[MUSIC PLAYING]

CHRIS SONNENDAY: So I'm Chris Sonnenday. I'm the surgical director of the liver transplant program at U of M. And I'm grateful to all of you for spending your Friday with us. We're going to shift gears a little bit and talk about some of the new arenas in liver transplantation, specifically related to machine preservation. And I have no financial disclosures, but I am going to be discussing two investigational devices in this talk, which is why you don't have a copy of the slides, because the company wouldn't release them to us. But I'm going to show you some pictures and some video, and explain to you where the field is moving in this domain.

So I like to point out the fact that transplant is a pretty young field. And I think that kind of sets the stage for some of the things we're going to talk about today. So this is cheating, because you just had a hint, but I guess it will tell us if you were paying attention. So what happened in 1954?

AUDIENCE: The first kidney--

CHRIS SONNENDAY: First kidney transplant. Very good. Between identical twins-- it was done by Joseph Murray. Interesting trivia question about Dr. Murray is, he was a plastic surgeon. He got interested in organ transplantation because he was studying the immunology of skin grafts. So he noticed when he took skin from one person and put it on another person, that skin would die. But if you did skin grafts between identical animals, for example, the skin would live.

And he got interested in the immunology of transplantation. And he and his colleagues at the Brigham and Women's Hospital did the first transplant, for which he won the Nobel Prize for that operation, and that advancement in the field. After that, the first deceased donor kidney transplant wasn't done until the 1960s, actually. That was in part because, as you probably know, there weren't really standards and agreement in society about brain death, and whether organ donation could be done ethically and legally.

The first lung transplant, believe or not, was attempted in 1963 in Alabama, which is pretty amazing. That's before cardiopulmonary bypass was commonly available and worked out. First kidney-pancreas transplant in 1966. So who is this gentleman? Any--

AUDIENCE: Tom Starzl.

CHRIS SONNENDAY: Tom Starzl. Very good. I'm going to talk a little bit more about him in a second. But in 1963, he did the first liver transplant in the United States. 1967-- anybody have any guesses on that one? It's another first.

AUDIENCE: Heart transplant.

CHRIS SONNENDAY: First heart transplant. Correct. Done by Christian Barnard, who is a South African surgeon. One interesting story about this is that Dr. Barnard came to the United States, to train and work in the laboratory at Stanford, to learn about heart transplantation with a surgeon by the name of Norm Shumway, who is arguably the most famous contributor to heart transplantation. He's a surgeon.

And so Dr. Shumway had done all the animal models, and was approaching doing the first heart transplant in the US, had actually a recipient that he had chosen and was waiting for the right donor. And Dr. Barnard got on a plane and went back to South Africa, quickly found an appropriate recipient, did the first one, and beat Dr. Shumway by two weeks. And apparently, they didn't speak again for many, many years. An interesting.

It tells you, probably most of all, that surgeons have big egos. But I've already been told I'm encephalopathic, so that's not a big surprise. And then some other firsts that really allowed transplantation to occur. This is kind of a hotly debated topical issue right now, but as part of the Medicare Act, as you may know, a rider on that legislation was that patients who were on dialysis would get federal coverage for their health insurance, because no one could afford dialysis out of pocket.

But that was really because Medicare paid for dialysis. And it was eventually demonstrated that kidney transplantation was actually more cost effective than dialysis. That's why Medicare largely pays for most kidney transplantation in the US. And that's what allowed transplant centers to appear.

You could make the argument, though, that the most important development in transplantation happened in 1983. Anybody have a guess on what that is?

AUDIENCE: Ciclosporin.

CHRIS SONNENDAY: Ciclosporin. Awesome. So that was when the FDA approved ciclosporin, which was really the drug that made transplantation more successful. The field really started to accelerate. And then if you look at the mid 1980s to where we are today, that's when transplantation has really become a standard of care for end organ disease. Just to give you the context, prior to the use of ciclosporin, the one-year graft survival for kidney transplantation, for example, was about 55%. And really overnight, it went to the high 80s, and now is in the high 90s. So that was really remarkable revolution.

