Ruth Adewuya, MD (host):

Hello, you are listening to Stanford Medcast, Stanford CME's podcast where we bring you insights from the world's leading physicians and scientists. This podcast is available on Apple Podcasts, Amazon Music, Spotify, Google Podcast, and Stitcher. If you're new here, consider subscribing to listen to more free episodes coming your way. I am your host, Dr. Ruth Adewuya. This episode is part of our Pediatric Pulse Mini-Series, and today I will be talking with Dr. Mary Leonard. Dr. Mary Leonard is the Arline and Pete Harman Professor and Chair of the Department of Pediatrics Nephrology at Stanford University School of Medicine, and the Adalyn Jay Physician in Chief at Stanford Medicine Children's Health.

After graduating from Stanford University, Dr. Leonard spent 25 years at the Children's Hospital of Philadelphia and the University of Pennsylvania before returning to Stanford in 2014. Dr. Leonard is responsible for leading the innovative and transdisciplinary child and maternal health research and training initiatives of the Stanford Maternal Child Health Research Institute as its director. Additionally, she has helped create interfaces between Stanford's pediatric and adult medical research to facilitate scientific investigations across the lifespan. Dr. Leonard previously served as the co-chair of the Kidney Disease: Improving Global Outcomes in CKD metabolic bone disease.

Thank you so much for chatting with me today, Dr. Leonard.

Mary Leonard, MD (guest speaker):

Thank you for the opportunity. I'm looking forward to it.

Ruth Adewuya, MD (host):

Tell us a little bit about your journey in medicine and your path to becoming a professor and chair of the Department of Pediatrics at Stanford.

Mary Leonard, MD (guest speaker):

I was a medical student here at Stanford in the 1980s, well before we even had a children's hospital, so my pediatrics rotations was down at the valley. The pediatric ICU was just a little four bed unit in the wards of the adult hospital, so it was a very different place. So I left and went to the Children's Hospital of Philadelphia, did my internship, residency, fellowship in pediatric nephrology, a master's degree in clinical epi. Spent about 14 years just really running my research program and then became director of clinical and translational research for all the Children's Hospital of Philadelphia.

What made it really exciting to come back here 25 years later is that we have this spectacular children's hospital and really doing incredible work, but really remarkable fundamental discovery where we're tapping into all the other expertise across the entire campus. And so a really exciting time to be part of Stanford Children's because I just think we're on this really exciting trajectory.

Ruth Adewuya, MD (host):

Thank you so much for sharing your story. Your particular focus is in nephrology. Nephrology is a very complex field. Pediatric nephrology, perhaps even more so. Can you share a little bit about kidney disease in pediatric patients?

Mary Leonard, MD (guest speaker):

Adults with kidney disease, the lion's share are related to diabetes and high blood pressure. Those are not causes of kidney disease in children. Those are more lifetime complications. Children with kidney disease, I think we can put them into two major buckets. One is the children who were born with congenital anomalies of the kidney and urinary tract, and we call that CAKUT and they're a very substantial proportion of the children that we take care of right now.

And really on any given day in our neonatal ICU we have newborns who were born without kidneys or without any functioning kidneys who were on dialysis, but we have lots of children with other kinds of congenital anomalies of the kidney urinary tract. Their kidneys don't grow and develop over time. They've developed progressive chronic kidney disease and maybe by the time they're teenagers they need dialysis and transplant. So we have the whole spectrum of kids with congenital anomalies of the kidney and urinary tract, some which are just isolated kidney disease, others which are part of much more complex congenital malformations.

And then we have another group of kids that have glomerular diseases that are born with normal functioning kidneys but develop kidney disease really of the glomeruli or the filtering units. And those can be the teenagers who develop something called FSGS or has a complication of lupus. So we have that sort of constellation. And I guess the third bucket actually, and my numbers, there are kids that develop kidney disease as a complication of the treatment for cancer, for instance. Or kids that are really, really sick with complex congenital heart disease or stem cell transplantation or cancer or liver transplant, get treated with drugs that are nephrotoxic.

That damage the kidneys or just being so sick damages the kidneys. So the third group that we take care of are kids who have damage to the kidneys as complications of something else. So we have heart transplants or liver transplants who go on subsequently to need kidney transplants. So that's a third big group that we take care of. They're all very, very different in terms of when they present the other complications, the lifelong impacts of kidney disease.

Ruth Adewuya, MD (host):

What I heard is that for each of those buckets all unique and complex in and of their own way for different reasons. As you think about those three buckets, what are some of the most common pediatric nephrology conditions that we see?

