The Lead in Peds

Transcript: Season 1, Episode 3 – Growing Hope: Advancing Care for Kids with Growth Disorders

Guest: Dr. Andrew Dauber

Dr. Nathan Kuppermann (00:00):

Parents and pediatricians alike love to see kids grow. But when do we worry about growth disorders? When do we seek out specialty care? Here at Children's National, we have leading endocrinologists investigating short stature. They're all working to help children achieve our motto, grow up stronger. I'm Dr. Nate Kuppermann, chair of Pediatrics and chief academic officer at Children's National. I'm a pediatric emergency physician and I've spent three decades caring for acutely sick children. Endocrinology plays a big part of my life however, because I'm married to a pediatric endocrinologist, Dr. Nicole Glazer. That's why I'm particularly excited to have the Chief of Pediatric Endocrinology at Children's National, Dr. Andrew Dauber, with me today.

(00:45):

Andrew, welcome to the show. Before we start, and if it's okay, Dr. Dauber, I'm going to call you Andrew and you please call me Nate. I have to share that I have a box of my favorite donuts right here. And in fact, before we get started, I need to take a little bite out of one of them because my wife Dr. Glazer, she's not here and she's kind of a purist about sugar and she doesn't like me to eat much sugar. Excuse me, I need one more bite. And what I really want to know is, I mean, donuts, they've got holes in them, right? So eating a box of donuts with a bunch of holes in them, doesn't that spare me some of the caloric intake and it's okay to do every so often? What do you think about that?

Dr. Andrew Dauber (01:28):

I definitely think that's the case, Nate. My problem always though is after years in Boston, I became very partial to the Boston Cream Donut, and there are no holes. There's no holes. So I've always had to shy away, but I think everything in moderation.

Dr. Nathan Kuppermann (01:44):

Well, I have to say one other thing by the way about Boston donuts. I was raised on California donuts because I'm a California guy, but it just so happens I was living in Coolidge Corner, you know what that is, right? Near Boston Children's. And on the way to the hospital, there's like three Dunkin' Donuts along the way. And this is not an advertisement for Dunkin' Donuts, but I just got addicted to donuts, and their coffee is actually pretty good for being a donut store.

Dr. Andrew Dauber (02:13):

Yeah, it's quite a Boston tradition.

Dr. Nathan Kuppermann (02:16):

Boston tradition. So anyway, donuts as an aside, and I promise after the show's over, I will send you a couple just to tide over your appetite until dinner, but I just want to start at the beginning, Andrew. And really, I wonder if you could take us back in time, what got you into this field at the start?

Dr. Andrew Dauber (02:37):

I would say around 15 years ago, I was a budding pediatric endocrine fellow learning about all different areas of endocrinology. And really one area that I found fascinating was kids who were coming to us for evaluation of short stature. They weren't growing well and parents wanted to know why. And at that time, really the only mechanism we had to think about these kids was to start measuring their hormones. And it turns out that of the kids who show up in our office, which is a very common concern for parents, that their kids aren't growing, only a really small percentage of them have a hormonal problem causing them to not grow. And this time was the same time that the human genome had just been sequenced, and all these new technologies were coming out letting us look at the genomes of the patients in front of us. And I got hooked up with a great mentor, his name's Joel Hirshhorn. I think you know him from your time there as well.

Dr. Nathan Kuppermann (03:37):

Absolutely, yeah.

Dr. Andrew Dauber (03:38):

And Joel was doing cutting edge research on the genomics of growth. And it really felt to me like this was an opportunity to start to answer questions for our patients to figure out what was going on? Why were those kids not growing? Perhaps the genes might give us an answer where the hormones were.

Dr. Nathan Kuppermann (03:55):

That is really fascinating and it's like a lot of fields where there is just a handful, a subset where there is a fundamental cause for the disorder that we need to address. Just as an aside, how do you address the multitude of parents who come into your clinic with children who are short, but there is not a genetic basis? And how do you counsel them or reassure them when there isn't that gene or something that needs a specific therapy?

Dr. Andrew Dauber (04:25):

Yeah, that's a great question. So to reframe a little bit, I actually often think that there is a genetic basis, but it's not necessarily an abnormal genetic basis, right? And so we know that there are thousands and thousands of genes and different genetic variants that influence how tall a child's supposed to be. And most of them are common normal genetic variation that we all have, right? There are genetic changes that makes each of us different from each other. We have different color hair and different color eyes and come in all different shapes and sizes. And what I try and tell families is that most of this is just normal variation, that our DNA kind of is the instructions for how we're supposed to be and there are lots of changes that make us who we are, and it doesn't necessarily mean that there's any problem.

