

Windy City Whispers
67th Scientific Sessions American Diabetes Association
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Transplantation

It just would not be right to report on the meetings without making a fool of myself trying to understand the transplant surgeons. As a result, on Saturday I went to a session on Innovations in Islet Transplantation. Dr. Burnhart Hering presented the first talk on the Promise and Limitations of the Current Islet Transplant Approaches. He pointed out that there are two main reasons for islet cell transplants, 1) restoration of normal glycemia for patients with hypoglycemia unawareness and 2) insulin independence. He noted that 12.5% of patients who have had diabetes for 21-30 years have hypoglycemia unawareness. Thirty-seven percent of these patients had severe hypoglycemia during the preceding year and 21% had 2-3 episodes per year. He feels that hypoglycemia unawareness may be the only real indication for beta cell transplant. Five hundred thousand islets are required (which is a roughly the size of 1 teaspoon of fluid). They are injected into the portal vein over 20-30 minutes. When they evaluate the concern for hypoglycemia unawareness, the hypoglycemia score indicates that the problem is eliminated after transplantation. Eighty five percent of the patients had had severe hypoglycemia before the transplant and only 4% after transplant. As far as insulin independence is concerned, one year after islet cell transplantation, 82% of the patients are independent of insulin which is equal to the success with a pancreas transplant. Long-term results are not as good, however, with 11% of them free of insulin at five years although 82% of them are still C-peptide positive (this indicates that they are making some insulin just not sufficient amounts). Most of these patients at five years duration are on approximately 2-10 units of insulin per day. He felt that the significant deterioration in insulin independence was due to a cumulative burden of non-immune and immune related injury which may overwhelm the islet cell's ability to repair injury and replicate. He did say that a small study using antibody therapy as protection showed 60% independence at 5 years with 80% still showing positive C-peptide production. These results certainly are much more encouraging. He said that it was very likely that they would have to find better sites for transplantation which would give the islet cells sanctuary. They are considering the omentum as a protective microenvironment and perhaps other sites. He did note, however, that there are 3,000 pancreases available in the United States each year for transplantation. There are 30,000 new Type I diabetics so that obviously full pancreas transplants will not be a cure for the total diabetic population. *At the moment, it requires 2-3 donors in order to have enough beta cells to do a full beta cell transplantation so that is not the answer either. Either we are going to have to be able to grow islet cells in the laboratory, use stem cells to produce new beta cells or we will have to use cells of other animals. Once again the pig has risen to the forefront. Already pig islets have had prolonged survival in non-human primates so this may be an approach in the future for humans.* Dr. Bo Nilsson gave a talk on novel islet implantation sites and protection strategies. I did not understand much of what he had to say but he did point out that new sites are going to be necessary in the future. Low molecular weight dextran may serve as a protective anti-complement factor. Heparin coating may be useful in protecting the islet cells. He also said that some alternative sites being considered are the omentum and forearm muscle. Dr. Anne Bang talked about replenishable insulin-producing

cells. She was talking primarily about human embryonic stem cells which are derived from definitive endoderm. The sequence is definitive endoderm transformed to foregut endoderm, transformed to pancreatic endoderm, transformed to endocrine precursor and finally to endocrine hormone. So far only 12% of the cells were insulin positive. These cells release C-peptide to many stimuli but unfortunately not to glucose. Thus at this point they are not a viable option but she felt that ongoing work may well find the trigger to make them responsive to glucose levels. She also talked about xenotransplantation with pig cells. On Sunday, Dr. Hon Sollinger from my alma mater the University of Wisconsin, gave the state-of-the-art lecture on Transplant Options for Diabetes. I was a little embarrassed that he was so dogmatic but I guess that is the lot of many surgeons. There seemed to be no gray areas in his mind with everything being absolutely black or white. He went through the history of pancreas transplants and noted that the first pancreas transplant was in Minnesota on December 16, 1966. By 1980, the one-year patient survival was 63% while the one-year pancreatic survival was 21%. The use of Cellcept has now reduced the rejection rate by 30%. He went through all of the different types of pancreas transplants with pancreas alone or pancreas before or after kidney. For our patients, the concern is the pancreas alone transplantation since they don't need kidneys. He stated that the mortality risk of pancreas transplantation alone is 2.1 times greater than the risk with no transplantation. Thus he felt that it would be a rare patient who should have a pancreas transplant alone: pancreas transplants should be reserved for patients who also require kidney transplantation. He was very much down on islet cell transplants as opposed to the speaker the day before. He felt that there was a 15% graft survival at five years with only 7.5% of the patients insulin-free at five years. He stated that islet cell transplantation is logistically complex, would only be available for 0.01% of all diabetics, is very expensive, is an ineffective use of pancreatic tissue and has very poor long-term results. He made it clear that he did not feel there was any viability to islet cell transplantation. He talked about embryonic stem cells as a potential source for islet cells and also trans-differentiation of hepatic cells with DNA splicing, using a viral vector. They have now used some of these cells in animal studies and the animals are insulin-free 150 days after transplantation. Interestingly there is no evidence of auto-immune rejection with them. I am sure he had a great deal more to say but these were the points that I thought were most interesting. I hope that this satisfies everyone's appetite for transplantation information because it is all that I have this year.