

Daniel Weinberger Interview
July 21 2005

CLAUDIA WASSMANN:

Today is Thursday, July 21, and I'm doing an interview with Dr. Daniel Weinberger. My name is Claudia Wassmann. Okay, maybe let's start...

DANIEL WEINBERGER:

Let me ask you a question before we get started. Just give me an idea of...

[break in audio]

CLAUDIA WASSMANN:

Well then, let's start like that. You wrote *Psychiatry History*, and your work revolutionized the understanding of schizophrenia, and it has profound implications for our understanding of individual differences in cognition and emotion. Can you tell us how you got there?

DANIEL WEINBERGER:

Well, I'm not sure that's where I've gotten but thank you for that very flattering statement. I got here, in some ways, without the clearest of forethought, so this was not my plan and goal to get where we currently have gotten in my program. And we've been very fortunate to have been in an environment which the intramural program the NIH has traditionally been, where one had the opportunity to follow any clue that captured one's curiosity, and that looked particularly promising, and having the independence and autonomy to pursue those clues. And that's been the intramural program and environment of the NIH traditionally; that's been the way it's been, I hope it will remain that way. I became interested in psychiatry as a medical student in the 1970s at a time where I thought that there was a reduction in the humanism of medicine. And I became very interested in psychiatry as a more humanistic approach to sickness and trained at Harvard in what was then a very psychoanalytic program. I was very interested in neuroscience as a medical student and I was interested intellectually in psychoanalysis, but when I got into this program I became increasingly disenchanted with the concept of being a psychoanalyst, and longed for more of the medical end of psychiatric conditions. I was very much influenced by a mentor of mine. I was the chief resident under a teacher named Richard Shader, [spelled phonetically] who was a psychopharmacology expert -- also happened to be a psychoanalyst -- and was just a totally excellent doctor, teacher and very good clinical investigator -- had been at the NIH. And I was very much under his influence and aspired to that level of inquiry that I thought he really epitomized. And I had another mentor named Karl Saltsben [spelled phonetically] who was somewhat junior to Richard Shader but was also

very influential to me and was also at the NIH as a fellow. They both advised me to come here. I had two very dear friends from my residency who had come here a year ahead of me. One is Joe Kleinman [spelled phonetically] who is still with me, we've done two residencies together. So I came down here with the expectation that I would learn something about research, I was interested in a career in academic medicine. And at that time, which was the late '70s/early '80s, this was the only way you really got that kind of training. So I came here with that expectation.

When I got here, basically, psychiatric research was primarily following biochemistry leads that were based on trying to measure a variety of chemicals. It was just in the twilight of what was the bioanalytical era of quantitative chemistry, and there were all these chemical assays. And I was very disheartened by the approach that was being taken, which was to measure chemicals in the blood and urine of patients because I felt that these were brain disorders, and if they were brain disorders you had to study the brain. And I believed the notion that trying to determine what was going on in the brain by measuring some chemical in the urine was analogous to trying to know what was happening at the back rooms of city hall by measuring constituents of the sewage system; it just didn't seem to be a very useful strategy. So I became very interested in doing studies in actual brain. And there were only two ways to do studies in brain: you could collect tissue of deceased people -- that was hard to do at that time -- although my client colleague, Joe Kleinman, basically built his career around doing that; the other was that there were just emerging these early efforts at having actual imaging systems that could give you pictures of the brain. And when I got to NIH, the CAT scan had just arrived on the scene.

And I started in the program under Richard Wyatt [spelled phonetically], who was at the St. Elizabeth's hospital. And the NIMH had a building at St. Elizabeth's hospital, and I went to that program. I actually was never interested in coming to the main clinical center because I didn't understand how you could do psychiatric research not being in a psychiatric hospital. And so it seemed that that was the place you had to be, because that's where all the patients were. So I went to St. Elizabeth's, and that was a fantastic environment at that time in the '80s, because it was a little bit like the French Foreign Legion, it was a complete outpost. And it had this camaraderie and outpost mentality that I thought was extremely good for thinking new things and being creative, it was not encumbered by any of the bureaucratic or traditional hierarchical problems that might limit new ideas and new ways of doing things. So I started these CT studies, and the whole idea was to look at the brains of living people. And what was clear from CT scans of schizophrenics that I was responsible for was that there were no traditional neurological findings, but it seemed to me that the story with mental illness was not going to be