(05:16):

Rarely we do genetic testing to find those single gene disorders or defects where something is causing a pathological problem where those growth plates aren't reacting normally, aren't able to grow, and those are the rare and often more severe conditions that I'm most concerned with. But I think we have to talk with parents about what are the priorities? What do we really care about for our kids? We care that they grow up and are healthy and thriving and productive members of society, and there are plenty of people who can do that at five foot three inches, five foot four, whatever the height is that they're concerned about and really talk about which kids do need interventions. Who do not? And I spend much of my time trying to convince people that their children are healthy, and they really don't need any intervention. But for those that do, it's important to figure out why.

Dr. Nathan Kuppermann (06:12):

I have to comment that that is really one of the lovely aspects of being a physician, right? And specifically of course being a pediatrician, interacting with concerned parents where a lot of the therapy needed is really good explanations and speaking in a fashion and a manner that they can understand and whatnot. But now let's move on to kind of the more serious situation, that is where there are specific genetic defects that need to be addressed. And I guess for me it leads to the question of how did you start in your research specifically with regards to the genetic basis of certain growth defects?

Dr. Andrew Dauber (06:51):

I really was fortunate to be working at a time when the technology had exploded, right? There was the advent of this new technology called Next Generation Sequencing. The details aren't important, but basically it's the technology that lets us sequence instead of one gene at a time, all 20,000 genes in the genome at once and really look at all of them. So even as a fellow, I started recruiting a cohort of patients with what at the time was called idiopathic short stature, which meant you were short and we didn't have any specific cause for it. And we started doing larger scale sequencing projects from first doing panels of hundreds of genes and then doing whole exome and whole genome sequence where we're sequencing all 20,000 genes at once. And it was an amazing and exciting time because we started to find new genetic causes, just interesting families, interesting patients with more significant short stature.

(07:48):

Sometimes they had associated skeletal abnormalities or other abnormal hormonal features. And we were doing sequencing in these families and I started to discover a number of new causes of short stature. Some of them were involved with proteins directly in the growth plate that affected how the cells in the growth plate would grow and proliferate, others affected the regulation of hormones and growth hormone and IGF-1s. So it was really from studying in detail individual patients and individual families and starting to figure out which families had unique clinical features. And we would go back and forth, we would look at the genetics and then we'd get some insight. We'd go back to the family and we'd say, hey, we need to measure this in you now. We need to measure this hormone, we need to look a little bit deeper. And we started to really put together and understand what are the features of individual genetic disorders and what does that

mean for the prognosis for these kids? Are there other medical comorbidities we need to start to think about now that we understand the underlying path of physiology?

Dr. Nathan Kuppermann (08:53):

That's fascinating. So Andrew, everybody has an inflection point or two in their careers. How did you find yours? I mean, I can tell you one of my big inflection points is when I arrived at my new job at UC Davis, every child after trauma was getting a CAT scan and I knew that was wrong and I had to fix that. How about you? What was your first big aha inflection point?

Dr. Andrew Dauber (09:17):

Sure. So there's this one family that I'd been working with. They lived in New York initially, but they got referred to me after they'd seen multiple doctors. And this family had five children and three of the children all had very significant short stature, all well below the curve and they had this very unique abnormality in their hormonal evaluation. Their IGF-1, which is a marker of growth hormone, was sky-high, through the roof despite being quite short, but they didn't have mutations in the IGF-1 receptor and nobody could really figure it out. So we used this newer technology and we were able to finally come up with the answer. They had a new disorder that had never been described before, something called PAP A2 deficiency. The details aren't important, but literally this family had been undergoing a diagnostic journey for maybe 15 years and we got the answer, we were sure this was the right answer.

(10:11):

I called the mother and I said, "Hey, we figured it out. We know what's going on in your family. Here's what's going on? This is the mutation. This is why your kids aren't growing." And the mom's like, "Dr. Dauber, that's wonderful news. Thank you. I really appreciate all of your work. It's nice that you know what's going on, but what are you going to do about it? How are you going to help my kids grow?" And it was just like boom, a light bulb went off in my head and I was like, oh my God, that's such an important question. Of course it's such an important question. I was so focused on figuring out what was going on that I hadn't yet figured out, well, what were we going to do? And that mom pushed me to say, think about how you can offer some treatment. And we did.

