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John Williams: Hi, everyone. I'm John Williams Professor of Pediatrics and Chief of the Division of Pediatric Infectious Diseases here at the Children's Hospital of Pittsburgh.

Stephanie Dewar: I'm Stephanie Dewar Vice Chair of Clinical Affairs and Program Director of the Pediatric Residency Training Program. Welcome to, That's Pediatrics from UPMC Children's Hospital of Pittsburgh.

John Williams: I'm delighted to welcome our guests for today. It's Dr. George Mazariegos. Dr. Mazariegos who is the Director of Pediatric Transplantation in Children's Hospital of Pittsburgh. He's also the Director of Pediatric Transplantation at the Thomas Starzl Transplantation Institute, and he's a Professor at the University of Pittsburgh in the Departments of Surgery, Anesthesiology and Critical Care Medicine. George, welcome to the podcast.

George Mazariegos: Thank you so much John and Steph. It's great to be here with you today and to get a chance to talk about liver transplantation at our transplant programs here at Children's Hospital of Pittsburgh.

John Williams: Well, that is a perfect lead in because that was the first thing I wanted to ask you is about pediatric liver transplantation, that history, and how many are done, and why are they done? I think to a lot of people it's surprising that so many kids need liver transplantation.

George Mazariegos: It's a great question, John. Liver transplantation in children it really is a fascinating area because it encompasses so many conditions that children suffer from across the country. Typically, we think of them being divided into a couple of different categories that are really different and really require a lot of special expertise.

George Mazariegos: The largest bucket of those categories are children who present with liver failure from the complications of biliary atresia, and the second largest category are those that present with metabolic disease.

George Mazariegos: What's interesting about these two big categories of overall disease types is that one really shows and exemplifies what we would think of as a child with liver disease. Their liver show signs of liver failure. They may present with the signs or symptoms of what we would normally associate with a failing liver such bleeding and other complications.

George Mazariegos: Liver transplantation, when first designed by Dr. Starzl in 1963 when he first attempted the first transplant, was in a child with these types of conditions. This is a child who had no other options, who would have a very short lifespan were they not to be able to be saved by the lifesaving therapy that transplant has become.

George Mazariegos: The second category though is much different and is really an evolving one because it includes conditions where sometimes the liver actually looks completely normal but is presenting with a missing enzyme or group of enzymes that cause significant complications.

George Mazariegos: What's fascinating about these conditions is that sometimes the complications that the enzyme defect causes is perhaps not even in the liver, but can be neurologic, renal, or cardiac.

George Mazariegos: What this has required is really to bring together experts in our metabolic and genetic services as well as our colleagues in neurology, in cardiology, and in the related specialties to understand the unique indications and timing, the unique complications in the pre-transplant period of these children. And then to really understand if the liver transplant can save and properly replace that defect to replace the missing enzyme and result in a resolution of their symptoms?

George Mazariegos: This type of category of disease has really been growing. In the United States 20 years ago, about 50% or more of the indications were due to biliary atresia and related diseases that would lead to transplant. Now, metabolic disease is becoming an equivalent or greater component of the indications.

George Mazariegos: This has really required that we bring together experts that I've mentioned that we formed together here at Children's as a Center for Rare Disease Therapy that has helped to really bring together the teams that are required to share their expertise to make a proper decision for these children, and then advise and proceed on the transplant path for them.

George Mazariegos: But, what's also interesting and fascinating is that while transplant has been a dramatic improvement in their care, it's also opened us an opportunity to provide additional alternatives such as gene therapy for example, or other newer approaches that we're also incorporating in our care plan here at Children's Hospital.

George Mazariegos: For example, we were excited to just last month to be the first center in the world to provide a gene therapy vector for a child with Crigler-Najjar disease. It's very early and preliminary, but this is... It's important we believe to really be offering all of the therapies for children in one location under one roof and really be prepared to bring forth any alternative therapy that children need.

George Mazariegos: To get back to your first question, to this field of liver transplantation generally is shown to require about 500 liver transplants in the country per year for the variety of conditions that I've mentioned. These are spread out throughout the United States. We have had the largest overall experience with liver transplant in the country, and now we typically perform between 30 to 35 livers for a metabolic, or biliary atresia, or the other important conditions such as tumor or acute liver failure.

George Mazariegos: Because many centers typically only do two to five transplants, we are able to really amass a large experience in the national sphere and bring those results and experience to the community to take care of children.

John WILLIAMS: That's really exciting and fascinating that in some cases you and your team are transplanting the liver really to rescue another part of the body, correct?

George Mazariegos: That's absolutely correct. We have done transplants for liver metabolic disease where the indication was heart failure or renal failure and the liver transplant cures the heart failure. It's an important aspect of the care that's also not completely appreciated at times by the managing teams. We really need to continue to share that expertise to bring the right care to the children at the right time.

Stephanie Dewar: George, I'm curious, what age range of patients we're talking about, and what impact availability of transplantable organs has on your practice?

