Speaker 1: The HD Insights Podcast is brought to you by the Huntington Study Group. The Huntington Study Group is a nonprofit research organization dedicated to conducting clinical research in HD and providing critical training on HD to healthcare professionals. Funding [00:00:30] for this podcast is made possible through the generous support of listeners like you and sponsorship grants from organizations like Genentech, Teva Pharmaceuticals, Neurocrine Biosciences, Uniqure, Visunex, and WAVE Life Sciences.

Kevin Gregory: Hello and welcome to the HD Insights Podcast. Thank you for joining me today. As always, I'm Kevin Gregory, Director of Education, Communication, and Outreach at the Huntington Study Group. On this episode, [00:01:00] Dr. Daniel Claassen continues our series of conversations on the Venezuela project that discovered the Huntington disease gene. Today, he speaks with Dr. Leon Dure, Professor and Director of the Division of Pediatric Neurology at the University of Alabama at Birmingham. As a pediatric neurologist, Dr. Dure brings a slightly different perspective on his Venezuela experience. Additionally, he and Dr. Claassen have a more in depth conversation about the clinical impacts of HD on young people. [00:01:30] So without further delay, here's Dr. Claassen's conversation with Dr. Leon Dure.

Dr. Daniel Claa...: Well, thank you everyone for joining me for another podcast, where we're trying to highlight some of the disparities of care in Huntington's and come up with solutions to solve these issues. It's a great pleasure for me to be joined by Dr. Leon Dure, who's the Professor [00:02:00] of Neurology at University of Alabama at Birmingham. He is the William Bew White Junior Chair in Pediatric Neurology and the Division Director of Pediatric Neurology. Thanks for joining me, Leon.

Dr. Leon Dure: Thanks Dan. I appreciate it.

Dr. Daniel Claa...: So, Leon, I've always enjoyed talking to you about pediatric movement disorders. I think you have a really unique vantage point of looking how this field has [00:02:30] evolved over the years. I guess I'm really interested to know from your own kind of personal journey to getting to where you are now, how did the role of the Venezuela project come about? How how did you get involved in that?

Dr. Leon Dure: Well, when I finished my training in pediatric neurology, I wanted to get expertise both in the [00:03:00] lab and in movement disorders and I was very fortunate to get a position in the lab of Anne Young and Jack Penny. And I was doing work in their lab and I had read about the Venezuela project and I sort of went to Anne at one point and said, "I'm a pediatric neurologist and I'm learning movement disorders and I actually speak some Spanish. Would [00:03:30] this be something that I could take part in?" And Anne was really gracious and generous and sort of pitched for me and I think she ended up, paid for me out of her grant to go and be a part of it. And I'll be very honest, I mean, I was a very

insignificant cog in that giant machine. I mean, it was a very impressive project and one that taught me a lot [00:04:00] in my subsequent career.

Dr. Daniel Claa...: So, what was it like when you got there for the first time? Do you have any kind of impressions about the environment, those kind of your colleagues and also the patients that you saw?

Dr. Leon Dure: Yeah, I mean, I could go on. I mean, the first thing is, is that people need to realize that again, this was before we had cell phones. I mean, this was a [00:04:30] fairly low tech operation. And the usual plan was, I think the month of March was when the project was down there and there was a rotating cast of neurologists and psychiatrists and a variety of other people to sort of help out with all the tasks that were taking place. And the first thing was is that it was an uncomfortable environment because it was hot. I mean, really hot and [00:05:00] I mean, very hot. But we were housed in a hotel, a nice hotel, but we didn't spend a great deal of our waking hours there. And typically what would happen is, is that the group would pile into rental cars and go to a location, sort of set up a clinic for the day and then proceed to evaluate folks, recruit people for this study, [00:05:30] draw blood. There was just a number of different stations that one could occupy.

And when I got there, I was sort of given a orientation about the difference places. And my role was primarily with the neurologists. And so, we would typically have a subject sitting in front of us and there would be one examiner, typically one of the senior neurologists, then there would be somebody [00:06:00] more junior like myself videoing that encounter. And then maybe one or two other people who are also watching and filling out what was at that time, the UHDRS motor scale. And all that information was then captured and coded and we would do that all day long. And at the end of the day, then all these scores would be put together, they would be collated, they would then be entered into a [00:06:30] computer for subsequent analysis.

