PANCREAS AND ISLET CELL TRANSPLANTATION IN DIABETES

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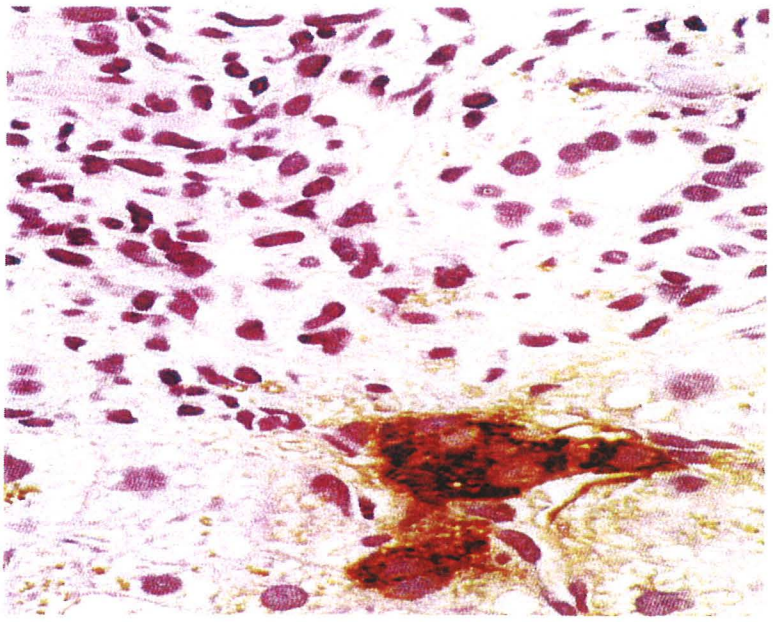

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Interests:

Diabetes management
Diabetes complications
Prevention of Type 1 diabetes

Pancreas transplantation is now a well-recognized treatment for diabetes. The International Transplant Registry reports 16,043 pancreas transplants done Worldwide[1], with over 11,500 done in the United States (Figure 1).

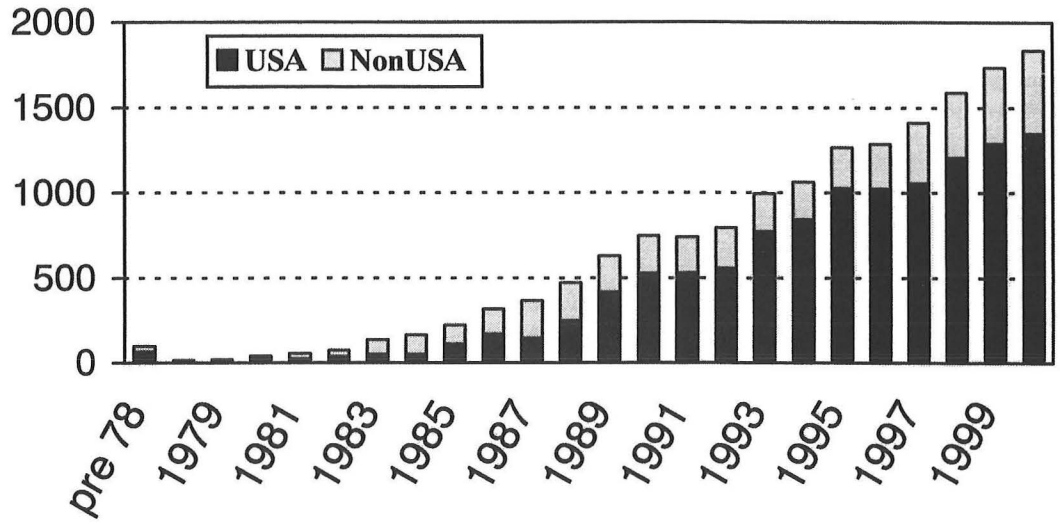


Figure 1: Pancreas transplants worldwide.

There are three circumstances under which pancreas transplants are usually done (Figure 2)[1]. A pancreas transplant can be done simultaneously with a kidney transplant, called "simultaneous pancreas kidney transplant" (SPK) in individuals with end stage renal disease. This is the most common type, accounting for almost 90% of all pancreas transplants. It can also be done at some time interval after a kidney transplant, this is called "pancreas after kidney" (PAK). Finally, in some specialized centers, pancreas transplants are done in non-uremic patients, so called pancreas transplant alone (PTA).