(10:59):

We came up with actually two individual clinical trials just for this family. We tried one transfusion-based trial, which kind of partially worked. The details, again, not so important. And then we tried a targeted drug trial for this family where it did seem to help a little bit where I wrote a protocol just for this family based on our new understanding of the physiology. And that really sparked my desire to say, okay, yes, we've got to figure out what's going on, but then we've got to figure out what can we do. And I've been trying to do that ever since with precision medicine therapy for these rare genetic growth disorders.

Dr. Nathan Kuppermann (11:38):

So let me ask you a follow-up question. First of all, so that was sort of a trial of one that you did with this particular patient. Is that right? And then why don't you just tell our listeners a little bit

more about precision medicine and how what you're describing here really falls right in the center of the umbrella of precision medicine?

Dr. Andrew Dauber (12:02):

Yeah. So let me tell you about a second trial one that we did because this is just a great example of precision medicine. So precision medicine is the idea of instead of taking your hammer, which could work for anything and just knocking away at whatever problem, really trying to understand what this individual patient's pathophysiology is. What's going on for this individual patient and how can we address it? So I had again, a patient, this one's from North Carolina and their physician reached out to me and this child also was not growing and was quite short and his father also was quite short. And after many years of evaluation, he had some genetic testing and it found that he had one copy of a mutation in the receptor for the growth hormone receptor. But he had a very unique type of mutation because typically if you have one mutation in the growth hormone receptor, but the other one's working fine, you grow okay.

(12:59):

But there are these rare mutations that cause what's called a dominant negative effect where the one copy messes up the other copy also. Okay? And the way his was working was that part of the growth hormone receptor – so the growth hormone receptor is what the growth hormone has to attach to to make it work, right – and the receptor sits on the surface of cells. It has part on the outside, part through the cell wall, through the cell membrane, and then part on the inside. He had a very unique mutation that was clipping off the part on the outside and it was hanging out in his blood and acting as a sponge and sucking up all of his growth hormone. And I had seen one other patient like this, so I had an idea. We had done some cell work on this other patient to prove that that was going on, that he basically had a sponge sucking up all his growth hormone.

(13:51):

So I said to the mother, I'm like, "You know what? I really think I understand what's going on in your son and I have a hypothesis of how we could fix it." In fact, this child's father had been treated with growth hormone and it hadn't worked for him because he had been treated with a normal dose of growth hormone and the sponge was just sucking it up. And I said, "I want to overwhelm the sponge. I want to give him so much growth hormone that we're going to overwhelm and then let the growth hormone start to bind to the normal receptor." And the mom's like, "Okay, that makes sense to me. Go for it." So what happened? Well, I got COVID. This was a few years ago and I got COVID. And thankfully I wasn't too sick. I had been vaccinated, but I was home and I couldn't come to work for a week.

(14:35):

And I'm like, you know what? I'm going to sit in my office at home and I'm going to write a protocol for this kid. And because we're going to use a dose of growth hormone that never has been used before, I needed to get permission from the FDA. So I wrote what's called an IND, an investigational new drug application to the FDA for this one child. And then we had to get the growth hormones. Growth hormones are pretty expensive. So I wrote a grant to Pfizer. I said, "Listen, I'm not asking for money, I just need you to give me a boatload of growth hormone for

this kid." And they said yes. So I did all of that in that week, sent it off and we got approval. The IRB got approved, FDA after a few minor modifications said go for it, and what we decided was I was going to start at a high dose of growth hormone and then every two weeks we were basically going to double the dose.

(15:19):

We're going to go to 50 to a hundred to 150 to 200 to 250, doses that have never been used in humans before. And we were going to monitor a marker of his growth hormone action until I could get that into the normal range. And lo and behold, when we got to that top dose, like five times the usual high dose that's used, all of a sudden his IGF-1 came up and showed us that we were overwhelming that sponge. It was working. And he's now been on this high dose for two years and his growth chart, it's like this, it's like a hockey stick. He's coming up to the normal growth curve on the growth curve and he looks like a totally different kid. And the family is just ecstatic that we've been able to figure out what's going on and really help him grow up stronger, as we say here at Children's National.

