Dr. Daniel S. Pine Interview

Claudia Wassman: If you could start with -- you came here five years ago in 2000.

Dr. Pine: Right.

CW: And you became chief of a section on development and effective neuroscience.

P: Correct.

CW: Can you maybe start with telling me what that is?

P: Yeah, yeah, so I guess there's probably a couple chapters to this story. Chapter one is that I've always wanted to be, and I always have been, ever since I was at the University of Chicago, an academic physician, and I have always been most interested in what we call pathophysiology, or what are the causes of different kinds of problems. And I had done my training at Columbia University after medical school and had been there for about ten years at Columbia University and had spent a lot of time doing research on pathophysiology. And there were certain things that were progressing very quickly in terms of research at the time on pathophysiology, and there were other things that were not progressing as quickly. So the things that were progressing quite quickly is that throughout the 1980s and 1990s, there had been really major advances in terms of how people thought about psychiatric diagnosis, to the point where psychiatric diagnosis had actually come quite far. If you looked at the kind of the state of the field in 1970, and you looked at the state of the field in 2000 when I came here, it was radically different. And some of the most dramatic strides had come in research with children or adolescents, so there were really dramatic advances, in terms of how people understood diagnosis, and that had happened while I was at Columbia.

CW: So can you be a little bit more precise, what exactly changed?

P: Well, you know, so many things, it's almost impossible to describe them. You know, even the very idea about talking about mental disorders in children in the 1970s was something that was a very radical idea. You know, people did not like to talk about it for a lot of reasons, you know, social, political reasons, scientific reasons, stigma, and it just was not the kind of thing that was regularly done. Moreover, for the kinds of disorders that I'm interested in, disorders of emotion, that was really not done. So for example in the 1970s, the idea that you would think about making the diagnosis of depression in a child was just unheard of. Even in 1980, that was a very controversial thing to do, so that was one major change. The other major change was in terms of the procedures for arriving at a diagnosis and the thought had been that children were really radically different than adults and that to use the kind of procedures that had been developed with adults was thought to be somewhat foolhardy. But then work in the 70s and the

80s showed that with appropriate modifications, you could apply those techniques reliably.
So the procedures, really, for arriving at psychiatric diagnoses had changed quite a lot, particularly for the kind of disorders that I study. And then the third thing was, with those advances, people were able to go into the community and were able to do epidemiologic studies and were able to answer questions about how common psychiatric disorders were in children. And people were quite surprised to find out that the disorders were exceedingly common, much more common than people though they would be, and then kind of the fourth advance, and this came much later, is if in the late 70s and the early 80s, people kind of began to use these diagnostic methods, 15 years later, by the late 1990s, these children who had been assessed when they were young had grown up to become adults, and people could look at the relationship between having a disorder in childhood and having a disorder in adulthood. And one of the things that emerged was that some of the strongest predictors of having problems as adults, we're having similar kinds of problems as kids.

CW: So is this the epidemiological studies -- the studies you started with?

P: It was so -- all this work that I've described so far, everything so far was really all based at Columbia. This is all -- and this is -- I spent much of the first ten years of my career looking at these kinds of issues, number one, issues of familial relationships, so the relationship between problems in parents and problems in their kids, and we also found that there was a relationship there. Number two, that parents who have depression tend to have kids who have emotional problems as well, and then number three was treatment. That was another major advance in the 1970s, 80s, and 90s, that there were major advances in treatments, both medication treatments, and then also psychotherapies, and again, all of this work is work I was very involved in at Columbia, and then I also began studies that looked at aspects of brain function. In the late to mid 1990s, kind of the concentration of scientists, and the concentration of resources, who were looking at that specific type of question. What's the relationship between direct measures of brain function and direct measures of clinical problems? That was a very difficult thing to do, and it's a long, complicated story about why that was so difficult to do. Part of it was technological, you know the techniques that were available were radically changing. Part of it was economic, you know, there has to be a fairly large investment upfront, on kind of technological issues.

CW: You mean the scanner?

P: Figuring out how to use the scanner, figuring out how to analyze the data, issues like that, and to be quite honest, it's still not clear if these methods are going to be clinically useful. At the kind of place where I was, there was kind of a stronger emphasis on really pushing the clinical relevance of the types of studies that you're doing, such that the work that I was doing at Columbia was kind of closer to clinical questions than the typical kind of studies that get done here at the NIH.

Partly based on what was happening in science, but then also, partly based on what was being assembled here. That's what really drew me here. So what happened was Dennis Turney, [spelled phonetically] who is somebody who had done work very much like I had just started to do had done work like that for 20 or 30 years at Yale University. He was assembling a group of people to come to NIH, and to really take advantage of some of the new techniques that had been developed here and elsewhere, and to build a new program. And so it was the opportunity to really focus on Neuroscience work very narrowly that really got me to come here, so here can I -- excuse me one second. [break in audio] So the kind of work that I really do involves using many techniques, but most notably functional MRI to look at the relationship between emotional phenomena in children and brain function, and that's really the basis of my work, and both normal emotional phenomena, or emotions in healthy children, but then also abnormal emotional phenomena, or emotional disorders.