about brain tumors or white matter lesions or Alzheimer-like changes, it would be that brain scans would be a proxy measurement of a quantitative change in brain anatomy. So I began a series of studies to quantitatively measure brain features, and that led to the finding -- which was not the first finding at all of its type, but the first from a large controlled study of young patients -- that there were bigger CSF spaces, particularly ventricles in patients with schizophrenia. And we did many studies on this, not just characterizing this, but trying to understand its relationship to treatment. I remember early on in my career I had Norman Geschwin [spelled phonetically], who had been a teacher of mine at Harvard, who was the father of behavioral neurology, come down and look at some of these patients. And he commented -- he was very important -- he said if this large ventricle tendency towards bigger ventricles has anything to do with schizophrenia then there should be lawful predictions that you can make about the clinical state of patients based on whether they show some of these changes or not. So we did a number of studies to do that, and it basically led to a fairly archival understanding of the fact that there were subtle but objective changes in brain anatomy that could be observed in patients. We started a series of postmortem studies and that led to a whole field which continues to grind out papers about quantitative neuroanatomy. It also became clear to me early in the '80s that, while there might be subtle anatomical changes, ultimately the illness was an illness that had its manifestations based on how the brain functioned, not on how the brain looked, but on what the brain did. And so CAT scan studies were not studies of how the brain worked, they were studies about how the brain looked, and that it was like a roof: the roof could be photographed, and you could see that roof had some bows in it and some bends in it, but you couldn't determine that the roof was leaking until you forced it to hold water. So I thought it was critical to develop another strategy for imaging, which was functional neuroimaging.

And this was the early days of the PET scan, and we were beginning to do PET studies with flourodeoxyglucose, which was a measure of glucose utilization, developed largely based on the work of Lou Sokoff [spelled phonetically] in 2D oxyglucose [?]. But the problem was the temporal characteristics of glucose PET scanning was about 40 minutes, and that means you averaged brain activity over 40 minutes, which didn't seem to make any sense to me because the brain processes information at the level of microseconds, not at the level of 40 minutes. So we needed a technique that would look in a much more dynamic way to change the brain function. And I went to a talk given by David Ingvar [spelled phonetically] from Denmark at that time --from Sweden, but the talk was in Denmark -- where he described the method for looking at regional cerebral blood flow [?], which was a highly dynamic physiological measure of brain activity, and I thought this was the way to go. And I thought back in 1983 or '84, I convinced Fred Goodwin [spelled

phonetically], who was then the intramural research program director of NIMH, to give me a half of a million dollars to purchase -- no, at that time it was a hundred thousand dollars, the first systems -- a hundred thousand dollars, which was a lot of money, to purchase a regional cerebral blood flow system that we housed at St. Elizabeth's hospital.

It was the only regional cerebral blood flow system of any psychiatric research program in the world, and it was the first regional cerebral blood flow system at the NIH. It was a system that was comprised -- it was like a medieval torture device, although it was completely harmless and involved no discomfort to patients. But it was a strange helmet that had 32 essentially scintillation counters applied to subject's head. And we had them breath radioactive xenon gas, while they did cognitive tasks. I did this with a younger fellow who became my principle associate in these studies, Karen Burman [spelled phonetically], who's also still here at the NIH. My thought was that the critical issue with these kinds of studies was not to get a measure of blood flow but was to use blood flow as a proxy of how the brain processed information. And in order to do that you had to contrast blood flow patterns while the brain did a task that exercised a system in the brain that you're interested in, in comparison to when it was doing that kind of an exercise. So based on discussions I had with Al Mursky [spelled phonetically] and others here at the NIH about frontal lobe function, I picked a task called a "Wisconsin Card Sorting Task" that we had patients in normal controls do while we measured their cerebral blood flow, and we compared that to what their brains were doing while we measured their cerebral blood flow when they were doing a simple magic task. The idea was we would isolate by doing a contrast between these two conditions; the brain systems that were involved in the higher order problem solving of the card sort. I became very interested in the frontal lobes and schizophrenia. Because in 1982, I was lying on a beach in Ft. Lauderdale, and I was reading a book by Yoachim Fuster [spelled phonetically], who was a professor of neurophysiological at UCLA called "The Prefrontal Cortex." It was the first edition of that book, and I read that book, and I thought to myself, "Why has nobody ever talked to me about this." His description of aspects of frontal lobe disease malfunction, etc., had many characteristics of the cognitive and other problems associated with schizophrenia. So the early blood flow studies were designed to test specifically the hypothesis that if we could isolate frontal processing components we could identify a cognitively specific and system specific deficit associated with schizophrenia. And that, which was a paper published in 1986, really was the first study that documented, at the level of a mechanism, that there was a system specific physiological deficit in schizophrenia involving the frontal lobe, and that has led to probably a hundred papers by many, many groups around the world. We subsequently did a number of PET studies on that, we've done a lot of imaging studies on that using functional magnetic resonance