Dr. Nathan Kuppermann (16:11):

Exactly. By the way, so two things. First of all, I want you to tell us all, how long will he need to be on that? And is there any growth hormone left for everybody else?

Dr. Andrew Dauber (16:24):

That's a great question. It's unbelievable what happened. So he's going to need to be on this now until he's done growing. So he'll probably in total be on this medicine for maybe seven years or so. It's been, as I said, two years now. So thanks to the generosity of Pfizer, they're continuing to support the growth hormone for free, but he uses an entire 12 milligram cartridge of growth hormone pen in less than two days. Normally this lasts people a month and he uses a whole one. And so every time he comes, we have to give him a hundred cartridges to get him through. It's so much his daily dose that it can't even fit in one injection. He has to get multiple injections a day, but he's happy to do it because they see the results and they see that it's working. So it's pretty amazing.

Dr. Nathan Kuppermann (17:10):

So what you're describing to me, Andrew, and what we're trying to highlight in this show is the importance of not only clinical care, which I put in here, my left hand, but the importance of science and research that really informs our clinical care so that we can ensure that the care that we're providing to our patients here is absolutely at the leading edge. And you can't do that without doing the research. So really the stories that you've provided are really great examples of that.

Dr. Andrew Dauber (17:44):

Yeah, no, I couldn't agree with you more. I think that there are several examples of that. All of the time, patients get genetic test results, let's say, or any test results. And the interpretation says, well, clinical correlation is required, right? Is this real? Is this not? How much of an influence? And sometimes we can't answer that question without going to the lab, without doing some basic

research to really understand it. And then on the flip side, all the time I hear about patients who say, oh, maybe we figured out an answer, maybe we didn't. But then my doctor said, "I don't have anything else to offer in clinical care. Like that's it. We're done. I'm sorry, I can't help you." And to me, that's so dissatisfying, and that's where research has to come in.

(18:30):

You need people who are thinking of new ideas, who are willing to try something, who are willing to go out on a limb and say no, we need to write a protocol for your kid, and we need to try something new and different. And because it's new, because it's different, we need to study it, right? We need to do it in a safe way, and we need to have our researchers really involved to come up with those new options for patients. So I agree, and Children's National really has everything it needs to make that happen, which is really exciting, why I love working here.

Dr. Nathan Kuppermann (19:03):

I would like to ask you about other ongoing research that you're doing, the vosoritide trial and perhaps anything else you want to talk about what's ahead?

Dr. Andrew Dauber (19:14):

Yeah, sure. So yeah, the vosoritide trials are really exciting. Also, precision medicine trials. So for many years, growth hormone was our only real option for kids who weren't growing well. And like I said, it was the hammer and nail. Everything looked the same, we just tried to hit it with the hammer. But recently this new medicine's been developed, it's called vosoritide, and what vosoritide is, it's a different mechanism. It's what's called a C-type natriuretic peptide analog. Again, the detail is not so important, but it hits a different pathway in the cells in the growth plate directly stimulating them to grow and make the bones go longer. Now, this drug was developed for achondroplasia, which is the most common form of dwarfism because it affects a pathway downstream. This gets back to my sequencing days, I started to find patients with that idiopathic short stature who had mutations in all different parts of those pathways downstream, including in the receptor for this drug.

(20:17):

The drug's made by a company called BioMarin, and I contacted them and actually surreptitiously met with one of their executives in the lobby of a consensus conference meeting in Lisbon that I was speaking at. Anyway, a longer story, we had a chat and I said, you know what? Understanding the biology, I think that there are these other growth disorders where this medicine could really be an exact precision medicine. It could target the exact pathways that's affected by these other genetic growth disorders, and I want to do a trial for this. And they said, "We're interested. Come out and talk to us." And Nate, you'll love this. This is a real East Coast, West Coast story. I know you spent a lot of time on the West Coast.

(21:03):

I went out to their headquarters in the Bay Area prepared with my presentation, and I'm as East Coast as they come. I came out there, I had my gray suit, my tie, and put my wingtip shoes on. I

was all prepared. And I walk into the office there and I look like a total fish out of water. They're all there with their colorful shirts, a few buttons open, maybe some chest hair showing. They were like, look at this guy in his suit. It kind of looked funny, but we had a great conversation and they greenlit the project. Again, I applied to the FDA for an IND. Again, after some conversation refinement, we got it approved. And now we're the only site in the world that has been offering this medication for these other selected genetic causes of short stature, for hypochondroplasia, for rastopathies like Noonan syndrome, and for mutations in these genes NPR-2 and [inaudible 00:22:00] which affect that pathway. And some of the results we published, some are still ongoing, but we're really seeing some amazingly exciting results in individual patients where we're hitting their exact pathway and they're growing absolutely beautifully.

