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Clinical Relevancy of Islet Cell Transplantation

SCIENCE AND RESEARCH BEHIND ISLET CELL TRANSPLANTATION.

Islet cell transplantation was performed as early as 1893 when a young diabetic patient had minced sheep pancreas transplanted into his thigh. What's the latest research telling us about islet cell transplantations? You are listening to ReachMD, The Channel for Medical Professionals. Welcome to the special segment, Focus on Diabetes. I am your host, Dr. Mary Leuchars, and joining me from Seattle, is Dr. Paul Robertson. He is President and Scientific Director for the Pacific Northwest Diabetes Research Institute and Professor of Pharmacology and Medicine at the University of Washington. We are discussing the basic science behind pancreatic islet cell transplantation and what current research is telling us.

DR. LEUCHARS:

Welcome Dr. Robertson.

DR. ROBERTSON:

Thank you, Mary.

DR. LEUCHARS:

Thanks very much for joining us. Now, tell me when did the concept of islet cell transplantation first arise for patients with type 1 diabetes?

DR. ROBERTSON:

Well, I think you just quoted that very early experience with. It was actually a digest of sheep islets in the late 1800s. Conceptually, I think that was probably the first publication. It really got fire, however, in 1970s, around 1972, an investigator named Paul Lacey published that he could rescue diabetic mice from diabetes by transplanting islets in these rats. It was relative to some sort of rescue then by transplanting islets in several different sites. So, I will date back to the early 1970s in terms of being a workup of preclinical piece of work.

DR. LEUCHARS:

What happened in the 1980s? What developments occurred?

DR. ROBERTSON:

1980s, the most spectacular thing was the successful transplantation of islets in humans in a very particular scenario. This involved auto islet transplants, which means that these patients had not diabetes, but they had chronic pancreatitis, which being that the inflammation of the rest of the non-islet part of the pancreas is being treated by removing the pancreas and then salvaging the islets from the pancreas that had been removed putting the islets back into the patient's own liver where the islets took a precedence and then began to function. In this case, we call this autotransplant obviously because it is returning to the same person, but in this scenario, the islets did work quite well and some of those recipients went on for decades of successful management of glucose level without a pancreas.

DR. LEUCHARS:

And what happened in the 1990s?

DR. ROBERTSON:

Then, as time went on, everybody was trying to make this work in using donated pancreases for treatment of people with type 1 diabetes and I think the first successful study was published in the 1990s. It was a study from Paul Acey's School actually at Washington University in St. Louis. It was a brief 30-day success story in a woman who received transplanted islets from a human donor.

DR. LEUCHARS:

Let's talk about islet cells in the pancreas for a moment. How many islet cells does the pancreas actually have and how many do you need to have a functioning organ?

DR. ROBERTSON:

Typically, we quote the number of 1 million in a human pancreas, 1 million islets and perhaps 2000 beta cells per islet, beta cell being the cell that's responsible with the synthesis of the insulin. The number of islets you need to control glucose levels has been known to the areas as being approximately in rough figures, may be a third of the pancreas. This has been data that's been gained from dog studies where progressive amounts of pancreas has been removed. It has been estimated from other animal studies in which a beta cell toxin has been given. They had progressively eliminate more and more beta cells, but the generalization is that we need about 250,000 islets to 300,000 islets to really control glucose levels, which is about a third of the complement that the normal pancreas contains.

DR. LEUCHARS:

How did your personal interest develop in this procedure?

DR. ROBERTSON:

Well, my personal interest is because when I was on faculty at the University of Minnesota, I had a good fortune to run into a man named David Sullivan who is a very famous transplant surgery. So, he and I began working together at that point.

DR. LEUCHARS:

How was islet cell transplantation being reformed, we talked about this 70s and 80s and 90s. What's happening now?

DR. ROBERTSON:

Most recently, the most noteworthy progress has been made at the University of Edmonton at Alberta. This is James Shapiro's research group who in year 2000, I believe was fairly electrified the diabetes world by reporting a successful islet transplantation in certain consecutive human recipients who had received islets from people who would donate their pancreases upon dying and he had successes like that for a finite period of time. A larger study was done thereafter, ensuing 5 years. The most, I would say, noteworthy effort was a multi-studying trial with really 8 or 9 centers throughout the United States and Europe. Each of the centers transplanted on average 4 patients and then there were about 36 patients done in total and then they grouped their data and found that on an average, the results were not as good as the Edmonton group had experienced. So, it's now saying that the Edmonton group was wrong as just saying they were so super specialized that there actually the results could not be generalized to all these other centers that tried. Some centers had no successes. Some centers had poor successes. The very most recent information from Edmonton group is that when they go through all their recent data that out of 1 year things are looking very good by 15 months, about 50% of people who have been recipients have gone back to taking insulin. By the 5th year after islet transplantation, there are only about 10% of people who can still function without using insulin again. So, there is an initial success, but there is a rapid falloff thereafter.

DR. LEUCHARS:

Is that what may turn the Edmonton protocol and is that still the protocol that you use?

DR. ROBERTSON:

Yes and no. That is what led to the name of the Edmonton protocol. Personally, we are not transplanting patients right now. We have returned to the laboratory and we are trying to sort out how to improve the results of islet transplantation before we do any more human studies.