Mary Leonard, MD (guest speaker):

One of them is just what we call acute kidney injury, and that would be the kids who get really sick from sepsis or some complications of their cardiac transplant or stem cell transplant. Or kids who get something like HUS, hemolytic uremic syndrome and HUS is that thing you hear about in the newspaper. If you don't fully cook your hamburgers, you can get E. coli. HUS is still quite common. Perfectly normal, healthy kid who suddenly gets this infection that attacks the kidney and so they suddenly get acute kidney injury.

Our job in all of those patients is to come in and support them. To put them on dialysis, to support them, to get them through these really rough times and in many cases their kidneys come back and they do great. So we're really providing supportive care for acute kidney injury. So that's one group. The other most common chronic disease that we take care of is nephrotic syndrome. And certainly this is something that will be well known to pediatrician and something that's really important to be thinking about.

When a patient walks into your office, typically presents between three to six years of age, previously healthy child and then they have edema. And the parents may notice that the eyes are puffy in the morning or maybe their feet are a little bit puffy. They often go to the pediatrician. Pediatrician thinks they have allergies, quite understandable. They get put on something for allergies, and then the puffiness becomes more and more apparent and then it really is evident there's something more going on and the pediatrician just needs to dip the urine and check for protein.

That's what nephrotic syndrome. Your kidneys are functioning fine, they're getting rid of waste products, they're doing what you need them to do, but urine is slipping through the filtering units. Protein is getting into their urine, their blood protein levels are low, and so they get puffy. Nephrotic syndrome is our most common condition that we follow long term. The field is actually really changing now because of our growing understanding of how genetics contributes to nephrotic syndrome.

Ruth Adewuya, MD (host):

Given the complexity of the field in pediatric nephrology and long-term implications, what are the diagnostic challenges that clinicians face when they're assessing kidney health in pediatric patients?

Mary Leonard, MD (guest speaker):

Nephrotic syndrome is probably the best example to try to think about that. So when someone comes in with nephrotic syndrome, especially if they're on that sort of typical younger kid, previously healthy, suddenly really, really puffy. Odds are very good that they're going to completely respond to getting prednisone, and we put them on really high doses of prednisone. It's a lot that we ask of these little kids, but in 80, 90% of them, they're going to go completely into remission on the prednisone. It's the ones that don't that are a challenge for us.

But let's first talk about the ones that do, to your point. So they'll teach you in medical school, "Oh, it's great, they respond to prednisone." Well, that's just the beginning of the story. Now you have a kid who's on extremely high doses of prednisone, so terrible issues with the behavior from being on high dose prednisone. We have to worry about their bone health. We have to worry about their blood pressure. The problem with this disease and what makes it so challenging for the families is when you wean them off the steroids and you stop the steroids in the majority, it comes back.

And so now you are on this many year long roller coaster of on the steroids, off the steroids, on the steroids, off the steroids. We have lots of issues with obesity. We worry about the effects on their mental health. We know it makes our younger kids sort of... It's like the terrible twos. We know with our teenagers, we have issues with depression, so they're not in the hospital and their kidneys are functioning fine and in many of them, they will outgrow it around the time they go through puberty.

So in the long term they do really well, but it is a hard road for many of those kids and we call them steroid dependent, steroid sensitive nephrotic syndrome. The other group in the field that's really starting to change now, and it's really exciting. So in the old days, if you did not respond to the steroids, in four to six weeks, we would say, "Okay, it's something else." And we would do a kidney biopsy, but kidney biopsies are imperfect. You have a million filtering units in each kidney, a million glomeruli, and you might see just a couple dozen of them on the biopsy.

And we can't always really tell what's going on. And then we just start using massive doses of immunosuppression that has calcineurin inhibitors, that have toxicity, that have risk. And where the field is starting to change is now we're giving a growing list of genetic causes of steroid resistant nephrotic syndrome. And we're starting to get a little bit smarter to know, "Okay, so now we routinely do genetic testing if you have steroid resistant nephrotic syndrome."

The good news is we're learning a lot more and we can say in some of these kids, "Okay, this immunosuppression is never going to work, so we're not even going to expose you to all the risk." But that's great. Now we aren't exposing kids unnecessarily, but what we don't have yet, but I think it's really coming is much smarter treatments for all these different genetic causes. So there's a massive NIH funded effort called CureGN where they're doing very sophisticated research in 2,400 children and adults with nephrotic syndrome.