(22:14):

So starting to understand the physiology, starting to open up new options for patients. And we've had patients come from all over the world to Children's National to be part of this study. Literally we have patients from Russia, Argentina, Brazil, Panama, Croatia, the UK. I'm sure I'm missing other places just in the last few years who have come to America and actually have had to move here to be part of this trial to get access to this new drug because nowhere else in the world has this opportunity. So it's really been amazingly gratifying to be able to try something new and help these kids and see positive results for them.

Dr. Nathan Kuppermann (23:02):

That's fabulous. So Andrew, as we kind of get to the close of this podcast, what I'd like to know is what do you see as the future in research in your field here at Children's National? What is ahead for us here?

Dr. Andrew Dauber (23:16):

So we're doing a whole bunch of different things. So that trial is still ongoing. We're extending it, and what I've really been excited about is that it's pushed BioMarin now to do their own phase three trial in hypochondroplasia as they're going to try and get approval for this medicine in that condition.

(23:32):

So we're a lead site for that trial. We're involved with some other kind of industry trials. We're also doing some biomarker studies. Waiting to see if a kid's growing can take six months to see if your medicine's affecting it. So working with one of my fabulous fellows, we're doing a biomarker study where we look at one of the collagen proteins that's clipped off as bones get longer, and we're trying to see if we can see quick changes in that and see if that predicts people's response to therapy. So I'm excited that study's kind of halfway done. So that's another thing that we're doing. We've created a multidisciplinary growth clinic here with our genetics team and with one of my colleagues, Dr. Yunhee Ji, who's doing a lot of genome sequencing in kids with unknown growth problems. So a lot of exciting things going on in our growth center here at Children's National.

Dr. Nathan Kuppermann (24:26):

Before I do a quick summary, I'm just going to share a little story that's like the counter story. When I went to Boston Children's for my fellowship, and it's where I met Nicole, my wife whom you know, I was a California guy. I came from Los Angeles and I came like this, no tie, California-looking jacket, whatnot at this formal place. And my first few weeks, they were just a little rocky because the culture was a little bit different. And then I overheard someone saying, yeah, that's what happens when you bring people in from outside the system. But anyway, then I of course made my way into the system and became chief fellow and whatnot, and became part of that Boston culture. But it is funny how we have to break into different cultures from the East and West, just like you were saying. But what I heard you say today and also super important, so growth disorders or growth conditions in children are fairly common, and they obviously cause concern to parents. Parents really want to see their children grow.

(25:31):

What you're describing is that historically there was sort of just the hammer treatment. You just kind of threw a kitchen sink at certain disorders pertaining to growth. But now in the modern era of medicine, you've been able to identify specific genetic markers of disease as well as certain genes responsible for disease that you can now target therapies, whether it's gene therapy or therapies that target receptors for proteins, whatnot. So we've really entered the era of precision medicine, giving parents of children with genetic basis of serious disease hope for the future with the modern precision medicine approach. Is that a fair summary of what you've described to us today?

Dr. Andrew Dauber (26:23):

Yeah, that's an excellent summary, and I think there is a lot of hope on the horizon. I think that there are a lot of new drugs being developed. Our understanding just increases every day. So there's lots to be optimistic about.

Dr. Nathan Kuppermann (26:36):

I just want to close by telling our listeners, first of all, to thank everyone for joining us in The Lead in Peds today with Dr. Andrew Dauber, and for following us. With each episode, we're trying to describe the importance and the impact of the great science being done here at Children's National and how it impacts and is inextricably linked with the outstanding clinical care being delivered here. And you can go to wherever you get your podcasts, and you'll see episodes on the continuum of pediatric cardiology from fetal cardiology through adolescence. We have episodes on addiction medicine and others. So thank you for joining and looking forward to the next episode of The Lead in Peds. Please subscribe to our show wherever you get your podcasts and learn about what we're doing to raise the bar of care for all children here at Children's National and around the world.

** This podcast has been edited for clarity. Some content may have been altered to enhance the listening experience.**