imaging, EEG studies, many, many different, more refined, more sophisticated studies than our early blood flow techniques, but basically confirming with much more sophisticated methodology and much more complex single processing mathematics, the basic discovery of a physiological dysfunction of this dorsal [unintelligible] [prefrontal cortex] in schizophrenia.

So those were the many areas that we studied for probably 15 years until the early '90s when I attended a meeting of The National Academy of Sciences where Harold Varmus was there, and this was in the early days of the human genome project when it was just starting. And I became very convinced that the Human Genome Project was going to succeed, and that we would have genes for mental illness. And I thought to myself, "Once we have these genes, we're going to have to understand them because whether we like genes or not, they will represent the only absolutely objective clues to the basic causes of the illness." Everything that we'd done up to that point for basically 12 years of my career, everything that we'd done was based on characterizing the phenomenology of the illness. Even though the phenomenology would be very elaborate, sophisticated and cool at the level of brain physiology and brain anatomy, it was all phenomenology. We were contrasting people who were ill with people who weren't ill. Genes were not phenomenology; genes were basic mechanisms of disease. So I became very concerned that we would not be ready for these genes.

And actually, we were just talking about this at lunch, in 1993, I made everybody in the lab come with me to Catholic University to take a ten-day course in recombinant DNA technology in the laboratory. We began to retool the entire program around genetics and molecular biology. And then in the early '90s, about '93, I started working with Joe Frank [spelled phonetically] down here in the fMRI unit, when the early days of functional magnetic resonance imaging began. And when we first started doing these studies that involved no radioactivity, but had higher resolution than PET and higher temporal resolution, both spatial and temporal resolution, than PET, it dawned on me that since there was no radioactivity, and we could study the same subject repeatedly as their own control, we could actually do phenotyping at the level of brain function in individual subjects. And once you had individual subjects, you had a phenotype that you could relate to a gene. And it always seemed reasonable to me that schizophrenia was not really about schizophrenia, it was about brain processes that led to the emergence of this clinical condition. And the clinical condition was likely to be a real secondary phenomenon related to more basic brain processes, which ultimately had genetic origins. So I became very excited about the idea that there was a strategy now for imaging, with high temporal and spatial resolution that could be used as a target phenotype to understand gene effects in the brain.

And I actually -- one of the things that has characterized my whole career, by the way, has been presenting ideas for novel strategies to understand psychiatric illness that caused me to be laughed out of the room of the people I've told this to. So when I first started doing CAT scan studies, I went to Giovanni DiChiro [spelled phonetically], who was then head of radiology at NIH, and I said, "You know, I think we have bigger ventricles in these patients, what do you think about this?" And he completely kicked me out of his office, thought it was complete meaningless observation, had no relevance. When we wanted to first do blood flow studies and I tried to convince the department here to think about doing PET regional cerebral blood flow rather than glucose, they thought it was ridiculous; that it would have no value because it would be too transient. And then, when I went to the radiology people with the idea that maybe we can use functional magnetic resonance imaging to do genetics in brain; people looked at me like I had lost it completely. Well, the fact of the matter is, because the NIH has made it possible for people to pursue ideas that, at their face, may look a little bit extreme, these things have turned out to be very valuable strategies.