And this was mirrored by folks that were involved in genetic mapping studies, people that were doing neuropsychological testing in the field, folks that we're obtaining more updated pedigree information. It's was an amazing amount of paperwork that was generated on a daily basis and then put into a form that could be used for science.

Dr. Daniel Claa...: [00:07:00] Well, so I want to ask you a quick question kind of about your opinions of just recollecting how the UHDRS motor score was then and how it may have evolved over time. Do you remember much about that motor score? What were the things that you were particularly looking at?

Dr. Leon Dure: Well, I have to say that it was... And as a junior person, it was an amazing experience [00:07:30] because what I learned was is that here was a scale that could fit on two sides of a piece of paper and focus towards making a diagnosis of Huntington's disease by motor criteria. That's really what it was for. And it

also included a Shoulson-Fahn Scale and then essentially, a global impression of [00:08:00] whether you thought that the person really had Huntington's or not, but the goal was to make a diagnosis. And the reason was that we were taking blood for genetics for all these folks and you did not want to make a diagnosis in someone who truly did not have Huntington's Disease. So it was a great sort of screening and sorting tool in that regard. I mean, how it later evolved and to perhaps not be the best scale for [00:08:30] a longterm clinical trials, I mean, I don't know if that's really what it was designed for initially.

Dr. Daniel Claa...: That's really interesting. I mean, if you think about kind of the scale in terms of the challenges with diagnosing, I guess my sense is that you probably relied on chorea as a main diagnostic tool. Is that fair to say? Or were you seeing that had maybe more dystonic forms?

Dr. Leon Dure: Yeah. So [00:09:00] in the adults, it was a lot of things like saccade generation was really important and the demonstration of chorea and being able to bring that out in most of the adults. In kids, I would say it probably wasn't the best scale, because it's hard to capture anything other than dystonia [00:09:30] and perhaps rigidity on that old UHDRS. On the other hand, most of these kids that we saw were pretty obvious in terms of their findings, because they were not subtly different from their normal peers in terms of their slowness movement, their clumsiness, et cetera.

Dr. Daniel Claa...: Yeah. I mean, when you think back, any cases kind of jumped out at you, just kind of generally [00:10:00] their presentation that really stuck with you, just so you could share some kind of ideas of what these folks were coming to you with the sentence and such?

Dr. Leon Dure: Well, I think one of the things that... Maybe not one case in particular, I mean, there were some really tragic children who were every year you went down there, they were demonstrably worse. But really it had to do with, if you went back year [00:10:30] after year, you could look and see the progression of their overall scores. And that was something that, again, gave us some information about how gradual this could be. And the old scale, it was if a patient had a three, that meant that they were definitely diagnosed. And as I think Jack Penny said to me, that would be somebody that you [00:11:00] would tell Jim Casella and Marcy McDonalds that this was somebody who they had to look at because they definitely had Huntington's disease. That was the way we looked at it.

But you could look at it lower scores: zero, no signs, one, minimal signs and the two was somewhere in the middle of that, but you could watch those scores progress from a zero to a three over a period of years. And I think that informed us quite [00:11:30] a bit about how long this can take to be symptomatic.

Dr. Daniel Claa...: Yeah. So from a pediatric neurologist standpoint, what kind of insights did you bring to the team that maybe the adult neurologists really appreciated or in terms of the clinical evaluation, didn't really focus on?

Dr. Leon Dure: I think it was more a matter of [00:12:00] just being more comfortable with kids. I mean, when I say that I got trained in movement disorders, I spent time in the adult clinic, but I also had a pediatric clinic and I've always been impressed at how hard it was to get an adult movement disorder person to come over and look at a child. That may not be true anymore, but it was true back then. And it was a matter of how do you get a child to perform [00:12:30] tasks or to engage in examination in such a way that you can get meaningful observations. And so, excuse me. So I think that for the most part, it was figuring out a way to get kids to cooperate with that exam. And for a pediatric neurologist, that wasn't a big chore. I think it was something that for most adult neurologist, it's [00:13:00] an extra step that just seems sort of a little too difficult at times.

Dr. Daniel Claa...: Yeah. And we've talked a lot about motor symptoms, but of course, with Huntington's, we appreciate a lot of non motor symptoms, particularly some of the psychiatric and cognitive and behavioral manifestations. Were those symptoms apparent to you, particularly in the pediatric population? [00:13:30] I ask because I think [inaudible 00:13:31] that we are really struggling with now, I believe, in the field is try and define when do symptoms really start.

