

I'm Max Muenke. I'm a physician scientist at the National Human Genome Research Institute and the chief of the medical genetics branch, which is one of nine intramural branches on NHGRI and I am the director of the NIH Medical Genetics and Genomic Medicine Residency and Fellowship Programs.

I was born in Germany, in Northwestern Germany in Westphalia, very small town with a long history, and grew up there until I was five. Then we moved from Westphalia to further north, almost at the Northern Sea, almost at the Netherlands border, and that's where I lived from the time I was five until I was six, and then we moved back to the same place.

My father was a loch keeper so we always lived near a loch and the loch was always outside of town. So if the town had 500 people where I grew up, then around the loch, there were maybe 10 people, maybe two families or three families. My mother was a homemaker. She would make dresses for everyone in town and she was also the town psychologist. Every woman in town would come to her and would share her problems with my mom. So.

I know my mother--I know my grandmother on my father's side and my grandfather on my mother's side. My father grew up in Pomerania, which is now afterward, where to Poland, and he was a Lutheran and then he grew up in a small family where there were many babies born, but they all died. And in the end there were four children who grew up, and my grandfather was blind. He first worked as a forest worker in some duke's forest and then by the time he was blind, he would raise peas. He could do that while he was blind and he died on the track from after--he staffed on the track from Eastern Germany to Berlin at the time--at the end of World War II. And my grandmother made it. Was her youngest son and my father, by that time, was a soldier in the war and had corresponded with my mother. That was what young girls were supposed to do then, write to soldiers at the front, and so after the war was over and he was released from being a prisoner of war in an American camp--he was released and he gave the address not as Pomerania, but he gave mom's address. When he showed up, they were all very startled that someone would really have used the address and show up. So. And then they started dating and it became clear a Lutheran cannot marry a Catholic. So my dad became a Catholic and they got married. 10 months later my sister was there and five years later I was there.

I think it really planted the seed for appreciation of nature so that I always had my small garden that I always had to--or the other way around, that there were not always playmates here. I had to do things by myself and garden was one of them. Getting piano lessons was another one of them, but this was at a time where there was no Karate, soccer clubs, or any of that. You just had to entertain yourself and I certainly enjoyed the various things that I could do from planting plants underground and being surprised that--once I'd dug them back up again--that they had lost their green, that they were just white and that they had lost their chlorophyll and that was just fun to see.

It was a small school. It was--we were at least with one other grade. So it was first grade and second grade, and I think temporarily we were four grades, first to fourth grade, in one grade. We had children who had various intellectual and physical disabilities in the same grade, became very clear at age six when I could read and write that I was supposed to and enjoyed teaching someone who was nine-years-old who was physically impaired. And what I thought was already, as a six-

or eight-year-old, what I thought was striking. We had many, many children who were, what you call now, intellectually impaired. At the time the language was not politically correct at all, and they all worked on a farm and it all worked out fine. There was no special ed. there. And what parents made sure is they felt, whether you're intellectually impaired or not, you need a mate. And at 16, they found someone who usually was also intellectually impaired and they had many children afterwards and as an eight-year-old, I thought, "I wonder what those children would be like." So.

And then that probably contributed more to my choice of career than any of my nature experiments beforehand. In Germany, at that time, that was in the mid-60's, you would go either to one school for nine years, so that was from first to ninth grade, or you would be for four years in that school and then in fifth grade you would go to Gymnasium [spelled phonetically] and that was for the ones who were better than the others. I say that in quotes and, out of my grade, there was one that went to Gymnasium and that was me. And so going to Gymnasium for four weeks, it turned out that in four weeks, I developed something that most likely was Polio and that, despite the fact that I was Polio vaccinated, was in a very small children's ward in a hospital in a nearby town. And it was striking to me that, as, again, as a ten-year-old or as an eleven-year-old, that I see that they did not know what I was having and I was struck by that. I thought, "How come you don't know what I'm having?" and so I got physical therapy. I got massages. I got water baths. All of the things that I liked, but nothing of the western medicine that we talk about now. I think it had a number of effects since I couldn't turn the page on a book, I had to ask the other boys. I was in what was called the Big Boy's Room, so there were eight there and the Big Boy's Room was anywhere between 10 and 16 or so, and I was one of them. So I had to ask them to turn the pages, someone would come to feed me, and I still remember it was striking that if I didn't get the person's attention, the fork would go into the cheek or the soup would go down my pajamas and so I knew from the very beginning to look the person in the eye and talk to her and once I had her attention, I would get the food exactly where it had to go. So. It was very--it was quite intriguing, I have to tell you. And so that--I was in that hospital for about nine months and then they said that, "Max is cured," except for that after nine months, when I couldn't walk, my parents didn't think I was cured and then our family physician made sure that I went to a university clinic, which was in Münster in Westphalia and that was quite--that was about a 100--almost 100 miles away from where my parents lived. And I was in there for another eight weeks. They diagnosed what it was. There was more physical therapy and then they sent me back home and from then on, things started to get better. And what was very clear, something had changed. I had learned that communication is the most important thing. If you cannot communicate with the other person that you want to talk to, it doesn't help. And that's good for languages, it's good for your own language, for different dialectics. It means being present with a person. So that gave quite an impact and then the other impact that it had was that even being born in a family where my father would've been proud if I would've become a lock keeper, becoming a physician was something highly unusual. In my family, I was the only one who went to college and then to medical school. So.