When I first started our genetic study, where we were focused on genes, about brain development, brain functioning, temperament cognition, and not genes from mental illness, I went to the genome institute, and talked to the then scientific director at the genome institute, and I said, "We think that we can define intermediate phenotypes. Not clinical phenotypes, but aspects of brain function based on imaging and cognition that will show greater gene effects than the clinical diagnosis. We want your help with this." They literally kicked us out of the office -- thought it was the most preposterous thing they ever heard, because it was very different from their traditional Mendelian linkage-based strategies. They said, "Bring us high-density families, we'll find you genes." That strategy has not found genes, and this strategy has helped us understand the genetic mechanism, psychiatric illness. So it's basically evolved over the last ten years.

We changed the program dramatically beginning in about 1995. We were still at St. Elizabeth's; we moved here in 1998 to reorganize everything that we did -- imaging, patient assessment, cognition -- around trying to characterize phenotypes that would be related to the genetic origins of the disease. And we began to organize a study, which we called the Sibling Study, The CBDB NIMH Sibling Study, where we collected families that had an affected offspring and an unaffected sibling and two parents. All we got from the parents was the DNA, we got DNA from the siblings, and we put them through a two-day study here at the NIH involving imaging, cognition, EEG, many, many personality and other kinds of inventories, and we've also acquired normal controls at the same time. Over the last nine years that we've been doing this study, we've studied over 1,500

people. We have imaging cognitive data sets, temperamental inventories, and over 500 normal people, over 500 patients with schizophrenia, over 500 of their healthy siblings, we have human cell lines on over 1,500 of these people, we have DNA from about 800 of their parents. So it's become a phenomenally rich archival data set to look at how genes affect aspects of human brain function related to psychiatric illness, related to temperament, etc. And I think where all this has led now is that we have discovered not just genes for schizophrenia -- which many groups have discovered -- we have now probably 10 to 15 schizophrenia genes, but we've been able to begin to explore what those genes do in brain that accounts for why they translate into psychiatric illness. And this has emerged from the application of cognitive analysis, imaging studies, in addition to postmortem brain gene and protein expression studies to the genetic variations that are associated with mental illness. And that's where the work is right now. That is the story.

CLAUDIA WASSMANN:

That's great. So you say, when did you start to collect this database?

DANIEL WEINBERGER:

About '96.

CLAUDIA WASSMANN:

'96.

DANIEL WEINBERGER:

It began about '96.

CLAUDIA WASSMANN:

And when you conceived of the phenotyping studies, you conceived of it first, searching for schizophrenia genes, or you thought immediately of normal people?

DANIEL WEINBERGER:

We always thought that the issue was not schizophrenia genes. I mean, the genes are not about hallucinations and illusions. Genes are about molecular processing and cells. And we always assumed that, just as an intermediate phenotype for colon cancer is a colon polyp, the genes had to be about how your brain developed and how it worked. And that ultimately, the psychosis and the other problems were downstream manifestations of these more proximate biological phenomena. And we reasoned -- I reasoned it was, to me, very obvious that the closer you got to the biology of the gene, the more strong the gene effects would be. And the biology of the gene related to mental illness is the biology of brain. And that if we could study genes in the brain, we would see much more robust effects. And now ultimately, the studies in normals are because the

variations in the genes are compensated for in normals, or normals don't have additional factors that interact with the set of [unintelligible] genes. But they also don't have confounding factors like alcoholism, drugs, etc., so you could see pure effects of the genes in the normals. And we've consistently shown now, that by using brain phenotyping, not clinical illness but brain phenotyping, that the genes related to clinical illness in people who are clinically ill translate into lawful, predictable variations in how critical systems in the brain relate to cognition and emotion, process relevant kinds of environmental stimuli. I tried to cover a lot of your...

CLAUDIA WASSMANN:

Yeah, you covered everything. [laughs] But I would like to ask, the clinical brain disorders branch was created in 1987...?

DANIEL WEINBERGER:

Right.