So as I mentioned, the first liver transplant was done in 1963. This is Dr. Starzl. And it's worth talking about him, because Dr. Starzl just passed away a few weeks ago. He was in his 80s. And he is a remarkable figure in medicine, in general, but certainly, obviously, in our field. In addition to doing the first liver transplant, he also made a lot of the important scientific contributions in the field, including helping develop ciclosporin and tacrolimus, the maintenance drug we use now.

He published almost 1800 scientific articles, including one about three months ago, which is pretty amazing, and is the most cited medical researcher. At one point, he and his colleagues were putting out a paper every three weeks, in terms of his productivity. And has won awards for that, including the Lasker Award in 2012, which is thought to be usually the predecessor to the Nobel Prize. So in some ways, it's unfortunate that they just passed away, because he arguably will win the Nobel Prize posthumously.

His autobiography, which is called *The Puzzle People,* is a remarkable book if you have a moment to read it. It's remarkable just because of the personal story that he went through to make this field happen. But it also gives you a window into what was happening in the '60s and '70s when transplantations started to become more than just science fiction. You also wonder whether we could pull it off today, because this is all pre-IRB medicolegal compliant. So it's an interesting phenomenon.

But all of this work led to great success. And we're the victims of our own success in transplantation. So these are the figures as of about a week ago. There's currently enough people on the waiting list to fill the big house in Ann Arbor. And we only transplant about a third of that number in any given year.

So for liver transplantation, it looks like this. There are about 15,000 people on the waiting list. Last year was a banner year in our field, the most transplants we've ever done-- just over 7,000. Ben just told you about the impact of living donation, which is small, but we think increasing. But I think the most important line on this graph is the blue line in the middle here. So it's important to point out that for every approximately three to four patients we transplant, somebody dies on the waiting list. So that really, I think, tells you the challenge that we have in our field.

This is what it looks like nationally. This is the waiting list death rate. It varies across the country, as you can see. In Michigan, we're right down the middle in terms of the average in the country. And Ben showed you this figure earlier. But the point is, for any given patient on our waiting list, including somebody who's in the middle of the list, our median MELD score transplant currently is 29.

So these people with a MELD of 15 to 24 are not going to have any likelihood of getting transplanted any time soon. And 20% of them are going to die or be removed from the list for getting too ill. So we clearly have a problem to face.

So how do you get a liver? So as we heard earlier, 95% of liver transplants currently come from deceased donors. The majority of those are brain dead donors. An increasing number are what are known as donation after cardiac death. These are patients who have faced a devastating, usually neurologic, injury, but they're not technically brain dead. They and their family desire organ donation. And so care is withdrawn. And if they expire relatively quickly, we can then procure the organs and use those organs.

The challenge is, though, that many of the organs that we think we could utilize actually get discarded, either because of quality or because of concerns about the safety of transplants. So if you look at this-- one third of the organs that we procure from donation after cardiac death donors actually do not get used-- again, because of concerns about the severity of injury that these organs faced-- and about 10% of brain dead organs. And this ignores the organ donors that we don't even consider for donation because of concerns about quality.

So this is the opportunity, if you will-- could we be utilizing more organs to close that gap between demand and supply? But here's the challenge. The challenge is that the battle we fight, in terms of solid organ transplantation, is mitigating ischemia reperfusion injury-- the injury that happens at the time of procurement through the time before the organ is reperfused in the recipient.

And these are complex cellular processes that essentially lead to cell death, and injury to the graft that we're then hoping supports our recipient. And the consequences of ischemia reperfusion injury are things that those of us that take care of transplant patients struggle with all the time. So early allograft dysfunction, again, because of this ischemic injury, can be associated with coagulopathy-- risk for ongoing bleeding, acidosis, and liver dysfunction, and associated renal failure. So acute kidney injury is almost expected in many of our liver transplant recipients.

Primary not function is one of the more feared occurrences in our field. Fortunately, it only occurs in about 1% of recipients. But when it does, it is immediately life threatening, requires immediate retransplantation. And if you can't get an organ quickly enough, those patients will die.

And then even more mysterious is this phenomenon of what's called ischemic cholangiopathy, where the bile ducts in particular are very sensitive to this ischemic injury, and particularly in grafts from DCD donors-- cardiac death donors. We can see this delayed biliary necrosis and dysfunction that essentially leads to graft failure. And the statistics nationally are that about 10% of patients that get an organ from a DCD donor currently will need to be retransplanted for that problem. So obviously a big challenge.