DR. LEUCHARS:

Who are the donors of transplanting cells, can we talk about that?

DR. ROBERTSON:

Typically, there are people who are predetermined pass by a note on their driver's license or telling the family members that in case that

they die, they would like to donate their organs for medical research, and if that is the case and it is usually an automobile accident, sometimes it is suicide, but if it is determined that there is no damage and no reason to be concerned about removing the pancreas and giving to somebody else, then that is the source so that people who die usually from a head injury, no malignant diseases, no diseases could be expected to affect the pancreas and had predetermined they want to be donors and then recovery team was notified that whatever transplant center have got and procure the organs.

DR. LEUCHARS:

And how many donor pancreases do you need for each transplant theoretically?

DR. ROBERTSON:

Well, currently an average of 2 are being used for islet transplantation. If you do pancreas transplantation, you can get away with half the pancreas.

DR. LEUCHARS:

If you have placed the porcine or other animal donors?

DR. ROBERTSON:

That's been a dream to be able to use animal islets. It's not yet worked in humans. This was called as xenograft or as going a cross species. Rejection rate is 100% if you try to do that. Some of the modifications have been trying to immuno-protect pork islets by putting them in capsules that are immuno-protective. There is quite a bit of basic research going on, but there is nothing that has been successful at a clinical level yet.

DR. LEUCHARS:

What is the isolation techniques that is used to get the islet cell?

DR. ROBERTSON:

In a general sense, the pancreas is procured and then for islets, often times it is just simply chopped up after being treated with collagenase and then treated with collagenase over a period of time, usually about a half hour and the islets begin to drop out, so that it is just a method of using an enzyme that digest tissue without harming the islets and then putting the islets to shake out and to isolate them based on procedure.

DR. LEUCHARS:

And you talked about the research that you are doing, can you give us some more detail about what exactly you are doing in the lab at

the moment?

DR. ROBERTSON:

One of the steps in islet isolation is to use cold sonification so to concentrate the islets into small amount of tissue because you remember this is infused into the blood stream, so it can't be a huge amount of material. It turns out that when we do the cold sonification that probably kills half of the islets, so we are trying to figure out a way to do the procedure without having to go through that particular step. One of those ways would be just to avoid the liver altogether. The only reason to purify islets is in order to get a small amount of tissue, so that is as large as a liver and does not cause serious obstruction of blood flow. What we are trying to do is to approach this procedure by putting islets in omental sac by preparing part of the omentum in a way that it will contain the islets, put in the peritoneal cavity. These are all established ways that have been known to work for the last or as I said this originally in early 1970s. So, we know these procedures can work. We know that you can put in the kidney capsule in animals and they can work. So, our dream would be to find another sites in the abdomen, we favor the omental sac right now, but has the same venous drainage going to the liver just like the native pancreas does, so it would be the most physiologic way to go. The other advantages that we are working on of getting out of the liver is that in the allograft situation, of course the patients are given immunosuppressive drugs and by just bad luck, virtually all of the immunosuppressive drugs have adverse effects on beta cells, I would like to refer to this as a therapeutic irony, you are giving immunosuppressives to protect the islets against rejection, but those same drugs actually wind up being toxic to the beta cells themselves. The liver is particularly a bad place for this because of course the pills are taken orally. They are concentrated in the liver before they go anywhere else in the body and that's where the islets are being put, so it's putting them in a toxic environment. If we put in the place like the omentum, then that problem doesn't pertain anymore.

DR. LEUCHARS:

And who are the centers in the US apart from yourself that are conducting the similar type of research deals at the moment?

DR. ROBERTSON:

That's not really clear who is doing exactly what we are doing. At the clinical level, the most high volume center as I would say are University of Minnesota and in Miami, Florida, at the University of Florida, Miami, those are the 2 that has the highest volume, another place with the quite high volume is the University of Pennsylvania, Philadelphia. Other centers also active, but not nearly as much as those 3. So those 3 plus the 1 in Edmonton, I think are probably the most busy centers.

DR. LEUCHARS:

And if funding or lack of funding limit the progress in the research of islet cell transplantation?

DR. ROBERTSON:

Yeah, in a huge way. It is no accident that the centers that are most successful and most active clinically have independent funding by donors, so they have to rely on an income of 1 to 2 million dollars every year just to keep their programs going. Those who do not have that luxury and have to rely on getting grasp from NIH or other sources, are really finding we cannot sustain the clinical islet transplant program, just cannot get enough grant money to do that.

DR. LEUCHARS:

And what's the future for your program?

DR. ROBERTSON:

That's one of the reasons we return to preclinical work, now someday we are fortunate enough to find person interested in sustaining an islet transplant program by contributing money or an organization that would contribute money for clinical demonstrations and support clinical use of islet transplantation, we could open up a clinical center here again.

DR. LEUCHARS:

I really hope that happens. Thanks Dr. Paul Robertson very much for being our guest. We have been discussing the science and research behind islet cell transplantation.

I am Dr. Mary Leuchars and you have been with me into a special segment, Focus on Diabetes on ReachMD, The Channel for Medical Professionals. To listen to our on-demand library, please visit us at www.reachmd.com. Register with promo code radio and receive 6 months free streaming to your home or office and thanks for listening.

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