Dr. Leon Dure: Yeah. And I think, I don't know if I can comment specifically about pediatrics, but I would say again, how ambitious and how difficult that Venezuela project was in terms of addressing these things. Because for example, none [00:14:00] of the chief investigators were what you would call fluent in Spanish and there were a number of folks... I mean, every year, there were people that came that had a background in psychology or psychiatry who were indeed fluent in Spanish, but obtaining a psychiatric history from folks was often very, very difficult. And [00:14:30] this is again in the context of a population of people that is really at the absolute bottom of the social scale. And so it's very hard to tease out how much of this is due to adverse early life events versus incipient Huntington's Disease. The things were most sort of, yeah.

And so, it was very difficult to try to tease out early subtle findings. But what I recall [00:15:00] were things about how these folks had to manage folks who were acting out, who were violent, who were really at that far end of the scale in terms of cognitive and emotional dysfunction. I mean, I'll never forget. There was some poor fellow who was actually kept in a cage and that was the only way that they were able to manage that individual. [00:15:30] That was not done out of a spite or malice. That was how that family was able to keep this person safe and in their home. And it was just shocking, but that was how they sort of coped.

Dr. Daniel Claa...: Yeah. That's a striking image. I mean, therapeutically, were there options [00:16:00] that you guys were able to recommend or were there advances in kind of therapeutic decisions during that time that you were able to see implemented?

Dr. Leon Dure: Not really. I mean, I've spent some time with Irish Shoulson who, to me, I didn't spend enough time with him, but was an amazing mentor. And I remember, and Ira wrote quoted, I don't know if he was quoting Harold [inaudible 00:16:28] or if it was something he said [00:16:30] himself, but, "That the best thing you can do for somebody with Huntington's disease was give them Haloperidol and the worst thing you can do for a person with Huntington's was give them haloperidol." And so I was trained in a group that really tried hard not to manage those types of motor symptoms. And so we were not typically endorsing anything like that.

Now, [00:17:00] there was an arrangement with a generic drug company and we did bring down lots of medications. We brought down vitamins, we brought down antibiotics. I think one trip, I brought down a month's supply of Fentanyl for an individual with sort of end stage cancer. I mean, this was pre 9/ [00:17:30] 11, so you can imagine. I mean, there wasn't a lot of screening back then. So we did bring a lot of things to provide medical care, but other than perhaps occasional antidepressants, we did not treat. And I think the main reason for that was is we were only there a month. And so, although there was a physician who was available to the Huntington's family all year long. [00:18:00] She also, I think, was fairly limited in terms of the interventions that she could provide.

Speaker 1: We'll return to the interview on the HD Insights Podcasts in a moment. We hope that you're enjoying this episode. As a nonprofit organization, the Huntington's Study Group relies on the generous support from the community and listeners like you to continue bringing you in depth content [00:18:30] on HD, like this podcast series. If you like what you're hearing and are interested in supporting HD Insights through a grant or donation, please contact us through our email address: info@hsglimited.org or by calling toll free at +1 800-487-7671. We greatly appreciate your support. And now, back to our episode.

Dr. Daniel Claa...: [00:19:00] So, I mean, you've had a really great vantage point to see how the field of pediatric movement disorders has evolved over the years. I mean, looking back now and to where we are currently, where do you see the biggest challenges for Pediatric Huntington's disease? Is it diagnosis? [00:19:30] And kind of figuring out which issues are related to kind of Huntington's and which are related to kind of adolescents and youth? I mean, can you give us some opinions on kind of the field, so to speak?

Dr. Leon Dure: Well, I remember, for a long time I was the lone pediatric neurologist in the HSG and I have felt for [00:20:00] a long time that we spend a lot of time talking about... I mean, for many years it was talking about testing and ethical issues related to the testing and why were so few people in the United States getting tested compared to people in Europe? And these were all really good questions, but once a rational therapy is developed, a rational therapy, one that makes some sense and has some likelihood of improvement, then I think all of these testing issues go away.