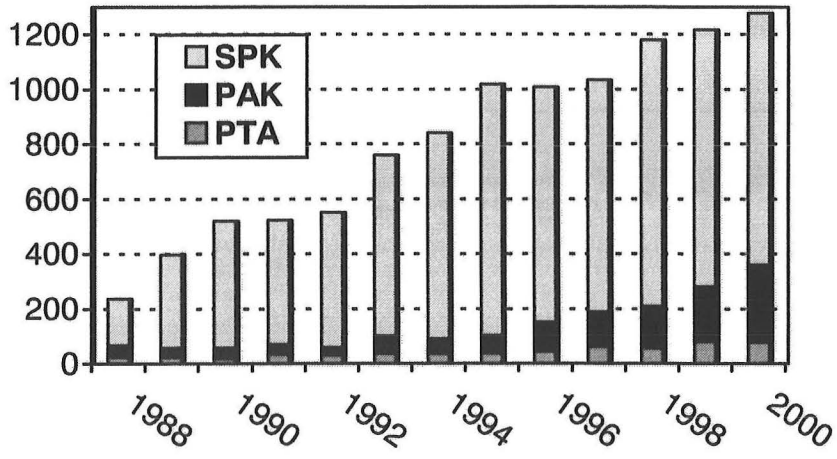
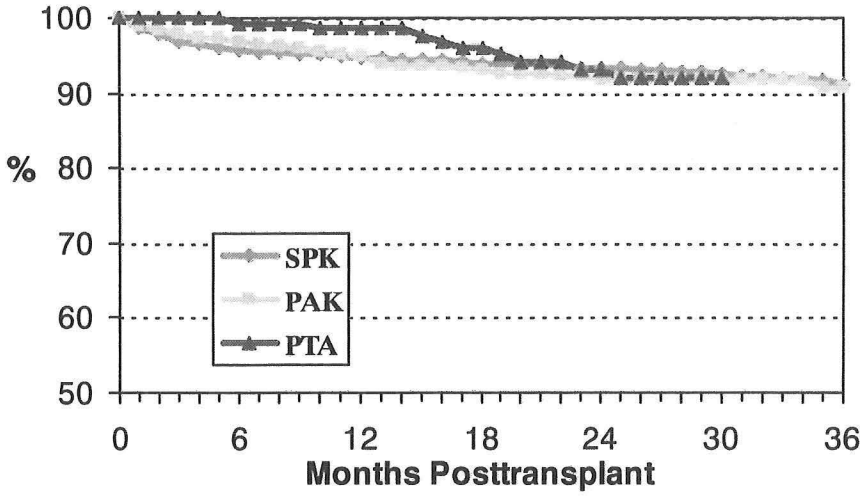


Figure 2: Pancreas Transplant Categories in the USA (SPK – simultaneous pancreas-kidney transplant; PAK – pancreas after kidney transplant; PTA – pancreas transplantation alone).

Pancreas transplantation now seems to be quite routine and are in general very successful. Figure 3[1] shows the patient survival from 1/1/1998 through 7/1/2002. As pictured, the one-year patient survival rate is more than 95% and at 3 years it is still 90%. There is no difference Figure among the type of transplant done (i.e. SPK, PAK, or PTA), in terms of patient survival.



3: Patient survival in pancreas transplants in USA.

Figure 4[1] shows the results of pancreas graft survival by type of transplantation done. Graft survival is approximately 80% at 12 months and about 75% for those receiving either a SPK or PAK. Please note that graft survival for PTA approaches 50% at 3 years. Graft survival rates are better in SPK because acute rejection can be treated earlier coinciding with the simultaneous rise in serum creatinine that is indicative of kidney rejection. Nevertheless, patients who receive a pancreas at the same time they get a kidney have higher rates of infection, surgical complications, increased rates of acute rejection and more hospitalizations than the patient who receive just a kidney transplant[2]. Please note that by three years the worst graft survival rates seems to be in the healthiest individuals, i.e. those who receive a PTA usually as treatment for poor glycemic control.

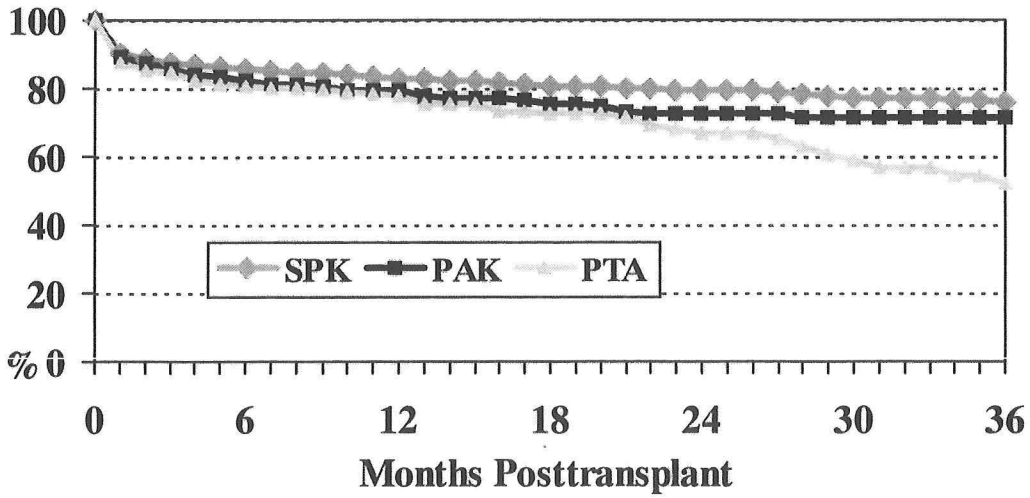


Figure 4: Pancreas graft function – primary pancreas transplants in USA.