In Germany, both medical school encompasses college and medical school all in one. So you do everything all in one. You do Gymnasium and that goes to thirteenth grade. For me, I was then a year older since I stopped a year and then went back. And I think on a somewhat personal note that had to do with my upbringing when I came back, as my sister says, I was spoiled rotten. I could've asked my parents for any favors and I would get them and so once I came back out of the

hospital, I had a dog. I had birds. I had pigeons. I had gerbils. I had golden hamsters. I had mice. I would go along with the dog who would have a pigeon on his back and we would go for walks. It was a little circus-y, but then what I also did do was that I was just delighted that I was able to breed mice and to my surprise, every once in awhile, out of two grey mice, they would have a white mouse as an offspring and I was hoping I could breed white mice because I predicted that they would have white offspring, but I never made it to that stage. So that was part of the upbringing in nature. I think the part that I forgot was that each year there was a lamb that I would get from the shepherd and I would raise the lamb through the summer. So. And so that certainly felt very special. There's not that many kids who raise lambs while they are kids.

Probably would be also smiling of the image of a little Max watching TV with a lamb on the lap, with the feet, and watching for shows that the lamb liked the best. And for the lamb liked best either Lassie or Fury, the American shows. These were way back when. We're talking in the mid-60s. So.

In Germany, there is one central system, since in Germany there are no private schools, every school at the time were public schools and they're plus/minus equally good. There's no Harvard of the medical schools and there's not the--I don't want to put a name to a school that doesn't rank very high. In Germany, they're all in the middle to upper third, middle or upper two thirds. So you get a good education wherever you go so I decided to go to Berlin, which was quite exciting coming from a tiny place in Northern Germany, going to the big city with over a million people. So. There was a slight difficulty there. When I got admitted to medical school, there was a--in Germany at the time, there was a compulsory army for every young man had to join the army and I was in the military and, of course, being an active soldier, you cannot--couldn't drive through former East Germany because it was a communist country at the time. And West Germany, where I come from, was part of NATO and all of that, so I had to fly from Hanover to, at the time, Berlin Tempelhof and so then I was in Berlin and was there for seven years and enjoyed it tremendously. And the fact of leaving the military to go to medical school, the discrepancy of drudgery to enjoyment and excitement couldn't have been further apart. It was exciting beyond belief. Just exciting.

To actually do what I thought were real sciences, to do chemistry, physics, organic chemistry. It was just thrilling to do biology, to do medical genetics, which we had already as undergrads. It was just thrilling. Just thrilling. And to me, there's something in Germany that's called [foreign language]. It's the first major exam that you take before you start your clinic training and for me as soon as I had the [foreign language], I could teach the medical genetics class. I could teach students who were just a year behind me and that felt just wonderful. I enjoyed that a lot.

One topic was very close my heart because someone had put me on the right track. It wasn't even genetics but it was a teratogen [spelled phonetically] and I'm sure you've heard about Thalidomide and Thalidomide was a medication that was generated by a German pharmaceutical company and that was sold as a means--that was sold against morning sickness during pregnancy. And the connection between the Thalidomide, or Contergan was in the name of the medicine in German, and the limb anomalies of both the legs and the arms, where there were shortened limbs, almost flipper-like hands, depending on when the medication was taken, was identified by a German pediatrician and physician and by an Australian obstetrician. And the German pediatrician was

Professor Widukind Lenz, who at the time was in the--worked at the children's hospital in Hamburg in Germany and he was an expert in limb anomalies and people from all over Europe would send him their X-rays and he would consult and he would write them back and to his surprise for some time, he would get one or two inquiries per year. All of sudden, he would get two to three per week. So eventually it turned out what they all had in common was that the moms had taken Thalidomide and that happened in the late 50's and early 60's and he was the one to make the connection. And so I had listened to him in Germany. As a high school student, there was something called [foreign language] which is sort of the high school for laypeople and I went there and he was Professor Widukind, was talking about this and I got so excited that I went to him afterwards and asked, "How can I do something like what you are doing?" And he said, "Go to medical school, become a pediatrician, go to basic research, to clinical training in genetics." And I followed his advice and here I'm sitting. And so, I taught that and so what I had, in my section on medical genetics, it was basic drawing pedigrees. It was basic chromosome analysis. It was taking a family history. It was taking a prenatal history, and then it was showing photos. It was showing photos of individuals who have Down's Syndrome, that is chromosome anomalies, who had very specific teratogenic anomalies, let's say fetal alcohol embryopathy, who had very typical syndromes, and I would talk about all of them as if I had seen them, as if I had known them, when I had really seen only photos and read lots of books about it. So. But my interest was really set then, as like, this is just so exciting. So.

What was next was easy because in Germany, you do--even as a physician, you do a thesis, and I did the thesis work with department chairman Professor Kyle Spelling [spelled phonetically] at the free university in Berlin in the human genetics department and mine was on cell cycle regulation and different chromosome--what chromosomes look like. Obviously, we all know what metaphase or what mitotic chromosomes look like, but then looking throughout the cell cycle in G<sub>1</sub> S phase and G<sub>2</sub> phase and I looked at nuclear organizations, regions that are on the [unintelligible] chromosomes, chromosome 13, 14, 15, 21, 22, and it was interesting. And before I had finished medical school I had an offer to continue my work there and so then I had a contract as to work at the institute for five years, and I left after nine months because I really wanted to work with patients and started. And then left Berlin after seven years and went to the children's hospital at the University of Kiel in [foreign language] which is almost--which is at the Baltic. It's a Baltic Harbor, almost maybe, 40, 50 miles from the Danish border and I did my pediatrics residency training there and the chair of that department was another famous geneticist, Professor Wiedemann and Professor Wiedemann is--in the U.S. the syndrome is called Beckwith Wiedemann syndrome and in Europe it's called Wiedemann Beckwith syndrome and it's a syndrome where we of course know the underlying causes and it was very interesting to have him as a department chair, even though he was professor emeritus by the time. He changed during my training, but he stayed there so I would see patients with him, even after he was professor emeritus.