CLAUDIA WASSMANN:

So that was St. Elizabeth's, and then you moved here in 1998. Why did you move here?

DANIEL WEINBERGER:

We moved here because the NIMH was having -- we moved here primarily to save money. The building at St. Elizabeth's had begun in like the mid-'50s, and was started by Seymour Keddi [spelled phonetically], who was the scientific director of NIH. And it was based on the idea that the Mental Health Institute should have a research center at a mental hospital, and St. Elizabeth's was a federal neuropsychiatric hospital. We had a great building there, about 250,000 square ft. It was old, 1950, but it was a great building, great labs. And as I said, we were like the French foreign legion: we operated completely autonomously. We had our own crew, staff, we had our own building crew. If we had to get an office renovated, we did it ourselves. If we had to build a lab, you know, everything -- you know, Floyd Bloom [spelled phonetically] had been there; it was a great environment. We had our own monkey program; we had about 50 rhesus monkeys there, We had terrific animal facilities.

Anyway, but by the mid '90s, the landscape had changed. What had been a very rich neuroscience community where there were always four or five labs there had become really two labs: my own lab and Richard Wyatt's [spelled phonetically] lab. We were losing the critical mass of scientists that we needed to have there, because it became increasingly hard to get people to go there. In the '80s and '70s, everybody wanted to go there because it was such a great place to work. But as things at the main campus moved much more into molecular neuroscience, it became more isolated. Really by the mid-'90s it was clear that its heyday was passed.

And then because that building that we occupied cost about \$4 million a year in rent to St. Elizabeth's, the contractions in the program, it really made sense to just bring it back. And this has definitely been the right place to do this kind of work.

CLAUDIA WASSMANN:

There is the unit for systems neuroscience and psychiatry, when was that created?

DANIEL WEINBERGER:

I'm not sure what that is, actually.

CLAUDIA WASSMANN:

Well that's part of the -- I found that on your website.

[laughter]

DANIEL WEINBERGER:

Okay, well we have a number of units in the program, so this program has changed. It was a basic lab until two years ago, and the lab has two sections, the clinical research section and a post-mortem study section, and within each section there are multiple units that are really groups of investigators based on different strategies for doing these investigations. So the unit on systems neuroscience has basically been a unit trying -- do you know who heads that unit? I don't remember the name

CLAUDIA WASSMANN:

Andreas Myer [spelled phonetically] --

DANIEL WEINBERGER:

Oh Myer-Linderberg [spelled phonetically]. Okay, so that's a very new unit. That's a new unit based on one of our newest tenure track investigators. So we just we formed that unit this year based on Andreas Myer-Lindenberg becoming a tenure track investigator, he is a neuroimaging investigator who has a much broader vision about applications of neuroimaging than the traditional vision. And he is one of the really talented, young signal processing/imaging investigators, who's using genetics, systems neuroscience, and complex strategies for functional imaging analysis to explore novel ways of using imaging to understand neurosystem function and ultimately genetics and brain.

CLAUDIA WASSMANN:

So I was wondering, because, then there is the genes cognition and psychosis program that was created in 2003, but that would also address systems...?

DANIEL WEINBERGER:

Yes, well there are many different -- everybody is [unintelligible] systems. The genes cognition psychosis program, which began two years ago, was an effort to capitalize, this was largely because of Tom Insel's [spelled phonetically], I think, support and really active interest in the work that we've done. And for the first time ever in my entire career at NIMH, we have had an institute director who is trying to enhance our efforts and not to frustrate our efforts. I've never had an institute director, previously, who has tried to help us. And Tom was the first institute director who was not threatened by the work that we did. So Tom was very, very eager to encourage us to pursue this work. And he recognized immediately that these genetic insights were of enormous importance. So we realized that we could no longer keep this work in a small -- in a lab, it was not a small lab, but we needed to bring in investigators with expertise across the NIH community, and the idea of the program was that we never have resources to recruit investigators in other institutes. There are four institutes now involved in the program. So we are funding investigators in the Cancer Institute, in Child Health and Development, in Neurology, and in NIMH. So the program is across institute, it's based on engaging investigators who have expertise or skills that are not in NIMH, and have all of these people work with the same vision, which is to understand the mechanisms of genetic susceptibility to mental illness, but to use a variety of different strategies: imaging, cell biology, animals, basic molecular genetics, stem cells, to try to understand these mechanisms. That's what the Gene Cognition Psychosis Program is now. It engages four different laboratories in four different institutes in various ways in trying to map, at the cellular and brain level, the mechanisms by which these genes operate.