So we can start actually having treatments that really get to the underlying problem. We're not there yet. But at least we're at the place where the genetics is helping us not exposing these kids to all these immunosuppressants with the hope that it will work for many of them, for whom it won't. So then we're starting to shift to your question about some of the lifelong implications. So then we have to start thinking, "Okay, you have steroid resistant nephrotic syndrome. You're not going to respond to steroids.

We're not even going to try. But now we have to really focus on preserving your kidney function that you have." And so drugs like ACEs and ARBs, we know they're renal protective. So now we shift our focus to making sure your blood pressure control is impeccable, doing everything we can to preserve your kidney

function for as long as possible. Unfortunately, some of them will go on to need dialysis and transplant, thinking about the lifelong part. So that's really what our focus is. But I'm hoping through CureGN, this big national effort, that we'll start to have much, much more to offer to these families.

It's obviously progress that we aren't unnecessarily exposing you to a lot of drugs, but that's a far cry from where we need to be in terms of having treatments specific to the different causes of nephrotic syndrome.

Ruth Adewuya, MD (host):

You teed up my next question about genetics really well where you talked about some of the innovations that are coming down the pike and how the knowledge that we have around genetics already helping to provide better care plans for patients, and that's amazing. I'm wondering if you could also just generally explain some recent advancements or breakthroughs in the research that you find are particularly promising. You talked about this national study already. Are there other things that are happening in this space?

Mary Leonard, MD (guest speaker):

So I think there's one that was simply transformative, a huge breakthrough in the time that I've been in the field I'll talk about and then I'll say a couple of things that are right on the horizon. When I was early in my career, when a kid would get hemolytic uremic syndrome, which is this thing that's caused by E. coli, they would typically come in with bloody diarrhea for a few days and then suddenly hemolytic, meaning they're very, very anemic [inaudible 00:13:08]. They're in kidney failure and thrombocytopenia. And it was very clear what was happening.

And you would test for shiga toxin and that's what they would have, and you would give them supportive care and dialyze them and they'd get through and they would do great. There was another group of kids that when one of them would come in, my blood would run cold because they would clearly have HUS but no bloody diarrhea. And we're like, "Oh, this is something very different." And my prior mentor published a paper saying, "There seem to be two kinds of HUS.

There's the kind with a bloody diarrhea, and if two siblings get it, they get it around the same time. And in the long run they do fine, but there seems to be this other form that has no bloody diarrhea and your sibling might get it 20 years later, 20 years apart." And this is clearly not infectious and it's very different because your kidneys might get better, but then they get worse again. And it comes and it goes. And then the devastating part is you get a kidney transplant and it comes back in the transplant. And so the hypothesis was there's a genetic form.

And we didn't know what caused it, but we were so scared of it. And I had a patient whose HUS relapsed 48 hours after a kidney transplant. I had kids who had devastating relapses 10 years after their initial presentation, and it was the most devastating, scary disease. And you'd have to say to the family, and you might have to worry about this in your sibling, and now we know what causes it and we know what the genetic defect is and we have a drug for it. For the people who did not practice pediatrics nephrology, 15 years ago, you don't understand what a big deal this is.

We test it and we treat it. And the things we used to put these kids through, we used to do something called plasmapheresis, which felt like the dark ages. Where you would take their blood out of them, you would spin it down in a centrifuge, we'd give them back their blood cells, but we would take away their plasma and give them fresh frozen plasma. And we thought we might be removing something that's bad or we might be giving them something they need and we really don't know, but we're desperate.

And now we don't do that anymore and we have a drug and it's called eculizumab and it feels like a miracle now. It's a long-term treatment. They have to stay on Eculizumab. But for those of us who experienced those kids with HUS where you would ask five times, "Are you sure there wasn't bloody diarrhea?" They're sure there wasn't bloody diarrhea because you just want it to be the infectious form. Just can't overstate what a breakthrough that was.

Turning to the future, something that we're doing here at Stanford that I think is incredibly exciting. For everyone, the holy grail, it was tolerance that when you give someone a kidney transplant, that they will tolerate it. And as part of the reason I love being a nephrologist is we have dialysis and we have kidney transplant and we have so much to offer. But if you do a kidney transplant, you are not curing anything. You are replacing one disease for another.

Because you are now on an armamentarium of really aggressive immunosuppressive drugs to prevent rejection of that transplant. And those drugs have toxicity. Unfortunately, some of the toxicity is they damage the kidney, but really they so profoundly suppress your immune system that then they put you at risk of cancer and you can get a post-transplant lymphoproliferative disease. What's happening here is we have this brilliant stem cell physician [inaudible 00:16:29], who has developed a whole new method that a parent can give a stem cell transplant to their child.