Oh, it challenged the sympathetic nervous system. It was being on an infant ward for two months, when I started in July--was fantastic and learning all about middle ear infections, diarrhea, G.I. issues, that was wonderful, but after two months, I was on the NICU, on the neonatal intensive care unit, and that really got my blood and my adrenaline going. And it was scary and I was there for six months and after six months I was happy to say that my sympathetic nervous system had calmed down quite a lot. I had learned quite a lot. And then from then on, I would be working--when I came in, in the morning, before I saw patients, I would go to the cytogenetics lab, would

do what we call cytogenetics rounds, would look at all the cells, would look at all the aminocytic flasks. We did that for an hour and then by 7:30 a.m. or 8 a.m., I went to my ward and would see patients there. So that was then when really for the first time where I would see children who had birth defects of various kinds and many times, actually more often than not, we did not know what the diagnosis was. So this would've been in the early 80's.

A mere coincidence. I had met Dr. Francke at the Human Genetics meeting that at the time was in Essen and Professor Passag [spelled phonetically], who was the organizer of that meeting, had this wonderful picnic and I dared myself to talk to Dr. Francke at the time and she, of course, is very easy going and what made it particularly easy going was that she is German speaking so I spoke with her and told her of my interest and she said that she would be happy to talk to me some more about it. Then I visited different places in the U.S. and Yale was one of them and out of Minneapolis, Atlanta, Baltimore, Boston, I decided Yale and Uta Francke's lab was the best step for me.

She is significant for many reasons. On a personal level, she's just radiant and she is--her enthusiasm for work, for patients, for cytogenetics, for molecular genetics, is just infectious. And then she is someone who has won numerous teaching awards so she has been a mentor for me to be a good mentor. She has taught the human genetics class at Yale for years before she went off the Stanford and taught genetics there, taught--was the medical director of the genetic counseling training program at Stanford, and I think her--she has numerous accomplishments and some of them were that Hoy Unice [spelled phonetically] at the time, at the University of Minneapolis, and she is simultaneously generated the high resolution chromosomes from chromosomes that were when there were g-banded, in let's say metaphase, they had maybe had a 400 band stage and then the chromosome that Uta Francke generated had anywhere between 800 and 1000 bands. So in essence it increased the resolution of getting first glimpses of the genome. And the talk that she gave in Essen at the human genetics meeting in Germany in, I guess it was 1980, was a talk how she had identified various delisions [spelled phonetically] and duplications in patients and her ease of going back and forth between the laboratory and showing patients and the chromosomes and coming up with causes, defining minimum critical regions, I was in awe of that and I thought, "Whoa, I want to do something like she does."

They can--my name at the time, since I was set--my wife and I were set to go back to Germany, my name was spelled at the time in the German way, that is M-U-N-K-E. So if you go to PubMed and you search that, you'll find the 10 papers that came out of that time and they were mostly mapping papers and you find the chromosomes and DNA and patients all in one paper. And to me, that was exactly what I wanted to get out of that time. And one collaboration was to work with Leon Rosenberg, who was at the time the department chair, and Jan Kraus [spelled phonetically], who was a post-doc in the lab, yet identified the gene for homosistinuria, CBS or cystathionine beta synthase, and I had the good fortune to map it to a--to chromosome 21 and then to map it to a very specific region on chromosome 21 and that was--I happened to be at the right place at the right time and it was fun. It was just very enjoyable.

And I met Francis Collins. Yeah, I had, to my surprise, I met all three first year fellows there. I'm sorry, the three third year fellows. One was named Jake Agus [spelled phonetically] and he is now, I'm not sure, California or at the University of West Virginia. Then there is--I'm blanking on

his name, and then there is someone named Francis Collins and out of the three of them, again, I was very impressed. I was allowed, even though I couldn't see patients, since I hadn't passed the U.S. exams, medical exams, I would sit in the noon conference and Francis Collins would talk about patients he had seen in the morning, would give a presentation, an hour long presentation about a specific syndrome, and in the afternoon he gave another hour long presentation about chromatin remodeling or something that he did in chairman Weissman's lab. And I was--really the word awe is an understatement. And so we overlapped for a total of six months. I started at Yale in January of 1982 and Francis finished his three year training in clinical genetics as a internist in June of '82, before he went on to University of Michigan to become an assistant professor there. So yes, I've known him. He was one, other than Uta Francke, one of the first people I met there actually.

So it was very clear there was hierarchy there. So there was Francis Collins. It became very clear, very soon that he had published quite--some solid papers with Sherman Weissman and had then continued to publish papers as an assistant professor, papers that are being cited now from cystic fibrosis to neurofibromatosis and, and, and, and--so these were not rare disease genes, but he worked on common disease genes and was able to identify them so.

It wasn't just the clarity of communicating a presentation. What he has is--he had then and obviously has now is a gift of speaking to different--to people from different walks of life and to me, that has been always important. If you can speak to your peers, that's okay. That's a C plus. But if you can talk to people from--to people who are non-physicians, who are non-geneticists, that's a B plus. If you can talk to people who are--have either--are either noble laureates or who are intellectually impaired, as in not in the same boat, but in the morning in the clinic, talk to people who have an impairment and then talk to people who are on the very--on very different-- and to me, that's the gift of communication. That is, to me, the A plus of communication, of what Francis Collins has, and I admire that.

Uta Francke, being a good mentor, she had greased the wheels before I went for the interview. She had called two colleagues there at the children's hospital of Philadelphia and, I never had this feeling ever again, that when I walked into the chairman's office, my very first interview, I knew I had already the job and I could only imagine that was thank you to Uta. My C.V. didn't hurt either, but it was really the good mentor who had done that. And of course, the prerequisite for that was not only to be able to speak English, which I couldn't when I came to Yale in 1980--in 1982, but to also having passed, at the time it was called the ECFMG exams, and now they're called the USMLE exams part one and two. I had passed those I think in the fall of 2000--of 1985 and then I was admitted to be one of the first clinics genetics trainees in July of 1986.