[00:20:30] And I brought up in a HSG meeting in Philadelphia, I gave a talk on what could we do to include children in clinical trials for HD? And again, that sort of points towards the bias. It's sort of hard, I think, to get the adult neurology community to think about kids. It's just sort of rare [00:21:00] to them, but from an ethical perspective and from a clinical trial administration perspective, it's certainly doable. It's totally doable. The problem is, is overcoming some of these sort of prejudices about other children, they're very different, et cetera. And that's true. There are, but children participate in clinical trials all over the world.

[00:21:30] The hard part with juvenile or young onset Huntington's disease is that it's so uncommon and I think that it's going to be... And this is true for a lot of pediatric neurodegenerative diseases. They're just so rare. So it makes it a big challenge to carry out. You have to weigh a comprehensive evaluation versus the fact that that can probably only be done a couple of places and so people will have to travel for [00:22:00] that. And so, it's really more logistical challenges, that sort of thing. I think that carrying out a clinical trial, doing a therapeutic study in pediatric, young onset Huntington's, I hope I get to be a part of someday. I hope it happens while I'm still practicing.

Dr. Daniel Claa...: Yeah. Yeah. I mean, in your own practice, do you have any tips in terms of how you figure out the [00:22:30] decision to test a patient who's under the age of 18? I mean, is it still they've got to have clear symptoms that really make you want to test? I mean, can you give us some insights on how you approach this issue?

Dr. Leon Dure: Yeah. So, well, full disclosure when I came to UAB and in 1994, about two years later, I started the Huntington's clinic or restarted the Huntington's clinic at UAB and I ran it for about 15 years. [00:23:00] And so, I had the occasional... I mean, again, the number of pediatric cases that came to me is quite low, but still more than most people.

And I think that the decision to test a child, you always have to worry about [00:23:30] the possibility that you've got a, say a 17 year old who's maybe not acting, again, something is abnormal. And to make a diagnosis at the time, let's say they have 70 repeats, that's one thing. But I think the real concern that people would have would be, well, what if it was 41 repeats and they may not develop motor symptoms for 10 or 15 years. And that was always the concern [00:24:00] that I would have is what is the likelihood of having a highly expanded allele and would that change things a bit? And so I think that if... What people are now reporting that there is, again, a lot of premotor symptomatology in juvenile Huntington's disease, a lot of premotor symptomatology. I think those questions are really going to go away. [00:24:30] We will probably be more aggressive about testing or I say aggressive, but more open to testing younger folks.

Now, I have to mention also, I think that the sort of logistical question of testing in a child, and again, this is another thing that's sort of uncomfortable for adult practitioners, is that there has to be some level of [00:25:00] ascent to participate if this is involving a clinical trial. And all this testing would likely begin with that. And so I believe that we have to be careful of that. We have to recognize that there needs to be a way to understand what does that child know because you can't just round them up and draw their blood. [00:25:30] I mean, multiple bodies have decided that that is wrong. I agree.

And so, we did an internet survey, Kim Quade and I many years ago, and really just wanted to look at it, what the parents tell their kids and when do they tell them? And so I think that and our data was, again, it's a small sample size and it was an internet survey, but kids are taught something about Huntington's [00:26:00] disease, usually about 11 or 12 years old. They may not be told that they're at risk. They may not be told everything, but there is information that's imparted. And so, I think that that's the sort of thing that can be used to, again, inform us about who can we recruit for clinical trials and do it in a way that meets all sort of international standards.

Dr. Daniel Claa...: Yeah, yeah. One of [00:26:30] the other themes that we've noticed in this podcast is kind of thinking about folks that are kind of early in their career and they're trying to make decisions about how they want to position in their future and we've got a lot of feedback from folks that have been appreciative of some of the mentoring advice that some our guests have had. I mean, if you put yourselves in pediatric neurology resident shoes, what kind of advice would you [00:27:00] give that resident who may be considering pediatric movement disorders? Do you see it as a field of immense need? Growth? Any comments [inaudible 00:27:10]?

Dr. Leon Dure: I mean, I think that, and of course it's my field, so I'm biased, but it's the best field. But I mean, in pediatric movement, we're [00:27:30] behind the adults world from the standpoint of the phenomenology is just very different. We're still arguing about what to call certain movements. And I think that that is something that we need to sort of straighten out. Part of the problem is, is that I think we're finding out in a lot of the genetic conditions in kids that experience movement disorders that these movements [00:28:00] do not lend themselves to a single noun. It's not just chorea, it's chorea plus something else.