CLAUDIA WASSMANN:

Yeah, if one looks at the papers that came out in the last few years, it really seems as if it's a strategic effort to do all of these studies -- they are coordinated -- and then also the way that papers are published, it's really like building a solid -- [laughs]

DANIEL WEINBERGER:

Well, it's been mind-bogglingly rewarding to all of us. The other thing is, I think we have managed -- this was partly from our history at St. Elizabeth's, when you're in the French Foreign Legion so to speak, or you're in an out post like this, there's a tremendous amount of collegiality and camaraderie, and St. E's program was famous for this, which was not what people often said about the intramural program at NIH. We were famous for having a certain esprit de corps and that's probably because we were a little bit isolated, and we all had to work together. And so one of the things that I think has characterized the program here is that we have been a very well-functioning, long-together team of people working together, sharing many aspects of this work -- both the credit, the details,

the sweat, and it's been a very rewarding effort, I think, on many levels. We've brought many people into the genetics of this from areas outside of genetics. We very strongly encourage people to get much more familiar with the genetics, much more sophisticated with the genetics. We brought people into imaging that would never of thought of setting foot anywhere near imaging data. Because we've tried to treat all of these approaches as tools to characterize the biological mechanisms involved. And so I think part of the real, I think, reward of this whole thing has been this team of people. We have had, you know, a group of us now that have been together for 15 years working on this. The main pillars of this group have been together 15 years. We're actually at a very significant milestone because two of our principal pillars, Michael League [spelled phonetically] and Terry Goldberg [spelled phonetically], are both leaving. And they're leaving literally this month. And those people have been with me since the mid-'80s, almost 20 years – Terry's been with me 20 years, Michael about 18 years. And they have been absolute pillars of the community, among my most valued scientific collaborators. But you know, nothing lasts forever.

CLAUDIA WASSMANN:

Where are they going?

DANIEL WEINBERGER:

Michael League is going to Merck Pharmaceuticals, and Terry Goldberg is going to Albert Einstein Medical School in New York. Both accepting very significant positions, as they should have them.

CLAUDIA WASSMANN:

So how big is the group?

DANIEL WEINBERGER:

Well, the group has many different incarnations, so, you know, I don't know -- I mean, I think the GCAP, the program, which involves many independent groups of investigators, probably is a hundred people overall. But there are all these different labs, so they're linked by virtue of their some common projects. But the clinical brain is sort of a branch itself. I think, maybe, in terms of the number of investigators, maybe there's 10 or 15 investigators. But there's a lot of other students, and you know we have a nursing environment, which I think is part of why we all feel kind of invigorated by it because it's very multi-dimensional.

CLAUDIA WASSMANN:

I was wondering when I looked at the papers, on the one hand it's scientifically just fascinating and stunning, and on the other hand I was wondering what can be done with the results? Do you think about that, or do you control what's happening to your results, because there is this issue

of normativity that this study raised. When they talk about the [unintelligible] links for instance, the way it's put in the paper is often as if the [unintelligible] version was the standard, or the norm.

DANIEL WEINBERGER:

Well, we have some papers coming out on that. This is a very evolving area of work, because we're really scratching the surface of understanding human temperamental variation, cognitive variation, psychiatric variation. And as we get deeper and deeper into these genes, we begin to appreciate more and more that they're all about the flavorings of human variation. So while Met Mets [?] may have a much more efficient way of dealing with cognitive information, they actually have a much less efficient way of dealing with emotion information. So there are yin-yangs to these things, no gene is about only one thing. And that's partly why there's a lot of Vow Vows [?] and a lot of Met Mets [?] around. Because there are advantages and disadvantages to each form of the gene, based on what the specific environmental context is. And this is very complicated human biology of normal variation because these genes have been interacting with the environment, changes in the environment and other genes, for millions of years. And so a lot has happened to balance off different functional changes in these genes, and I think the environmental context of change, and they select for different properties. It is a very infinitely complex but very fascinating story.