It was very different. It was really--one was working just in the lab and visiting the noon conference at Yale but not being able to be with patients or see patients, and here for the first time, it felt that I was actually needed. At Yale, whether I was there or not, it didn't quite matter but there was enough drive and enough ambition that it mattered to me. At the children's hospital of Philadelphia, if there was a consult at 3 a.m. in the morning, it was clear who had to go there. If I was the fellow on call, I had to be there at 3 a.m. in the morning and it felt really good to be so important that you would show up at 3 a.m. to see this patient in the morning in the NICU, so. And so the training in Philadelphia--I think very highly of that training program, and that in the

first year, all you do is see patients, patients, and more patients. As in an outpatient setting, as inpatients, on the consult service, in the biochemical and the metabolism division, and the dysmorphology division, and so on and so. So it was a very solid foundation of what patients look like and there I actually got my first taste for that patients are not all of Northern European descent, of what I had of course--was trained in. In Northern Germany everyone was fair skinned, fair hair, light hair, blue eyes, and all of a sudden at the children's hospital in Philadelphia, about half people there came were of Northern European descent, maybe a third of other descent, and probably one third were African Americans. And for me, this was a very new experience.

I mean, there I learned at the same time--I learned dysmorphology from one of the masters, Dr. Eileen Zakay [spelled phonetically]. I learned from her, "Oh, this is a child with Downs syndrome and this is what a child with Downs syndrome looks like from this ethnic background." And no, she did not have to teach me how a child with Downs syndrome from a Northern European background looks like because I knew that. And so, at the same time, I didn't learn just dysmorphology of children with Northern European descent. I had learned that with Professor Wiedemann in Kiel in Northern Germany. But with Instructor Zakay, it was the patient is there and what comes next and how does the patient most benefit from your coming into the patients room, talking to the patient's mother, parents, sometimes grandparents, so.

It was very variable. Anywhere between one and 20 patients. So if we were in the craniofacial clinic, we would see 20 patients. There was a patient every 15 minutes because they came there. There's a multi--in either the cleft clinic or the craniofacial clinic, there's a multidisciplinary approach to speech pathologists to feeding experts to occupational therapists, physical therapists, neurologists, ophthalmologists, geneticists. We're all a team. Craniofacial surgeons. So you would see every patient just for a brief time, but over time you would meet them on a monthly basis so you would get to know them and you would see, "Oh, this is what this child looked like before surgery," and the surgery looks so amazing that you barely see the cleft of the lip afterwards or the child's face has changed where the shape of the head was very misshapen at birth, that after surgery there's a beautifully formed head there of the child with just a minor scar there so.

In Germany, people would always think of genetics only as an afterthought and to me, it was thrilling how important medical genetics is in the U.S. So for example, when a child is born in the middle of the night and this child had multiple anomalies, instead of the having the surgery already scheduled for the morning, the first person other than the neonatologist--the obstetrician, the neonatologist, who would see the baby was a geneticist. So sometimes it was already based on the fact of looking at the multiple congenital anomalies in the newborn baby, there was a very high suspicion, this baby may have Trisomy 13. This baby may have Trisomy 18. We then would, at 3 a.m. or maybe by that time it was 4 a.m., do a bone marrow aspiration, have the cytogeneticist come in, and then with the cytogenecist confirmation, "This is Trisomy 18," we knew that by 7 a.m. and that had a decision, where then the next larger conversation was with the parents. "Do you want a surgery in your child whose prognosis with regards to longetivity is very guarded?" having, let's say either Trisomy 13 or Trisomy 18. And just to see the value of genetics and the impact that genetics can have on decision making on parents and on the entire medical team, many times, more than ethicists, I think is something that I--where I really learned--begin to appreciate even more not just genetics as a little side show to medicine, but that it's really--this is one of the main players in pediatrics. And obviously it has changed now. It's a main player in every single

specialty. So.

Since anywhere between two and four percent children have a birth defect, some are mild, some are severe, and parents want to know, "What does it mean for the child? How will my child be doing? Can this be repaired? How does--how will my child be doing?" The most important question is always, "How is my child doing intellectually? Will my child develop normally?" And sometimes there are answers and sometimes there are not clear answers and the child is a guide. And then sometime later, not in those first conversations, at some point later, the parents want to know, "Is it genetics? Could this happen to us again, as in, what is the reoccurrence risk if we have another child?"

Probably the most important part is to go one step back and actually to just listen and to even start out with very general questions to see what's on their mind and after you have done that 100 times, 500 times or 1000 times, there's themes there and themes of concern. Every parent expects a child that is born normal and every parent expects a child that looks beautiful and if you have a child with multiple congenital anomalies, that's a shock to parents. And to just be there and to just see when are parents ready to hear what. And I think that I find very important, the communication with the parents, to have a relationship with the parents that not only is good for that one hour of counseling but that will allow parents to happily to come back when they are ready for more questions. And whether the happily coming back is in two weeks or four weeks or eight weeks, it doesn't matter, but it's something that I think this first year of life when a child is born with severe congenital anomalies is very critical to form a bond, not to switch healthcare professionals with follow up appointments, but to have the same healthcare providers throughout that year and ideally throughout all of childhood.