And so I think that people who are interested in this need to pursue it. The pursuit is hard though, because an adult movement disorder fellowship is probably not totally appropriate. Although, my last trainee, I had [00:28:30] her spend a great deal of time with the adults because you need to understand Parkinson's, you need to understand Huntington's, you need to understand tremors. But then when you move into the pediatric world, it's more complicated, a lot more complicated. And so, I think that that's the sort of thing that the pediatric person needs to recognize is, is that it's more than just a fellowship to really become an expert at this.

And what's interesting [00:29:00] is, is that in the field, it sort of started with, I guess, to a certain extent, people like Harvey Singer at Hopkins. There were people that were interested in pediatrics, like Roger [inaudible 00:29:13] in Rochester. But first really trained pediatric neurologist who then really did movement disorders were people like John Mink and myself, Terry Sanger in Los Angeles. You [00:29:30] did. We carved out a piece from an adult program and then went and did pediatrics and people have started to follow that. So now I can name 10 or 15 folks who I think are really on the way to being very competent, very knowledgeable people about pediatrics movement disorder.

So, I can't say that it's a field that we'll end up with this gigantic trial that will cure cerebral palsy in the near future, but [00:30:00] there's a real need for this because even pediatric neurologists aren't very good at the movement disorder aspect.

Dr. Daniel Claa...: Yeah. Totally agree. The other thing I just would make a comment to see if you agree with this, the other thing that we've noticed at least in our clinic is that a lot of our pediatric cases, they sometimes get tossed around from clinician to clinician and [00:30:30] specifically, they'll spend time with maybe a physical therapist and then they'll go over to maybe a psychologist because of developmental delay. And there seems to be, at least in some of our families, a hesitation to invoke Huntington's disease in some of the cases. Do you see the pediatric neurologist kind of stepping forward and kind of becoming a hub for questions [00:31:00] of children with parents with HD and trying to kind of decipher some of these clinical symptoms and whether or not they are or are not related to HD? Is that a role for the pediatric movement disorder specialists in the future?

Dr. Leon Dure: Oh, I definitely agree with that. I think, but it again, needs to be somebody who's got some level of comfort and understanding of the whole disease process. And [00:31:30] so you're right. I think a pediatric neurologist should do that. But I can say that given the number of questions that I get from my peers around the country, there aren't that many folks that are super comfortable with that. And so, it will be tough to... That's why I say if there's say a juvenile or young onset Huntington's disease trial in the United States, you may only be capable [00:32:00] of doing it at one or two sites. And I'd first make sure that at those sites you've got folks that are really good. And then you can branch out from there.

Dr. Daniel Claa...: Yeah. Well, thank you so much for being with us this hour. I really appreciate your comments both on your recollection of Venezuela and also your comments [00:32:30] on children effected by HD. We see in our clinic, a lot of kids are the caregivers and I really view this population personally, as a vulnerable population and I think many of our colleagues do as well. But hopefully we and HSG can move forward to creating that assistance for care for this population.

Dr. Leon Dure: I could not agree with you more. I think that the [00:33:00] role that these children play, I mean, this is seen in a lot of chronic diseases in childhood that siblings become, they take on different jobs within the family. What's unique about Huntington's though is, is that not only they take on a job, but they're at risk as well. And the literature on that is very sparse, but would not be that hard to obtain [00:33:30] for say an organization like the HSG to begin to develop that sort of knowledge base of the social impacts that are there.

Dr. Daniel Claa...: Absolutely. Absolutely. Well, Leon, thank you so much for your time. Really enjoyed it and hopefully we can do it again.

Dr. Leon Dure: My pleasure.

Kevin Gregory: That concludes this latest episode of the HD insights podcast. I want to thank Dr. Dure for joining us [00:34:00] and Dr. Claassen again for leading this special series looking back at how the HD gene hunting project in Venezuela played out from the researchers that participated on it. On the next episode of the HD Insights Podcast, we'll have a special guest on with Dr. Claassen to talk about the current situation for those in Venezuela now over 25 years, following the discovery of the HD gene and impact on HD families in neighboring South American countries. Until next time on the HD Insights Podcast, I'm Kevin Gregory. [00:34:30] Thank you for spending time with us, stay safe, be well, look out for each other and we look forward to bringing you our next episode.

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