One of the reasons we've put a lot of energy into COMT is because it has this functional variation that we can study by asking lawful questions. We understand a lot about the biology, COMT was discovered by Juli Axelrod. And before he died, I had lunch with him probably monthly for a period of time, because we were obviously very taken and enthusiastic and really quite taken by this whole COMT phenomenon. And he was ecstatic that this protein he had identified as an enzyme had a whole new life and was being understood at a level that they had never had the tools to study it at. And this was his favorite molecule, he won the Nobel Prize for catechol-O-methyl transferase. It's fascinating that Seymour Keggi, who was then the scientific director of NIMH, when Juli Axelrod found COMT, said, "If this enzyme, this protein, has nothing to do with mental illness, no protein does." It took about 40 years, 45 years to find out what it had to do with mental illness, because it was not really about the way it had been studied, it was about the frontal cortex and genetic variation. But that's the old story, that progress is new solutions to old problems.

CLAUDIA WASSMANN:

So it's serendipity that, at the moment when you were working, molecular biology and brain imaging technologies were both available.

DANIEL WEINBERGER:

Yeah, definitely. Absolutely. Well you know, there's always that. [laughs] Juli Axelrod said this, he said, "Being a good scientist is not about brilliance, it's about asking the right question at the right time." It's about perseverance, asking the right question at the right time. I personally don't think any of these questions are brilliant, it's just a matter of where your head is, and how you see what question interests you, and being doggedly persistent, because we've been just hammering away at this concept that mental illness is about brain function, not about behavior, and that what are the best tools to get at that imaging clearly was the best tool to study brain function. People, genetics, I like to say the basic science of psychiatry is nerve science and genetics — that's it. And the only in vivo tools for neuroscience are imaging. I mean, in some ways it's simple, it's like these are all we've got, and you've got to say to yourself, what are the best questions you can ask with the tools that are the best tools you have? And that's what I think it's been a little bit about. I always remember that this famous sculpture of Picasso's, called "The Bull's Head," which was a bicycle seat like this and a set of handlebars, and you look at this thing and you go, "Why is this a great piece of art? Anybody can take a set of handlebars and put them on top of a bicycle seat." Well the answer is, Picasso saw a bull's head in a bicycle seat and a set of handlebars. And I think the reality here is that there's no real magic in any of this. It is just about trying to shape the question based on a skeptical, critical view of what is the dogma — which has always been the way I've approached this stuff — and trying to optimize the tools that are out there to ask those questions. And I think we've been lucky to be in a position to be able to do. I've also been extremely lucky to be in an environment where there's all these talented people to work with, who've been willing to buy into this vision which many people didn't think would go anywhere. Our previous NINM director thought that this was a complete waste of time and was very, very negative about it, and did everything he could to thwart it. We all know who that was.

CLAUDIA WASSMANN:

[laughs] So it must be especially gratifying to have this classified as, where was it, in *Science* 2003?

DANIEL WEINBERGER:

Oh yeah, that was very gratifying. That was gratifying. I mean I, don't know if it's gratifying, I mean, to be honest, it's flattering. What's gratifying, really, is that we have real genes and real mechanisms by which the genes work. And what's really gratifying is to feel that we're no longer elaborating phenomenology but dealing with basic mechanisms of causation, and that I believe that some of these findings are truly meaningful at the basic level of causation. And that is gratifying. The *Science* thing was flattering, and it was a relief, because it meant that we would have a honeymoon for a period of time to continue to do this before

the next person who found it threatening or difficult would come after us and try to limit it. [laughter] So to that extent we have a reprieve now for a little time, we have a honeymoon for a little while to keep hammering away at this.

CLAUDIA WASSMANN:

Okay, well, great. Thank you very much.

DANIEL WEINBERGER:

So you've got the science and the politics in one place.

CLAUDIA WASSMANN:

Yeah.

DANIEL WEINBERGER:

Anyway, looks good.

[end of transcript]