Yes. So I--part of--at the time the way the program at the children's hospital in Philadelphia worked was the first year you see patients if not 24/7, but all the time, and then in your second and third year you have your continuity clinic, you participate in conferences and the didactics that are being offered, you present patients, but then you work in a laboratory. And the laboratory that I chose at the time was the laboratory of Bob Nussbaum and Bob Nussbaum at the time was a Howard Hughes investigator and so I was in his lab. I had a position that was paid through Howard Hughes. And that was wonderful on many levels. Probably the most practical level, I think I got a 100 percent or 200 percent raise in salary from being a clinical fellow to being a Howard Hughes fellow in Bob Nussbaum's lab. That was very wonderful, being married and having three small children, so that certainly was wonderful, but I know you're asking about what did I do in this lab. And at the time, it was quite exciting that Bob had been in St. Louis and before the paper was even out, he had learned about cloning and yeast artificial chromosomes in yaks and to me, the exciting part as to use--to work on yeast artificial chromosomes, even though I never made it to the goal, and the goal was to clone human DNA in a--and he had generated--as a trainee at Baylor, he had generated a somatic cell hybrid. A human-hamster cell line where he had fused human cells from a patient with fragile x to a hamster cells and had fused them together, had irradiated them and had many times grown them and could show that the fragile side of the fragile x was broken at the fragile side and fused to a hamster chromosome. So my easy task was to, in my time in this laboratory, to generate a yeast artificial chromosome that had part hamster DNA and part human DNA and there was a thought that this artificial yeast chromosome would have the fragile side in it, as in would lead to cloning of the fragile x gene. That wasn't meant to be, but in the process I



learned how to clone, I learned how to do long range mapping, I learned how to use [unintelligible], and learned how to make maps that actually were larger than just cloning a plasmid, cloning a whatever, one KB piece into a plasmid, but to have an 800 KB in a yeast artificial chromosome.

But it all--it's not very different from one another. It's between patients. It's between chromosomes and then having extended chromosomes, mapping these chromosomes in somatic cell hybrids in Uta Francke's lab, then using, at the time there was a method called Southern Blot Analysis, from very last millennium and to learn that and to be proficient at that to finding small pieces of DNA, let's say to find a polymorphism one that's 2.8 KB versus 3.4 KB, something that could be nice nicely separated on a gel, to on a larger gel where you could separate pieces from 10 KB to almost 1000 KB in Bob Nussbaum's lab. It's just increasing the level of analysis by an order or two of magnitude. But it's not different. It's not all of a sudden doing space science. It's doing the same thing, just going into more detail and actually enjoying it tremendously.

Doing chromosomes in my class that I gave the medical genetics class as a medical student, we would--I would draw blood on everyone--this would be completely ethically inappropriate nowadays, at the time, we would--I would draw blood on every one of the medical students and then we would analyze their carrier types and that was considered standard of practice. It was even something wonderful to do that in a medical genetics course that every medical student knew his or her chromosomes. And fortunately, I have done this for four years and never have I found anyone who had a different chromosome number than 46. I was very pleased with that. So, because I could've gotten into trouble way over my ears.

Bob was one of the initial branch chiefs here. Francis Collins was asked to lead the extramural effort of the genome center at the time. He came here and he came here with Jeff Trent as his scientific director from the University of Michigan and one of the first people they hired was Bob Nussbaum as a branch chief and Jennifer Pack [spelled phonetically] as a deputy branch chief and a few other branch chiefs. And David Ledbetter was a branch chief then. In the meantime, after I completed my Howard Hughes fellowship with Bob Nussbaum for three years and sitting for my boards in genetics, I was offered a position at the children's hospital of Philadelphia and the University of Pennsylvania on the faculty, which I accepted in July of 1980. 1990, sorry. And in 1990, I started a lab in part still doing tissue culture in Bob Nussbaum's lab for many reasons. One was it was set up. Number two was it was for free and fetal calf serum was very expensive so Bob was not just a wonderful mentor but he was also very generous. And then at some point, I forget if it was year one or year two into my faculty position, he said, "Max, I think it's time for you to start your own tissue culture lab." Which I then of course did. So I start the research in my lab on two disorders that were both craniofacial disorders. One was a disorder, a craniosynostosis disorder and that was called Pfeiffer syndrome, and this is a disorder where the sutures of the skull are fused prematurely. So that when the baby is born, where those sutures are always open so that it makes easier. There can be an overlap of the sutures, that the baby can make it more easier through the birth canal. Sometimes the sutures are fused a birth and the skull is misshapen at birth and at some point needs surgery to open up those sutures. So that was one project and the other project as a project on the most common anomaly of the developing forebrain and that's called holoprosencephaly. And holoprosencephaly is in essence two words. Prosencephalon is the forebrain and holoprosencephaly means that instead of having two brain halves of the forebrain, that there's just one single forebrain there. So that's holoprosencephaly. And so I've studied both

of those disorders at the University of Pennsylvania and the children's hospital of Philadelphia, was on clinical service but I had protected time in the laboratory, which I was very grateful for. I was very grateful for NIH funding. I had a first award. I had an NIH R01 award. It was very exciting. Then, I got tenure and I thought that life couldn't get any better and that was pretty wonderful. And then, I got a call first actually from David Ledbetter to join his branch as an investigator and it turned out that was at a time before I had tenure at Penn and I felt if I leave before I have tenure, that looks like I was on the verge of not getting tenure. So that was not an option. So once I did have tenure, and I got tenure in 1996, I got another call and I forget if it was Bob Nussbaum or Clare Francoarmano [spelled phonetically], who was the branch chief of the medical genetics branch at the time, and then after some negotiations where things all happened very quickly, I joined one year after I had achieved tenure at the University of Pennsylvania, came here as a senior investigator in 1997, into the medical genetics branch. And actually from day one, I became the director of the NIH medical genetics training program. I had been the medical director of the medical genetics training program at the University of the Pennsylvania for the three years before and I realized this is something that I really enjoy and people like that and wanted me to do this here as well. And I did that here and I've been the director of that program for the last 19 years so.

I think what it really does is, is I had extremely good mentors: Uta Francke, Bob Nussbaum, Eileen Zakay, and there's many others that I forget and there's many others either with similar name recognition or less name recognition, but these were my direct supervisors, my direct mentors that had quite an imprint on me. And to see what their input on my career did, to me, that was something where I felt if and when I can do that, that is very important to me. I want to do the same thing. And to know that in the--since 1993, I have trained close to 200 physicians and PhDs in this training program and see people now be program directors, now be department chairs somewhere else, is very rewarding. And medical genetics is still a specialty where there are way too few people who are board certified. We need many more so one way of getting more is to train more and to train more so that they train more. So it feels very rewarding to be on committee where former trainees of mine are running the committee. It feels very good.