CW: So how would you define normal emotional, and how would you define abnormal?

P: So there's usually two criteria that we use, and the one that's kind of easier, or easiest to apply is the one that has to do with something we call impairment, and impairment has do to with the degree to which a symptom or a problem interferes with a child's ability to do something that a child should be able to do or that other children the same age as the child can do. So number one, emotional phenomena are abnormal when they prevent children from doing things they'd like to do or they should do. When the prevent them from going to school, when they lead to avoidance, when they interfere with their social relationships with peers or when they interfere with the functioning of the family. So clearly whenever a child is exhibiting a symptom that involves an emotion that leads to those kinds of interferences, we call it abnormal. The second criteria is something we call the distress criteria, and it's not as easy as that first criteria, which we call the impairment criteria, to apply. For the distress criteria, an emotion is considered abnormal when either its intensity or duration is extreme, in terms of the distress that is causes a child, and by extreme, again, we mean relative to other kids that are that same kid's age. So that's a much harder thing to apply, because it involves a certain subjective judgment, both on the part of the clinician, who's working with the child, but also on the part of the child, in terms of how upset the child gets, and you could imagine scenarios where a lot of factors would bias the degree to which a child would report distress, and that's a big problem, because one thing you don't want your diagnostic system to be based in is certain kinds of biases.

CW: So how young are the children you studied?

P: So, you know, I've always traditionally worked with early adolescents, so we've always started with 8 to 12 year olds, up through 18, but for many reasons, we've been pushing our studies to go earlier and earlier, and we're kind of gradually

going younger and younger. We worked very closely with somebody named Nathan Fox, who is at the University of Maryland, who studies temperament, and temperament is usually characterized within the first couple of years of a child's life. So much like the studies I described for you in the 1980s showed that childhood psychopathology predicts behavior into adulthood, studies by people like Nathan Fox and others, like Jerome Kagan showed that even earlier behaviors in the first couple of years of life, behaviors that we usually call temperament, those also can predict behavior well into adulthood. So, you know, we've gotten very interested in behaviors really in the first five years of life, as well.

CW: So, can you say a little bit more about the studies that you are conducting, and the way that groups are set up, and [inaudible]?

P: Sure, sure. So pretty much all the studies that we do here in the mood and anxiety program in children and adolescents involve two or three core features. So one core feature is we're very interested in looking at emotions that are generated in the laboratory. So the essence of most of our studies involve bringing children in to the NIH, and inducing real genuine emotion.

CW: How do you do that?

P: So that's one of the really trickiest things, and you know, there are just diverse methods to do this, and one of the most exciting things, but also one of the trickiest things is to kind of walk the line between generating an emotion that's a genuine, real experienced emotion on the one hand, but not an emotion that's out of keeping with a typical emotional experience by a child in their everyday life. And depending on the specific emotion that you're interested in, we use different procedures, as simple as having them read certain lines of text or as complicated as very elaborate kind of interaction schemes that we have them go into with peers, where they interact with either real peers or imaginary peers, or things like that. We show them pictures, we might play frightening sounds for them, we give them opportunities to win money or to lose money, we have them do frustrating tasks, easy tasks, hard tasks, but that's one core feature of all of our studies, is to induce an emotion, and to look at the effect of that emotion -- on behavior, so that's number one.

Number two, we measure multiple levels of function whenever we do these procedures, so we measure behavior directly, either by what a child does, or based on what a child reports. Then we also get very fine grain physiologic measures of their behavior, either by using sophisticated reaction time types of methods, by tracking their eye movements, or by measuring their physiology, things like their heart rate or their skin conductance or their tendency to startle, and then number three, we measure what's going on in their brain, and we do that by functional MRI. So the first thing we do in all of our studies is we induce an emotion. The second thing we do is that we look at multiple different levels of response, and then the third thing we do is we look at different populations of children, so they

might be children who are suffering from a disorder, they might be typically developing children, they might be children who are not suffering from a disorder but are at risk for a disorder. They might be children that we're studying longitudinally as they grow up, they might be studying children who have had some kind of unusual experience, and depending on the scientific question, and depending on the specific investigator, there are different populations that people are interested in. My main interest is in fear and anxiety, so the studies that I tend to do look at kids who either experience situations that are very frightening, or who have a problem in regulating the amount of fear that they experience in everyday life.

CW: So, in your view of historical development, what brought about the change in the understanding of emotion, or of fear and depression in children?

P: Well, I mean, I think you're talking about a bunch of different changes. So one set of changes is clearly the way we think about Psychopathology, that that was a major historical change.

CW: And what brought that on?