So you hear all the time about how somebody needs a stem cell transplant and there's no donor, but she's pioneered away that a parent haplo sort of half identical can donate stem cells to the child and that's great. And we do dozens and dozens of haploidentical stem cell transplants here for cancer indications. But what Aliche did is she took some kids who had genetic disorders where you need a stem cell transplant to live. So one of these genetics orders called [inaudible 00:17:05] causes kidney disease.

What we did here is the parent donated the stem cells and so now the child has the parent's immune system, these kids with [inaudible 00:17:15] and saved their lives. And then six months later, the same parent donated a kidney. Because the child has the parent's immune system, They accept the kidney and they don't need all these drugs.

Ruth Adewuya, MD (host):

That's incredible. As you mentioned, it sounds like a game changer and really exciting. That goes back to what you said earlier when you were describing your reason for coming back to Stanford and this ability to be part of this type of research and your work does involve bridging that gap between pediatric and adult medical research at Stanford. I also want to make sure that I talk about your research which focuses on the impact of many different childhood diseases on bone strength and lifetime fracture risk.

Can you explain a little bit more about your research and some of the more recent insights that have been discovered on the topic?

Mary Leonard, MD (guest speaker):

We talk a lot about life course research and the whole childhood origins of adult disease. And because as pediatricians, our job is obviously to take care of diseases that kids have, but also just to send them into adulthood as healthy and strong as possible. There's so many things that women are exposed to during pregnancy and kids are exposed to that can have profound lifelong impact. And so the life course paradigm when people talk about this and they have these conceptual models about things that happen during childhood and how they affect you across the life course.

And we have amazing faculty in our department of epidemiology here focus on the life course model. Often they use bone health as the poster child or the example of this because you build a big strong skeleton during puberty and we send you off into adulthood. Your bones are the strongest they're ever going to be when you're in your mid-twenties, and sadly, it's all downhill from there. The more we can do to make the skeleton as strong as possible going into adulthood. When you have that inexorable decline in bone strength with aging and you drop to the point where now we have to worry about hip fractures.

We worry that our kids with inflammatory bowel disease or juvenile pathic arthritis or chronic kidney disease, they're going to start having those kinds of fragility fractures, those hip fractures, those things you think of happening in the elderly, that they're going to have them in their thirties or their forties or their fifties, and we know that's happening. Some very large scale population-based epidemiology studies are showing that kids with kidney disease are fracturing at twice the normal rate.

Or kids that are exposed to steroids and prednisone really are fracturing more, but we really worry about what's going to happen to them later in life. So a lot of the research has been understanding who are the kids where we need to worry the most about the effects of their chronic disease on their bone and what can we do about it? And so my research, even though I'm a nephrologist, I started to move into other diseases when we began to realize that inflammation itself was really devastating to the growing skeleton. So your skeleton, as you get taller, your bones get much wider.

If you think about your arms and your legs like a pipe and that outer dimension of that pipe of the shaft of the bone, the strength of that bone scales as a function of that outer dimension to the fourth power. So even teeny differences in how big your bones gives have really profound irreversible effects on your bone strength. And so my research, I've had the pleasure of mentoring junior faculty and gastroenterology, rheumatology, endocrinology, oncology, adolescent medicine. Looking at all these different chronic diseases and understanding risk factors for not building a strong skeleton.

So inflammation's huge but the other one is how incredibly important weightbearing physical activity is. So we say it's good for your bone health to do weightbearing activity, but we've shown in kids with chronic diseases, if you don't have good muscle mass, your bones are small. And so we're really starting to understand that, really focus on nutrition, focus on weight-bearing physical activity. I think sometimes people worry about kids with chronic disease exercising, but I do think weight-bearing physical activity is incredibly powerful, incredibly important way to help build stronger bones.

And then we've shown that a lot of the skeletal fragility in children that we assumed was prednisone is not prednisone, it's the underlying inflammation. And so inflammatory bowel disease, which is quite common. We showed those kids before they get any steroids, their bones are really, really weak. They have small bones and abnormalities in the density of the bone. And then we showed that when you use infliximab, so the revolution and the treatment of things like inflammatory bowel disease, these biologics.