I mean, first of all, he hired me, so that I am very grateful for. I like this job. You can tell. I've been here for 19 years. And then the other part is he was a very generous person and generous both financially, and obviously that's easy at time when there's more money there, but also generous with regards to that he would just give broad parameters. What he saw as a vision of the intramural program, but then really trusted the individual investigator, for example me, that I would do the right thing. So I would come to him and tell him--part of the reason to come to NIH--I could've studied craniosynostosis and holoprosencephaly just fine at the children's hospital of Philadelphia and the University of Pennsylvania with NIH funding, with Hughes funding, with other funding, but I couldn't start a project that I felt I only could do at NIH and that was a project on attention deficient hyper activity, which is the most common behavioral disorder of childhood. And now we know that it's just not in childhood, it continues into adulthood, so if we find ways of finding causes that lead to either treatments or potentially cures eventually, to me that seemed very worthwhile goal for a pediatrician like me, who's on the one hand interested in birth defects. And this is a little different than birth defects that are rare, it's something that's a behavioral trait and that's quite common. And that was something that I couldn't do at the University of Pennsylvania.

So I had applied for grants, but they were telling me, "You don't have preliminary data that we trust you. You can't do that." But at the NIH, I could present this as part of my job and tell you, "This is what I want to work on," and there were some preliminary data there, either by my own group and/or by others that Francis Collins and Jeff Trent felt, "This is something that can be worked on. This is a worthwhile goal and we in the genome project can do this better than at other places." And that was actually the case. So.

Obviously, I can't speak for the leadership, I can only speak for myself and I--to me, what I see, I see two major things that if I say cannot be done anywhere else, people would argue with me, but where the NIH is in a prime position to do this as part of an intramurally funded project. One is all of the benefits of the close collaboration with NIH clinical center. To me, this is the crown jewel of the NIH, where we can see patients at the NIH clinical center and work with a blood sample. We can do all of the testing and I can give you examples where this has changed the course of diagnostics and treatment of children with a specific disorder, where my group, and it's not about my group--every single other group who has patients at the NIH, has done that and will do that in the future. That's one part and that if this is independent of healthcare insurance and availability of test, but this is something that can be done here better than at most places. The other part is for certain projects that are high-risk, high-yield, sometimes they take longer and they take longer than a funding cycle. I still remember my NIH grants were five years. Nowadays you're lucky if you get three or four years and four years is the absolute luxury and you almost apply--you reapply once you're one year into your grant. For me, to talk about ADHD and the connection to a high-risk project to work on ADHD was very clear to me. The more defined the phenotype, the better the chance of finding underlying causes for any disorder, but ADHD in particular when this is a complex disorder. And so what was clear to me was I wanted to decrease the heterogeneity by working with a group of people where ADHD is more common than in the rest of the world and where this is a genetic isolate. And I inquired with different genetic isolates and this was a wonderful learning experience in speaking to leaders in the field of the different isolates and it turned out there's a genetic isolate. They call themselves the Paisas. They live in Antioquia, which is a district in Colombia, South America, where the local capital is Medellin. And the Paisas are a highly-educated group of people. They came some 20 generations ago from the Basque part of Spain and have mostly very little at mixture and have been marrying amongst and having families amongst one another. And so what Jeff Trent was able to do, he was able, on top of the budget for my lab, to pay the bill for five years in a row so that we could do the very detailed phenotyping work, the very detailed testing work that we needed to do in South America and then get blood samples from almost 1000 people from South America. And here we had large families, where we had three generations, where we had grandparents, sibships of anywhere between eight and 16, where all of these people had children themselves, and we could follow ADHD almost like we did in a plain autosomal in mendelian segregation. So that was a way how we had the successes that we have had really courtesy of the long term funding from within the intramural program.

So other people have done most beautiful studies on ADHD and you can do many different studies. You can do--my favorite studies are twin pair studies where you have monozygotic twins, so these are twins that have if not 100 percent, but close to 100 percent of genetic material in common. So this would be just in essence like one person except for there's two. And then of course there's dizygotic twins and they're as closely related as siblings except they were in the womb together at the same time. So when you look at those studies, the numbers are very consistent. That is, if

you study 100 mono psychotic twins where one has ADHD, you would expect--if it's 100 percent genetics, you would expect every one of the other twins has ADHD as well and the number is more like that if you have 100 twin pairs, out of other twins, anywhere between 70, 75, and 80 will have ADHD as well. So in genetics, I don't have to tell you this, the heritability factor would be somewhere around 70 to 75 percent, and that means that three quarters of the contribution to ADHD is genetics, where as one quarter or maybe one fifth is environment. And to me, it's a very--there are many times when you talk ADHD, a very likable topic at parties and there are many people who come, "We have more ADHD now. It must be all our living conditions, and is it genetics in the first place?" and those numbers are actually very helpful. They calm the discussion. They're just the facts. It's a little bit like one and one is two. It's very straightforward and it takes the emotions out of discussions. Is it genes or environment? And the answer is yes. Of course. And so it makes it much, much easier and then the question is, "What are the environmental factors?" and then the question is, "What are the genetic factors?" and I have--my lab has less focus, actually not much focus at all on the environmental factors, but really focused on the genetic factors.

If the child is impaired, if the parents feel the child is impaired, if the teachers feel the child is impaired, if the classmates feel just because I don't want to let this child be part of their group, this child is the outsider, so if there's impairment there. And then there are--it's not like you do a chromosome test where you identify a third chromosome 21 like in Trisomy 21, but you do this by questionnaires. But in the end, "the above all word" word is impairment. And if there's impairment there, then what can we do to help this family, what can we do to help this child? And if there's no impairment there, then the parents have done a great job and the kid is doing a great job and obviously if you have a higher IQ, it gives you a little bit more range of coping mechanisms, versus if your IQ is average or is lower. And of course ADHD is not attached to any IQ and it comes among anyone of--from low IQ to a very high IQ. So.