George Mazariegos: In the United States, we still face an organ shortage for patients requiring liver transplant.

George Mazariegos: In the pediatric world, it is important to make sure that we offer all of the organ types to help children be rescued from their liver disease or metabolic condition. This has meant that we've needed to evolve expertise in techniques such as split liver transplantation and living related liver transplantation to solve the organ crisis demand.

George Mazariegos: With the combination of these techniques, we've been able to to address all the needs of our patients on the wait list without having any wait list mortality. This is an important factor in this era of organ shortage.

George Mazariegos: We employ the techniques based on the patient acuity, how sick the patient is, their metabolic condition, and their unique anatomy sometimes helps shape which organ type is the best one, but we do feel strongly that all the organ types have an important role and should be employed in the care of children.

George Mazariegos: That's why we've really developed the Living Related Program. In the past five years, we've done the most live donor liver transplants in the country for children as well as an active program in split liver transplantation when we have a deceased donor, and trying to maximize that wonderful gift and benefit as many patients as possible as we can through that technique.

Stephanie Dewar: I understand that recently you've reached out to cooperate with other institutions to help to support their transplantation programs. Could you tell us a little bit about those efforts?

George Mazariegos: Yes. I'd be glad to talk about the network and our vision for this. When we look about... at the country, we understand that although there is 500 liver transplants being performed in the country over all the geography and the needs of these patients, we also have seen that there is a variability in the outcomes of these children.

George Mazariegos: As the delivery of care has and access to care has widened, it's been difficult to transfer the same level of expertise and outcomes as could be obtained by an experienced center in one area that's accumulated decades of experience.

George Mazariegos: Dr. Starzl came in here in 1981. His real focus from the beginning was to assure not only a perfect technical outcome as best as could be obtained, but also a long-term follow up of these patients and children, so even through his retirement and up until all the work that he did here at the hospital and in his role at the University of Pittsburgh, he would frequently ask about a child that we transplanted 30 years ago.

George Mazariegos: Last year, for example, I saw a child now whose 32 years post-transplant who still comes back for their care in some fashion under our group's direction. And that was really the vision of Dr. Starzl, the continued lifelong care.

George Mazariegos: When we looked at how to best serve patients in our area as well as across a larger region, we felt that it was important to partner with institutions that had this similar vision for long-term outcome and expertise, and who would be willing to work with us to serve the patients of their region as well as help patients from the Pittsburgh region and wanted to double list.

George Mazariegos: We initiated this collaborative with the University of Virginia first. Then last month, I did the first liver transplant with our colleagues at Florida Hospital for Children in Orlando with the principles being that we would have a collaborative where we would be able to share our expertise directly performing the surgery with the same teams that work here in Children's. Then, working collaboratively to help follow up and providing our protocols, nursing, ICU, anesthesia expertise as they... as needed in a way that would be a long-term commitment to the children of the regions in Virginia and in Florida.

George Mazariegos: We're really excited about that vision because it is a direct extension and allows a program that is beginning its experience in pediatric liver transplant to have the same results and outcomes because of our direct impact and work in that area.

John Williams: It's really interesting, in academic medicine we focus a lot on mentoring, senior physicians training younger physicians, fellows and residents, and senior researchers training younger researchers. It sounds like what you're describing is really with your team's expertise and years of experience you're mentoring these young programs?

George Mazariegos: Yes, it does take a unique group of individuals. I think both our teams from the surgery, medical, and related disciplines as well as the colleagues in Virginia and Florida who are very willing to integrate our learnings from the past and our expertise into their flow of work and are willing to share their protocols as well and modify them based on our experience. It's been a very exciting openness and a pretty transparent process to work together with these institutions.

John Williams: Well if you need a volunteer infectious disease doctor to do some mentoring in Florida during Pittsburgh Winter, right here.

John Williams: George, let me turn to a different topic if I may, which is to ask how you got to be where you are? When did you realize you wanted to be a surgeon or a pediatric transplant surgeon?

George Mazariegos: It's a journey that has taken me to this spot here in Pittsburgh. It really began in the late 80s during our residency training when at that time there were no programs that were doing transplantation except in Pittsburgh.

George Mazariegos: As part of our experience in transplantation, I decided to come to Pittsburgh to learn and have a one-month rotation with Dr. Starzl in that area, and really was overtaken by the opportunity that a transplant demonstrated to have an ongoing development of both technique as well as care. Then, the areas of knowledge gaps in immunology and the related fields still were quite large at that time.

George Mazariegos: After that one-month rotation, I knew that I wanted to come back and make transplantation a part of my career, and so I came back to Pittsburgh and to Children's Hospital in 1991 to do our transplant and intensive care fellowship. At that time, actually I began that experience in Children's Hospital of Pittsburgh with our ICU colleagues, and then completed the transplant training.

George Mazariegos: It wasn't however, until about eight years later that my interest and real love for long-term follow up as well as pediatrics developed as the Children's Program itself was growing and required some intentional focus with dedicated staff. And that gave me the opportunity to work with George Reyes and the colleagues who were here at the time in a first part time and then a full-time capacity. This really aligned well as the Children's Program began to grow and then required a real dedicated physician and surgical staff to take care of the growing population.