So how do we do things currently? So currently we take organs from organ donors. And the process is that, in the donor operation, when we cross clamp and take out the organs, the organs are rapidly cooled. We use a cold flush solution. The organs are flushed out of all the blood in the donor. Cooling the organ temperature, they're then essentially stored on ice until the organs are transplanted.

So we rapidly cool them down to about 4 degrees Celsius. The problem is that cell death and the abnormal metabolic processes that take place when you deprive oxygen from an organ actually continue down to a temperature of about 1 degree Celsius. So even though this organ is cold on ice, it is still undergoing ongoing injury. And unfortunately, we can't truly freeze the organs, because the thawing process is injurious as well. So we're on the clock when this happens.

The biggest advancement in the field as it relates to organ preservation really occurred in the 1970s, when a variety of preservation fluids were created that tried to mitigate some of this damage. Essentially, they are preservation fluids that had very similar composition to the intracellular make up, such that the cells did not die at such a high rate. But the truth of the matter is, we don't have a way to really reverse this ongoing injury that's happening while we're waiting to put the organ into the recipient.

So what would be the ideal method of organ preservation? So ideally, we would have a way to preserve organs without this time-dependent damage. We wouldn't be so pressed by being on the clock. We could, in theory, also resuscitate the organs, if you will-- allow the organs to recover from any injury that occurs either in the donor themselves, or at the time of brain death, or at the time of procurement.

Also in theory, it would be nice if we had a way to measure function of the organ after procurement. Currently, the way we measure the appropriateness of any given organ for transplant is, to be honest, quite frankly, a judgment call, based on surgeon experience and parameters that we look at from the organ function in the donor. But that doesn't always predict the organ function in the recipient.

And it would be nice if we could minimize this ongoing hypoxic injury that happens as soon as we cut off the blood supply in the donor, because that would, in theory, mitigate this ischemia reperfusion injury that causes all the other complications I just told you about. So this is an area of much research. And we think we're really smart.

Well, it turns out that Dr. Starzl was thinking about this in 1963. This is a little known fact-- the first liver transplants were done, actually, from donors after cardiac death. They were not brain dead donors. So with all the risks that those teams are already taking on at that time, they were also using more marginal organs. And the idea was that, he thought, well, what if we immediately from the time that we cross clamped and moved to take the organs out of the donor, we essentially perfused them as if they were on a heart lung machine? So that the organs were constantly being perfused.

And that was the idea, to cannulate the donor and do this. And the technology at the time, to be honest, just wasn't adequate to support that. But that's the concept that he thought would be most appropriate for organ donation. It was soon after that that these preservation fluids that I just mentioned were invented. And so this part of the field got left on the back burner until just recently. And so I'm going to tell you a little bit about that.

So the first level of innovation in this field is related to the question, could we continue to do cold preservation? It's simpler. It's not that much different from what we already do. But could we do that better? And all the work in this field has largely been generated out of the group at Columbia, and Ben's colleague, James Guerrero. And I'm going to show you some of his slides over the next couple of minutes.

James thought that, well, what if we continued cold preservation, but just made it smarter cold preservation with machine perfusion of the organ? And the thought is that this would allow you to continuously circulate these preservation fluids, providing a substrate for cellular function, even at that cold temperature. There's also this idea of continuous flushing of the waste products of cellular metabolism out of the organ. The thought was that perhaps this would prevent some of these biliary ischemic consequences that have been seen.

And also, the actual use of the pump or the device might tell us something about the organ, in terms of the resistance and flow of the perfusion through the organ. And there's precedent for this. So in kidney transplantation, many organs are perfused in these pods that are shipped around the country as we transport kidneys to different centers and recipients. And so James and his colleagues have done 15 years of work trying to adapt that principle to liver transplantation.

And this is a picture of James and his lab. And so they first started with essentially a centrifugal pump device that pumped this perfusion solution through livers. They looked at both porcine pig livers, as well as discarded human livers. And showed proof of principle that you could keep the organs cold, you could minimize the effects of abnormal cellular metabolism and cell death.