Right. So now we're switching from a complex common trait, ADHD, to a rare, anatomical disorder, which is holoprosencephaly. So holoprosencephaly starts very early during gastrulation and there are, again, environmental factors there and there are genetic factors there, but these factors have to work as early in humans at day 17 after conception. Any day between day 17 and day 21, day 25, after the first three weeks. So this is literally speaking just within a week of the last menstrual period is missing, and the woman may not know or barely know that she is pregnant. That is when holoprosencephaly starts. And even though holoprosencephaly is rare at birth and ever rarer for one year old and ever rarer in adulthood, it's extremely common during early pregnancy. One in 250 embryos have holoprosencephaly. And that's certain more common than most disorders that there are and since holoprosencephaly is such a severe disorder many times, over 90 percent of affected embryos and fetuses are spontaneously aborted. So they end up in miscarriages. So these babies are not born alive, but they are miscarried beforehand, so. And so, to answer your question, what can we learn by studying a very severe abnormality of the developing forebrain, in essence we can study normal development of the forebrain and what we can study is--my lab had identified the first and probably still the most important gene in holoprosencephaly. If you have loss of function, mutation in a gene called sonic hedgehog, then this leads to holoprosencephaly. Of course, the converse is true. If you have a normally developed--a typically developing brain in humans, in mammals, in vertebrates, then sonic hedgehog is needed during early gastrulation. And so, I think probably one of the main contributions of my

lab is the link that we made between human holoprosencephaly and hedgehog signaling and other signaling pathways that are expressed early during development. And what's intriguing, even after--so this is 2016. The very first patient with holoprosencephaly I saw in September of 1986. So this is the thirtieth anniversary of me seeing that first patient and knowing this is what I want to study, and it was very important to me to get a blood sample--this patient's diagnosis, but also a blood sample, potentially for research after consent forms, signed consent forms, and so on. So what this work really has done is it has allowed us to put signaling pathways together. It has allowed us for even using regulatory regions on one gene, how they interact with another gene. For example, a regulatory region, if it's interrupted by a translocation. Just separated from the gene coding regions. What that means is it's not--the gene isn't expressed because it's not started by a regulator, that can be very far away. We could show if this is not activating the gene, and the disease can be present. And so there's lots of basic science excitement. Of course, some of the work has not only been confirmed, but brought much further in animal model systems for other colleagues and it's very pleasing to see how the work between humans and model systems. Mouse, zebra fish, fruit fly, all go hand in hand. Of course, it makes me smile to know that [foreign language] that they were the ones who identified the hedgehog gene in the fruit fly and were the noble laureates for that. So.

Absolutely. Yes, so that we can look at what we get as a benefit of ENCODE, what we get as a benefit of just comparing evolutionarily conserved sequences so that we know evolutionarily, these sequences in the vicinity of, again, let me pick my favorite gene, sonic hedgehog have evolutionarily conserved, not surprisingly, not just among all mammals, not just among vertebrates, but going to fish and even to the fruit fly. And when these evolutionarily conserved sequences are conserved there has to be a reason for it. And the reason for it is many times, not always, many times that is evolutionarily conserved region is a regulatory element for a gene in the closest proximity or very distantly away and both are critical for expression of this gene. So.

So there is--let me make a commercial for it, there is a website [www.genome.gov/atlas](http://www.genome.gov/atlas). And if you go there, then you find the project and this is an atlas of human malformation syndromes in diverse populations. And it really--it started way back when. It started maybe in Germany and was carried along, but it really had the spark that it was clear we have to have a website and a trip to Nigeria. Since I mentioned already, I worked--in the department of Professor Wiedemann there was an atlas of malformation syndromes that Professor Wiedemann was the sole author. And the photographer was actually not an author, but she was highly recognized in this book. Every single photo in this book was taken by her and every single person was taken from a patient from the clinic and every single patient was of Northern European descent. So that was my first experience and I thought everyone with this syndrome, with Beckwith Wiedemann syndrome will look like this. Everyone with Downs Syndrome will look like this, and so on. Turner Syndrome and then when I was in Philadelphia, no, this is different. What really sparked something different was when two colleagues and I were in Nigeria to initiate a collaboration with Dr. Ekanem Ekure at the Lagos University teaching hospital in Lagos, Nigeria, and she is an outstanding pediatric cardiologist, has a busy, busy clinic. And we were in her waiting area, just looking around and the three of us, Paul Kruszka, a family physician and medical geneticists in the medical genetics branch at [foreign language] from the Dr. Charles Rotimi's branch and the three of us--and he is a pediatrician medical geneticist, and we were in that clinic and just looking around. Oh--at every one and this child, what they had in common in this practice work, they had in common--they had