These infusions and the kinds you see advertised on TV all along. We showed when you take a kid with Crohn's disease and we've published this in huge numbers of kids, and you give them infliximab. The skeleton comes back like magic. You can just see all this new bone takes off within just weeks. The biomarkers that show they're building new bone, it's really, really dramatic. People used to think that the best way to preserve bone health in kids with Crohn's disease was just minimize steroids, but actually that's not what you want to do.

You want to get in and treat them with these biologics early because if they're still growing, you can actually recover a lot of that bone health now. If they've stopped growing, the course has left the barn. So I think we're understanding that there's these windows in childhood where you're very vulnerable to chronic disease having lifelong impacts on your bone, but there's also times where there's a huge opportunity to get in and help preserve the skeleton and restore it.

Ruth Adewuya, MD (host):

To that end, for clinicians, pediatricians, are there specific growth parameters or milestones that clinicians should be monitoring at certain periods in a child's life?

Mary Leonard, MD (guest speaker):

For kidney disease, yes. Kidney disease, one of the very first things you're going to see is just they start to fall off the growth curve. Kidney disease in many cases is silent and so they'll develop anemia, but really starting to fall off the growth curve is the first thing. A really important indication of a kid who might have a congenital anomaly of the kidney and urinary tract and you just don't know it. Or they might have some of these other acquired causes of kidney disease that can start to fall off the growth curve.

Bone health, if you're a kid with Crohn's or juvenile idiopathic arthritis or any of these diseases that are treated with steroids, you should be very attentive to vitamin D to calcium to physical activity. In kids where you aren't treating a chronic kidney disease, fractures are hard. Because perfectly normal healthy

kids fracture and 50%, depending on what population based studies you look at of the general population, kids are going to have a fracture by the time they're an adult.

But if you have a couple fractures that seem, the mechanism, sure if they're running full speed across the football field and they have a fracture or there's sometimes where it's not suspicious, but if it is, seemed like it was an unusual fracture. We are at the place now finally, where we know how to use DEXA scans, which is the same scan we use for osteoporosis in little old ladies. For a long time we didn't have good evidence that DEXA predicted fractures in kids or DEXA was a good measure of bone health in kids.

But now because the NIH funded something called the bone mineral density in childhood study, where more than 2000 healthy kids had DEXA scans every single year for six years. We have extraordinary normative data. We now know what a normal DEXA is in kids. We can create DEXA growth curves like how your bone density should be changing as you grow. We have data on what's normal bone accrual velocity so we can be much more sophisticated. And if a kid has had a couple fractures that seem unusual or a little worry.

Now we're finally in a place where you can order a DEXA scan and get good normative data. And I have had cases... I had one where a kid ended up being diagnosed with a thyroid disease and that can affect bone. The DEXA was the first thing that led us to send them to an endocrinologist to try to figure out what's going on with this kid. So we are getting better.

Ruth Adewuya, MD (host):

As we wrap up this incredible conversation, what I heard from you is that there have been some incredible advancements and innovations that have already happened in the field. Looking ahead, how do you envision the field evolving in the coming years?

Mary Leonard, MD (guest speaker):

There's a lot of things that make me super excited. What's going to come out of Cure, so much to be excited about, for somebody who's taken care of kids with kidney disease for so long and so often felt so helpless and we had so little to offer. I think all of that is really exciting. I think what personally is exciting for me in terms of some of the stuff I'm focused on in chronic kidney disease and bone is that we're learning that the way you treat bone health in kidney disease has to be very different in children.

And that in adults, there's really good data that when you give adults with kidney disease a lot of calcium, it could cause calcification of their vessels and cardiac disease. And we're now just doing research where we're beginning to understand that in children with chronic kidney disease, you absolutely, positively have to give them lots of calcium because they're building their skeletons. So personally, my international collaborators, the people I'm working with, we're really trying to design the research to help us understand the very unique way you treat bone disease in children with kidney disease may be absolutely the opposite of how you do it in adults.

And so I think in pediatrics so often we're using treatments that were tested and developed in adults and taking them into children without the data. But we think this is actually an example where what was tested and developed in adults might be absolutely the worst thing you could be doing for kids. And so it's not just that we can't take these adult recommendations, but we need to really develop precision approaches to treating bone health in kids with kidney disease. And it's a lot of fun to think about how to do those kinds of studies.

Scientifically, it's just really, really interesting to think about how the growing skeleton is so different than the mature skeleton. Research is really fun. I really think we are going to be able to do so much more for these kids. That personally is what makes me excited, but there's a lot that makes me excited in the field of nephrology in general.

Ruth Adewuya, MD (host):

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