George Mazariegos: What was exciting, and is still I believe unique is that, it was really the vision of the hospital and the programs to allow for a dedicated pediatric service to develop rather than developing a service that was always shared between the adults and pediatrics, sometimes with people coming over from another hospital or adult program.

George Mazariegos: Really from the beginning, the teams were supported to be onsite 24/7 for whatever issue came and whatever issue was required from the children. This has really continued to shape our view of how we should care for children.

George Mazariegos: It's a full-time commitment and priority for all the surgeons and hepatologists to be dedicated to the care of these kids. I think it's demonstrated, and in terms of outcomes and also the collateral benefits that the service has shown by having that focus, so when they asked me if I wanted to stay at Children's the answer was a clear yes. It was exciting to see everything that's happened since that time in 1998.

Stephanie Dewar: You mentioned earlier a little bit about not just providing transplantation for patients, but to look at their condition and provide the therapy that's best for them through vector therapy, I think you mentioned. Also, I'm under the impression that you

also are very interested in subsequent management of immunosuppression through your research. I'm wondering if you could share a little bit of that with us?

George Mazariegos: When you look at what the main issues that trouble children after transplant, they're blessed that they don't typically suffer from recurrent disease, so typically the disease that is transplanted such as biliary atresia or another condition is cured by the transplant. Whereas, in adults we still have concerns over could a viral hepatitis come back or an autoimmune disease come back? That typically isn't the problem for children.

George Mazariegos: What opportunities and challenges they have really related to the management of long-term consequences of immunosuppression and helping to avoid and minimize those complications while giving enough immunosuppression for the liver to work well.

George Mazariegos: Therefore, and this again really began with the research of Dr. Starzl, was to look at some of the tolerogenic properties of the liver and understand why was it that some of these patients required very little or no immunosuppression as well as making a determined focus to continue to assess immunosuppression needs long after transplant?

George Mazariegos: Now, even as we continue to follow patients at the five- or 10-year mark, our key questions besides the allograft health and how the liver is doing is also to look at the key questions of are there any morbidities or immunosuppression related issues that we need to be addressing?

George Mazariegos: I think that this has helped us to really have low rates of some of the immunosuppression related problems that are important for children nationally, such as post-transplant lymphoproliferative disease, which Dr. Williams's team has been a great partner in helping us as much of this as Epstein Barr virus related or reducing complications of hypertension, or renal injury that sometimes has been reported with the immunosuppressant drugs that are common and have been helpful to reduce rejection, but need to be managed in terms of these other issues.

George Mazariegos: Then finally, we have linked that those important goals with research investigations that have tried to develop a signature for the tolerant profile after liver transplant to predict which patients potentially could be weaned from immunosuppression or wean to a lower level earlier rather than later.

George Mazariegos: We were the largest center to participate in a trial that's just closed enrollment called, The Immunosuppression Withdrawal Trial in Stable Liver Transplant Recipients. We enrolled about 23 of the 100 patients in the trial, and that was a 10 center trial in the United States.

George Mazariegos: This trial, I believe, will give us important information about which patients can be safely withdrawn from medicine and which patients need to have a different approach to their medications. Hopefully with the goal to reduce those complications that may be an issue for them at 20 years or more after a transplant.

John Williams: That's an exciting development. Thanks for the shout out to infectious diseases. I should note, my colleagues Mike Green and Marianne Michaels have long been transplant infectious disease experts here due to the experience of the institution.

John Williams: George, you highlighted the long experience and the number that your group has done. In addition to the research, what are you and your team doing to ensure that you keep getting better and that you stay as good in quality, improvement, and those kinds of things?

George Mazariegos: It's so important that the teams really keep the vision of how do we get better? We continually do that through our multidisciplinary group. But, we've recently had a even greater opportunity to take that... those local principles and try to help a network of centers beyond our clinical network, which we're working on to a quality improvement network that we've named the Starzl Network for Excellence in Pediatric Transplant. Through the generosity of Cindy and our foundation's help, we have a pilot four-year grant to bring together seven centers in pediatric transplant led by our group here in Pittsburgh that's going to bring together their knowledge and opportunities for improvement.

George Mazariegos: But also, couple that with a patient and patient advocate voice as well as technology and innovation such as a linking with industry partners to bring technology advantages to the improvement projects that the teams advise. We're excited about that network which will launch in September.

Stephanie Dewar: Well George, on behalf of all of us here at Children's and the patients and families in our region, I'm so thankful you were able to get that away elective during your surgical training, so that you could have the opportunity to not just meet Dr. Starzl, but work hand in hand with him and contribute so much to the community of medicine here in Pittsburgh.

Stephanie Dewar: Thank you also for joining us on the podcast today. This was fascinating.

John Williams: Thank you all. We'll see you next time.

George Mazariegos: Thank you.