And then, in the late 2000s, published the first series of these patients. This was a group of 20 patients who were transplanted using organs that were cold perfused on this prototype device. And what he showed is, when you compared the cold perfused organs to organs that were preserved in our standard way-- cold storage-- that they had equivalent graft in patient survival, a trend towards lower biliary complications, and they got out of the hospital faster. Suggesting perhaps that you mitigated some of this damage attributable to ischemia reperfusion injury.

Perhaps most notably from the standpoint of hospitals is, therefore, these patients-- because you had fewer complications and got them out of the hospital faster-- these patients cost a lot less to take care of. Which created the business case for this concept of smarter perfusion of organs.

The next study they did, though, was really the clincher to this concept. And it was a daring study. Basically what they did is they took organs that had been discarded by all other centers. So all other centers thought that these were not appropriate organs to use. They imported them to their center, put them on the pump, and then transplanted them into patients under a research protocol.

So here, for example, is a 79-year-old donor liver. We do use 79-year-old livers occasionally, but they are not commonly used. And they're considered to be more risky. Here's another example of a liver that you can see has this yellow blanching tone to it. This is a fatty liver. Again, a liver that might be discarded from a deceased donor currently.

And what was shown, that when you compared these so-called orphan livers-- livers that nobody wanted-- and you compared those to historical controls, that their organ function, as measured by laboratory parameters, was equivalent to organs that had been previously transplanted come from standard donors. He also showed that, actually, the recipients of machine perfused organs actually got out of the hospital faster, and again, had improved laboratory parameters.

So to summarize what James and their group had shown was that this technique of machine preservation perhaps improves early allograft function with fewer complications, shorter length of stay, and lower costs. Again, creating the business case, if you will, for why this could be an effective therapy.

So out of the prototype that James had developed, this device has been created. And it tells you how hard it is to get something like this to completion. So they've been working on this almost for two decades. This is the Life Port liver device. This is a cold perfusion device that is currently entering into clinical trial here in the United States. And the idea is to try to validate the experience at Columbia in a broader, multi-center experience. This device is made by the same company that makes the kidney pods that are in common use currently.

So that is, again, cold preservation, but used with machine perfusion. So if cold is good, is it possible that warm is better? So the idea behind warm perfusion is, like Dr. Starzl thought back in the 1960s, can we recreate, basically, the physiologic environment that organs live in in vivo? So can you create a system that delivers oxygen, that exists at normal body temperature? And you can also supplement the system with nutrients to sustain the organ in the period of time from donor to recipient. This could, in theory, mitigate all these consequences of ischemia reperfusion injury.

So this is a schematic of what such a system would look like. So you need an oxygen carrier, right? So you either have to use synthetic hemoglobins, or you use donated blood. And this current system actually uses packed red blood cells. So you pump using a centrifugal pump in a membrane oxygenator. So this is exactly like a heart lung machine, on a small scale. It pumps that blood through the donor organ.

And remember that the liver has dual blood supply, right? Hepatic artery and portal veins. So you need to deliver blood to both of those systems. Blood returned back to the system from the vena cava. You can actually measure bile production of the organ, as well as flow, and resistance, and biochemistry of the organ on this system.

There are several investigators that have done warm perfusion. But most of the work that I'm going to show you has been done by Peter Friend, who's a transplant surgeon and scientist in the UK. They originally began with pig livers, again. And what they basically did is, they showed that they could keep a pig liver viable for 72 hours on this machine, which is remarkable in and of itself, but showed that you could maintain essentially normal physiologic function on the perfusion device.

They then created a transplant model where they would, after these prolonged periods on the perfusion device, they would transplant these organs and show that, whether it was a brain death model or donation after cardiac death model, they could produce survivability in this model. So this was the preclinical work that led to a clinical trial in Europe.

The first experience with this was a small phase one study, taking organs that would be normally used, but instead of going to cold perfusion, were placed on this warm perfusion device. And showed that, in this limited experience-- again, 20 organs-- that the outcomes were equivalent to cold storage controls. And actually, there was some laboratory evidence that the liver sustained less injury. So this was, again, proof of concept, and led to a randomized clinical trial that recently finished in Europe-- 220 patients in each arm at all of the major liver centers in Europe.