P: So that really began with the whole process of DSM3. Do you know about DSM3? So I would recommend that you read many pieces -- historical pieces about what happened in psychiatry in the 1970s and the 1980s, with the publication of DSM3, there's a wonderful article, if you email me I can send it -- I can send you a bunch of these historical articles, but about the real dramatic changes in terms of how people think about mental illness, and that really happened in the 70s and 80s, and what it really did was it opened up a whole new way of thinking about mental illnesses, and then studies in really the 80s and the 90s kind of applied those insights and generated, you know, really dramatic changes, in terms of how common we now recognize mental disorders to be, and what we understand about their treatments and their development, and pretty much most of those insights were driven by breakthroughs in clinical medicine, as it's applied to psychiatry, and as it's discussed in these historical documents. In terms of breakthroughs in neuroscience, I think we're still very, very early in that process, and that, you know, as I sit here today, there really have yet to have been any neuroscience breakthroughs that have applications for mental disorders in children. There are really none of them, and I really came to the NIH to kind of start that process, but you know, those kinds of processes are arduous and slow, and very difficult, so it's going to be a while before things like brain scans or genetic tests are useful for the clinician. That's not going to happen soon, and --

CW: So what are your research questions then now? So what is it that you're really interested in?

P: So most of what we're trying to do is map the relationship between emotional experiences that are experienced in the laboratory and engagement of brain

structures, that that's what we're really trying to understand. How does emotional experience and emotional processes and emotional events, how does that get processed in the brain? And that's what we're trying to understand, and I would say that we're making really good process there, not really just from me, but from a lot of people, and as we get better and better at understanding that, then we can start asking things like, "Well, how does that change with development? How does it change when people are sick or ill? How does that relate to genetics? How is that clinically useful?" But we're not quite yet at the point of using the knowledge to address any of those questions. On the other hand, until we understand how emotion is represented in the brain, we don't have any hope of using Neuroscience to understand emotional disorders. So a good way to think about it is if we were in Cardiology, we just discovered the EKG, something like that, and we're trying to figure out how to use that tool to make is clinically useful, and that's going to be a 20-year process, at least.

CW: So, how many groups are in the mood and anxiety disorder program?

P: So, you know, for talking about the mood and anxiety program in general, I would ask you to speak with Hussein Imangi. [spelled phonetically] He can give you the -- he can give you the broader -- I can really speak to the issues of children.

CW: Okay, so you are the person who studies children, and the other [unintelligible]

P: The other main investigator is Ellen Liebenluft, and she studies bipolar disorder, and we work very closely together. Another good person to talk to is Sue Swedo.

CW: So, how many studies are you conducting right at the moment that include FMRI?

P: Oh, you know dozens. You know, there are probably four or five basic populations that we work with, but for each population, there are two or three different kinds of studies. So we work with children at risk, we work with children who are affected by anxiety disorders, we work with children who are affected by depression, and we work with healthy children, so pretty much four groups of kids. Within each of those four groups of kids, there are three or four different studies that we're doing, studies of fear, studies of happiness, studies of sadness, studies about how kids learn about emotions, studies about how emotions and cognition interact.

CW: Okay, and do you also compare siblings?

P: We do some of that, yeah, sure. We're very interested -- you know, one of our indices of risk is familial relationships, so we're interested in siblings, we're interested in parents and children, we're interested in the effects of genes, or familial non-genetic familiar stressors. We're very interested in that.

CW: So, and with regard to fear, you said you start usually at age 8, but you are going down to a lower age --

P: Yeah, yeah, yeah, yeah.

CW: And you say that the problem has been underestimated?

P: It had been, it had been.

CW: It had been.

P: You know, in the 70s and 80s it had been. There's been a major kind of appreciation over the last ten years about how common and how important problems with anxiety or fear are with children. That's been a major development.

CW: And in your FMRI studies, what do you look at? Do you look at the activation of the amygdala and how that effects interactions with other brain --

P: Correct, correct, and the -- the amygdala and the prefrontal cortex are the two parts that we're very interested in.

CW: And would you think that it is correct to say that FMRI, that these brain-imaging techniques have really changed the understanding of what emotions are?

P: I don't know that I would say that.

CW: You wouldn't.

P: No, no.

CW: Because if you look at the literature, you can see emotions before, in the NIH publications, it's always like it's a disorder, and then suddenly it becomes of function of the brain, and that's something very --

P: Yeah, [unintelligible] what I would recommend for that is that you -- have you read Joe LeDoux's books?

CW: Yeah, sure.

P: So that kind of describes that, you know. I think that the work in neuroscience really kind of changed the way people looked at emotions, much more than brain imaging. I think all that brain imaging did was applied, you know, basic Neuroscience work.

CW: Okay, okay. So what are your projects for the next 20 years, then?

P: Yeah, well, pretty much right along the lines of what I outlined. You know, I --

CW: What do you hope to discover? I mean, what would be the great breakthrough that you would like to accomplish?

P: Yeah, so probably the biggest problem, and the problem that I'm very concerned with is that right now, psychiatric disorders are really defined and diagnosed based solely on measures of self report from patients or reports from other people who are basically describing the problem that they have, and that my goal would be to come away with a psychiatry that uses those measures, but that combines them with measures from brain science, so that ultimately, psychiatric diagnosis is based on an understanding of brain function. And that's clearly not where we are, and it's many, many years away, but that's what I want to do, and that's kind of the basis of my work, and then once you do that, things like new diagnostic tests or new treatments really become possible.

CW: Okay, good.

P: All right?

CW: I think that was a nice ending.

P: All right --

[end of transcript]