a heart defect in common. And then we saw, oh, this is a child with Down's syndrome and we looked at one another and nodded. Oh, this is a child with Turner syndrome. Nodded. This is a child with Noonan syndrome. Nodded. This is a child with William's syndrome. And when we and we all agreed on that, and when we then talked to Dr. Ekure and told her, "Oh,"--she knew of course. "Oh, there are two children with Down's syndrome," and then she was surprised, "Wait, which ones have Noonan syndrome, which ones has Turner syndrome, which ones has Williams syndrome, which ones has Deletion 22q11 syndrome?" She was very surprised and we were equally surprised and I asked Nayifi [spelled phonetically] has your geneticist--your medical geneticists not seen those patients, and she just laughed and said, "We don't have a medical geneticist in Nigeria." And so with that it became very clear that even though their heart defects were very well characterized and the ones who learned what the heart defects were, we were 100 percent of our diagnosis because these happened to be the most common heart defect in a child who is [unintelligible] anomalies in a child with Deletion 22q11 syndrome, specific heart defects in Down's syndrome, specific heart defects in Noonan syndrome. And then it became clear that if the child has this fantastic diagnostic tool, cardiac ultrasound, EKG, and so on, and has a very real definition of what this child hearts look like, but the physician and the parents do not know what the child's underlying diagnosis is, it's hard. The counseling is very hard. So it's very hard to answer questions when parents ask, "What does this mean for my child? Does this have intellectual impairment go with it? What's a surgery needed? What's a recurrence risk?" If you don't know the underlying diagnosis, it's hard to give a recurrence risk. And so then it became clear, we need an atlas that has children not just of Northern European descent. There are a number of famous atlases around and there was a time when every single patient was of Northern European descent, the photos in there. Nowadays it's probably more like 90 percent of patients of Northern European descent, maybe 10 percent are from diverse populations, and what the idea was between Paul Kruszka, Adeyemo, and myself--we need an atlas that focuses specifically on children and adults who do not come from Northern European backgrounds because there are many atlases around from people from Northern European descent. So, that's when it started. And so now--took a lot of community building, a lot of talking with leaders in the field, a lot of talking with Sara Hull, our bioethicist and the chair of our IRB here in our Human Subjects Committee in the--in our institute and eventually, there are two papers out there that describe the process, the pros and the cons, and after very careful weighing both sides, it was felt this is a useful contribution, that in essence it will help with health care disparity, so that not just individuals and people in developed countries who happen to be able to go to a tertiary medical care center where there are just one or several medical geneticists, but that even in countries where there is no medical geneticist, that the pediatrician, the cardiologist, can look and compare facial features with atlas from children from that same country. So.

I think what he has brought is he is one of the few physician scientists who have an equal foot in the lab and an equal foot in the clinic. There are very few of them around. There are many--I heard a statistic that in the Bethesda area, one in eight people have a PhD in all of Bethesda. That's the highest PhD rate of anywhere in the world. At the NIH, I'm sure, its one in two people have a PhD and probably one in five people have an M.D. PhD. I'm exaggerating slightly, but many of the MDP--M.D. PhDs, even though they are physician scientists, they are not as active both as scientists and as successful as a scientist as Dan Kastner, and equally successful as Dan Kastner as a physician. And I am well aware of higher numbers, give you better data, but many times a case report, the N equals one makes something that persuades you to do something. The N equal

one for Dan Kastner is a colleague from a country from very far away from the U.S., where this colleague happens to have a very specific order that Dan Kastner works on. When this person came as a patient to the NIH clinical center, I visited her just as a friend and a colleague, not as a physician, a number of times in the NIH clinical center and she was telling me this was the first time that someone would take this much time with her. It was the first time that she got the largest workup ever and it was the first time that a diagnosis was made where the treatment could help her. And she's back in her home country and is doing all the wonderful things that she does as a physician scientist in her home country. And so this N equal one experience is an experience where this friend of mine was telling, as a patient, about Dr. Kastner and I find that more convincing than a questionnaire of a 100 patients who have been seen by Dr. Kastner. So that, to me, goes a long way. So.

I think over the last--probably over the last 10 years, there was a push not to neglect ever basic science, because really basic science drives translational science. At the same time, it has been my impression that with all the work that the genome has allowed us to do, the deciphering of the genome that was done, and the continual work on the genome and understanding it, that that has led actually from diagnosis to really treatment. And I think that the NIH clinical center is one of the premier institutions where you can do those things. Where you can work, not just on what brings in money, but you can work on treatment and cures for rare disorders. And, of course, my push would be to give more funds to the NIH clinical center, that there's more support personnel there, that there's--that the--with shrinking of budgets, that stay the same, that the NIH clinical center definitely needs more budget. There's no doubt in my mind. It goes to expanding the services, the pediatric services. We can't have newborns here obviously. No one delivers their babies at the NIH and maybe that is better left at outside hospitals but it would be wonderful if we had all the services of a neonatal intensive care unit, a pediatric intensive care unit, where we could have children who are less than 10 kilograms and who are younger than x number of months. So that would be an expansion that I would very much encourage the leadership of the NIH to do.

Surprisingly, it's still holoprosencephaly. There were a number of times where I thought, "Do I stop it?" and then sat down very quietly, maybe took a silent retreat for a week and thought about things and in the end came up with the thoughts of, "At this point, we understand"--I didn't mention this. Half of the causes are known and they are chromosomal in origin and we knew a few other slivers that explain holoprosencephaly, but about two thirds of those non-chromosomal causes, we don't know. And to me, over the last 30 years, we have learned so much and we have certainly more than scratched the surface. We have dug in deep, but there's way more to find out. There's two-thirds more of the causes to find out so it's something I feel very strongly about. And so, doing--working more on this. And then very carefully consider, based on the recommendations of the board of scientific counselors of the review committee--we just had our quadrennial year review and site visit, which has gone exceedingly well.

But also, the site visitor's comments were not just insightful, they were constructive. It was really rethinking and reshaping some of the future plans. And some of those, you cannot do those in a day or a week. Our site visit was literally speaking two weeks ago, so it's something to discuss in detail with other colleagues. "Where can we get the most benefit?" It's always about how do we benefit the patients, how can we get the most benefit for the patients over the next year and whether that is in holoprosencephaly, whether that is in ADHD, cardiac anomalies or other disorders that

we work on in the lab, so. So part of it is very clear, others it is very clear where to work on to get more clarity, and I'm grateful to the review committee, who was actually instrumental in making some suggestions of where to make some shifts and some adjustments. And I will not just consider those, I will follow those and come up with a plan, not just for the next four years, but for the years after that. So.