The results from this trial were just reported at our American Transplant Congress a few weeks ago in Chicago. And they showed that, again, there was laboratory evidence at least of a diminishment in the degree of injury that's sustained by these organs. And what was really compelling was that the degree to which the injury was mitigated was even more profound in donation after cardiac death donors, which are our riskiest donors. So again, showing the potential of this machine to potentially mitigate some of the complications we see in these organs.

Obviously, the clinical outcomes in these patients are still being collected, in terms of graft survival, et cetera. So we will be learning about the outcomes of these organs in the coming year or so from this trial. Basically, they concluded that, again, you see less of this early allograft dysfunction. And despite longer preservation times, there were fewer organs discarded in the study group, while maintaining transplant rates.

So the University of Michigan is part of the US clinical trial studying this device. So this is what the US study is like. It's very similar, slightly larger numbers. But the idea is, again, to take organs that we are considering for transplant. They would be randomized to either standard cold storage or the warm perfusion device. There's 15 centers around the country that are participating.

We just got lifted off of our initial FDA hold review. So we will be enrolling patients in the coming weeks and months, with the idea to complete the trial within about a year or a year and a half. Primary endpoint, looking at this idea of immediate graft injury, but obviously, all the secondary outcomes that we care about in terms of graft and patient survival, complications, et cetera.

And it's a pretty broadly designed trial. So essentially any brain dead donor over the age of 40, and essentially all adult DCD donors are eligible for the trial. Again, trying to prove that we could utilize this across the spectrum of the organs that we transplant.

This is what the device looks like. It's a big device. So it requires an ambulance, literally, to transport from the donor hospital back to the recipient hospital. It's a fully cannulated system, as I'll show you in a video in a minute. But the artery, portal vein, vena cava, and bile duct are all cannulated. This preparation has to be done at the donor hospital by the procuring surgeon, which does add a little complexity to what we do.

You get real-time feedback from the device. So this is pretty cool. You get arterial and venous pressure measurements, we can measure lactate production, oxygenation, et cetera. And when you put an organ on this machine, you can see it literally improve, in terms of its physiologic function. The lactate clears, the oxygenation improves, and you can measure bile production. And that can be plotted and followed while the device is on the circuit.

This is what it looks like. It looks just like when we perfuse an organ in transplant. So you put a pale organ on the device, and after just a few seconds, it looks like a normal, healthy perfused organ. I can show you this video. And I will, in the interest of time, jump up here a little bit.

So the cannulation system is really pretty easy to use. These are all cannulation type devices that we're used to in other surgical applications, like bypass, for example. There are cannulas, as I mentioned, in the artery, and the vein, and the bile duct. You can see here that the blood has been primed from the device. They're taking the clamps off now.

And you'll see in a moment the device will be activated. The liver sits in a bowl, which is then, once you're finished with the cannulation, is covered. And the whole device is sustained under a big hood. And here you can see the liver perfusing with blood. Now, the artery just perfused, and then the portal vein. And blood is returning from the vena cava back to the machine.

And the machine has a variety of software in it that regulates the flow through the arterial cannula and the portal venous cannula to imitate what happens in vivo. So it's a very intuitive device. It makes sense that it would work. And we obviously want to prove that that's the case.

So in summary, I would say that I hope both Ben's talk previously and the introduction to my talk makes the point that our current state-- our current utilization of deceased donor organs-- is not adequate to meet what is an increasing demand in our field. And Bob told you earlier, we're curing hepatitis C, but there is no end in sight to the number of cancer patients. And we're peeking at the tip of the iceberg, in terms of the Nash epidemic. So there's going to be no shortage of patients to transplant, and we're not going to meet our demands with our current supply.

Machine preservation appears to have the potential to expand our utilization of deceased donor organs and decrease the impact of cold ischemia time. And there are ongoing trials now that will hopefully help us answer the question of whether cold perfusion or warm perfusion is most appropriate. And perhaps they will both have a role in different organ types, based on cost, and distance of travel, and a variety of other factors. So stay tuned. But this is the direction in which we're going.