his family decided to endow a chair in memory of him and his wife.

KM: Of the father?

DN: His wife, yeah. And they wanted to -- the chair to be in pharmacology. And so I was enough of a pharmacologist, I guess, with the grants and papers that they decided on me as the appropriate candidate.

KM: Sure.

DN: Yeah, they're a very nice family, I enjoyed meeting them, and it was a great honor for me.

KM: Right. Did he graduate from Purdue in pharmacy?

DN: Yes.

KM: And then went to work for Lilly?

DN: Yes.

KM: Oh, OK. Any other awards that you care -- you got some teaching awards at the time? Nice.

DN: I got the pharmacy best teacher award back in the '80s, when I was still teaching organic chemistry. And then in 2004, I was named the Irwin Page lecturer of the Serotonin Club.

KM: I was going to ask you about that.

DN: Yeah, that's an international club of serotonin researchers, and so they pick one person who has been sort of exemplary, and done a particular type of research, and so I was invited to go to Portugal, and gave a plenary lecture there, that was a lot of fun.

KM: Is this an every -- you continue to be their lecturer, or some lecturer things it's only for one year and then they have somebody else.

DN: Yeah, just one year. And they don’t do it every year, it's every few years.

KM: OK.

DN: And I think there may be a Maurice Rapport lecturer as well that they alternate.

KM: Right. I think I asked him about that.

DN: Yeah, it's very nice, because all of your colleagues have worked in the serotonin field, and they know what you've done, and they know your contributions.

KM: Right. What about professional associations, which ones do you still keep pretty active in?

DN: The one that I'm probably most active in is the American College of Neuropsychopharmacology, ACNP. It's a relatively small organization that's primarily academic psychiatrists. And these are all of the opinion leaders and top researchers who study affective disorders, depression, anxiety, bipolar disorder, schizophrenia. There's no chemistry at those meetings, and I go to those meetings every December. And they talk about advances, you know, how drugs compare. And I really use that to get a perspective on some of the things that I should focus on. Where is there a lot of interest in the clinical field, what are the problems with these, how can I understand, sort of translate that back to the extent that I can, and to the work that I do with rats and chemistry. There aren't many chemists in that organization, it's very exclusive. You have to apply for a membership, and there's a credentials committee, and you have to write a big long statement, and they look at your papers, and they look at your history.

KM: You get peer-reviewed to get in there, right?

DN: Basically. It's very difficult to get into that. So I feel kind of lucky there, there aren't that many chemists that are in that organization.

KM: That's a good combination for you. And we talked about consolidating -- and you've done some work with government research review groups?

DN: Yeah, well I served on lots of study sections. I was on a regular study section for many years, and then that's so much work. And they'd keep coming back and they'd ask me. Still, I get invitations all the time to serve as an ad hoc reviewer because I know chemistry and biology. And there's so many of the reviewers that just know chemistry, or just know the biology, and can't do the synthesis of the two.

KM: Right.

DN: So I've been pretty popular. So I kind of pick and choose. If I'm really busy I say I just don't have time for it, and if I've got time, I get those requests a lot. So I do that sort of as a service, but I don't really want to be in a regular review group anymore, it was just too much.

KM: You can pick and choose, it's better.

DN: Yeah.

KM: Yeah, let's talk about family, did your children, did they come to Purdue?

DN: They both, my youngest son graduated from Purdue, and he has a degree in communications, and he is a TV -- he works at TV-2 in Greensboro, and he is an editor, production manager, he does work with...

KM: Greensboro, North Carolina?

DN: Greensboro, North Carolina, it's again, at station TV-2.

KM: OK.

DN: And he films, edits, writes scripts, he does promos, all kinds of stuff in there. And then my oldest son is the -- he's an assistant professor at LSU in the medical school there. They tell him he's sort of their rising star in the department, and of course, you know he got the press release on his research with his first big grant. My understanding is he'll be promoted this year there. He's doing promotion document things: he's going to be an associate professor. So that's very satisfying. I joke about starting...

KM: Did he go to Purdue as well?

DN: Yes.

KM: Oh, OK.

DN: He actually graduated with a Bachelor's Degree with honors from biology here at Purdue.

KM: OK.

DN: He started in chemistry, and then switched over to biology. I told him, I said, I don't want you to -- don't do what I'm doing, you should do what makes you happy.

KM: Don't follow Dad?

DN: Yeah. He told me once, he said -- I said, you know, I never pushed you to go into science, I always told you, you should do what you want, what makes you happy? He says no, Dad, you biased me. I said, how? He says well, let's think about it. When I was little, did you get me baseballs, and toy trucks, and stuff? No, you gave me a microscope, a telescope. And I said well, those...

KM: [laughter] No Lincoln Logs or Legos?

DN: No, I said well, those were the things that were interesting. Well, and I hadn't even realized it, I had sort of biased him.

KM: [laughter] He did not forget?

DN: Yeah. But he's a good scientist. He's a good scientist.

KM: That's good. How about an outstanding event in your life. Anything come to mind that you'd like to share with us?

DN: Outstanding? You mean other than the Anderson Chair or something?

KM: Anything. Doesn't necessarily have to be with Purdue, I mean, it's open-ended.

DN: Oh, boy.

KM: There have been a couple, I'm sure. Well, the Anderson is one, you can certainly tell me...

DN: That was -- yeah, I mean, those awards have been -- and being selected as the Page lecturer, those are big awards. The funny thing is, I tell people that I think if I'd gone into heart research, or cancer research, I'd be getting all of these awards, but because I went in to study psychoactive drugs, you know, it's -- I didn't plan to be a martyr, but I think in actual fact, it's almost like that. Nobody recognizes the importance of these things. And it's been really my personal devotion because I was convinced there was something here and nobody -- they were being ignored, that I really focused a lot of energy on that. And so I probably have given up a lot of awards by choosing the field that everyone would consider so strange, maybe...

KM: That's OK, and the closing remarks, I'll leave it up to you. As you look back, or look ahead, any summary comments that you'd like to share?

DN: Well, as I look back...

KM: And ahead too as well.

DN: Yeah. The choice I made in graduate school, and the accidental finding that Barfknecht, Charlie Barfknecht was there doing something that just was perfect, and that I had a fellowship and could do what I want, and that I'd worked so hard already, working with the family to go to school, that graduate school just was like, I've got all of these publications, and everybody considered that I was the top student in the department, and one of the top students that ever had graduated, and then I got the position at Purdue. And as I look around at other places like wow, I was really lucky I was here because they had an infrastructure, they were building a research department, I wasn't hammered with so much teaching that I couldn't do research. We had good facilities and a good reputation. And of course, they'd been able to recruit good students. I've gotten some of the best students that came into the graduate program. I look back and think I've just been incredibly blessed by all of the things that happened to me, and...

KM: It all kind of came together, which is great.

DN: Yeah, yeah, and to look back and, you know, I don't know where the Heffter Institute is going to go, but we've got three clinical studies now where we're using the active ingredient from psychedelic mushrooms to treat dying patients. And the first study we completed with 12 patients, we got really remarkable results. And we've got a big study at New York University, it's all basically to look at finding new ways to treat people, improve the quality of life. And I'm looking at

some of these things going, you know, in a couple of years, if this stuff all works, I can look back and say you know, none of this would've happened. They say there's a renaissance in the study of psychedelics, but the renaissance is because I made MDMA for a pre-clinical study in 1986, and that's what everybody uses. And I made Rick Strassman's DMT, and so that got everything started, and I made psilocybin for the study at Johns Hopkins, and none of these things would've happened. And I don't ever go around telling people about it. They just see them happen, they don't know that Dave did this in the background and enabled it. So it's kind of -- I wouldn't say I feel like a godfather, but in some sense...

KM: Very rewarding.

DN: Some sense, looking at all of these things are happening now, and nobody knows that I was really behind the scenes doing a lot of these things, but I was. So it's satisfying to see -- when I really retire, sit back, and see these things, if they keep going, and developing, and we see new medical treatments, and better understanding of psychiatric disorders, and the D1 stuff, you know, if it actually works in the clinical trials where they're testing it now, in improving memory and cognition, then we start being able to improve the lives of schizophrenics. I can look at a lot of those things and feel like I left my mark when I'm gone.

KM: That's right, exactly. Thank you, thank you Dr. Nichols, I really appreciate that.

DN: It's a pleasure.

KM: My pleasure. This concludes the interview, thank you.

End of Interview

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