Doing a pancreas transplant in a non-uremic diabetic patient (PTA) is one of the most contentious area of pancreas transplantation. These patients are thought to have "brittle diabetes" including hypoglycemia unawareness. These potentially manageable problems are thought to be more harmful than the combined risk of the immunosuppression and surgical risks! I will have more to say about this later.

Although there are multiple variations (I refer you to Dr. Ingemar Dawidson's book for the details)[3], the pancreas graft is placed within the peritoneal cavity on the opposite side of the kidney in SPK. The vascular supply is usually the external iliac artery and vein. One of the non-physiological consequences of this technique is that insulin is secreted directly into the systemic venous circulation resulting in peripheral hyperinsulinemia. In successful pancreas transplantation when insulin independence is achieved hypoglycemia is a potential adverse event. The pancreatic exocrine secretions are managed in two ways, either drainage into the bladder or into the small intestine (Figure 5)[1]. Although there is no difference in outcomes (Figure 6)[1] between bladder and enteric drainage, I feel enteric drainage is superior to bladder drainage and so does Dr. Dawidson[4]. Bladder drainage is often associated with a metabolic acidosis, recurrent urinary infections, bladder mucosal dysplasia and reflux pancreatitis. Thus, most surgeons are now doing bowel drainage.

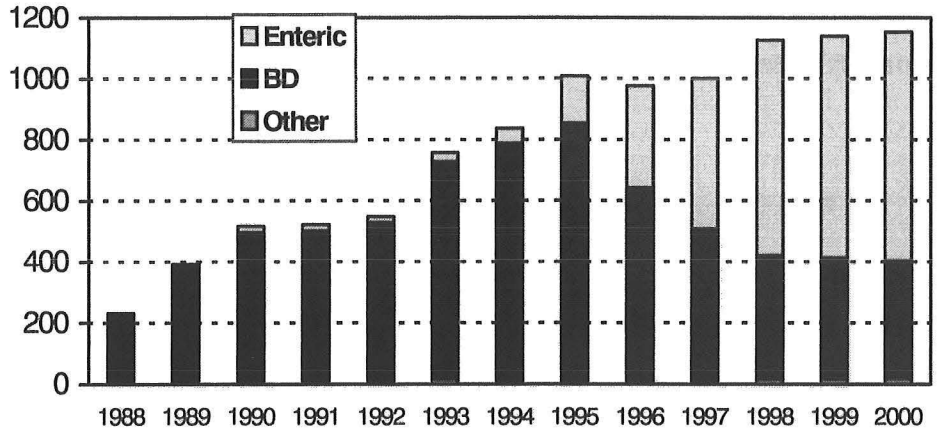


Figure 5: Duct management technique evolution.
USA Cad SPK, PAK, and PTA Pancreas Transplant

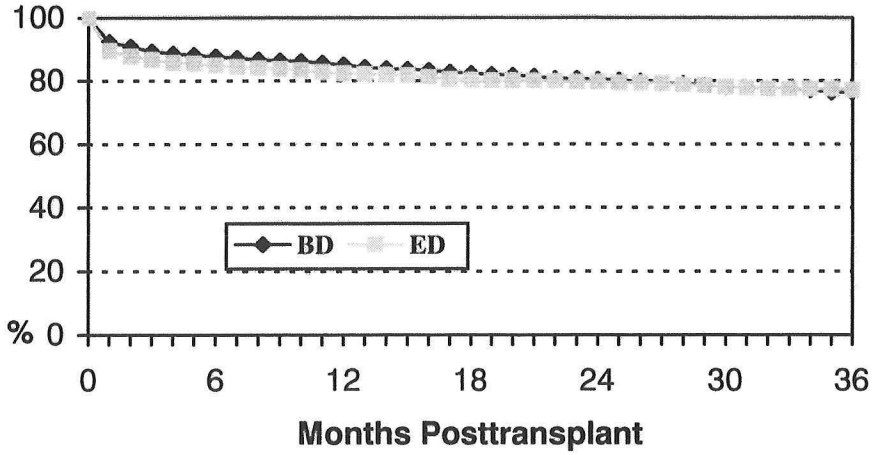


Figure 6: SPK graft function by duct management - primary transplants in USA.

ISLET TRANSPLANTATION

The first serious attempts to isolate islets were begun in 1969 when Dr. Paul Lacy described the method for the isolation of islets from rodent pancreata and shortly thereafter also demonstrated successful islet transplantation in rodents[5]. Transplantation of islets, usually placed under the capsule of the kidney, was effective in reversing experimental diabetes in rodents[6].

Human pancreata are considerably different from those of rodents and for the next 20 years there were multiple efforts to isolate human islets. Multiple kitchen tools (blenders, food processors, etc) were tried in an attempt to disrupt the pancreas and thus release viable islet tissue. None were successful. As it turns out, viable islet isolation was finally successfully accomplished without mechanical disruption of the pancreas. Dr. Carmillo Ricordi and his colleagues were able to do so using enzyme disruption of pancreatic tissues. For the details of this and the history of islet isolation I refer you to Dr. Ricordi's Lilly Lecture which was just published in Diabetes[7]. In 1988, they reported[8] an automated method for the isolation and purification of human pancreata. This method, with a few small refinements, is what for the most part is used for all islet preparations (Figure 7).

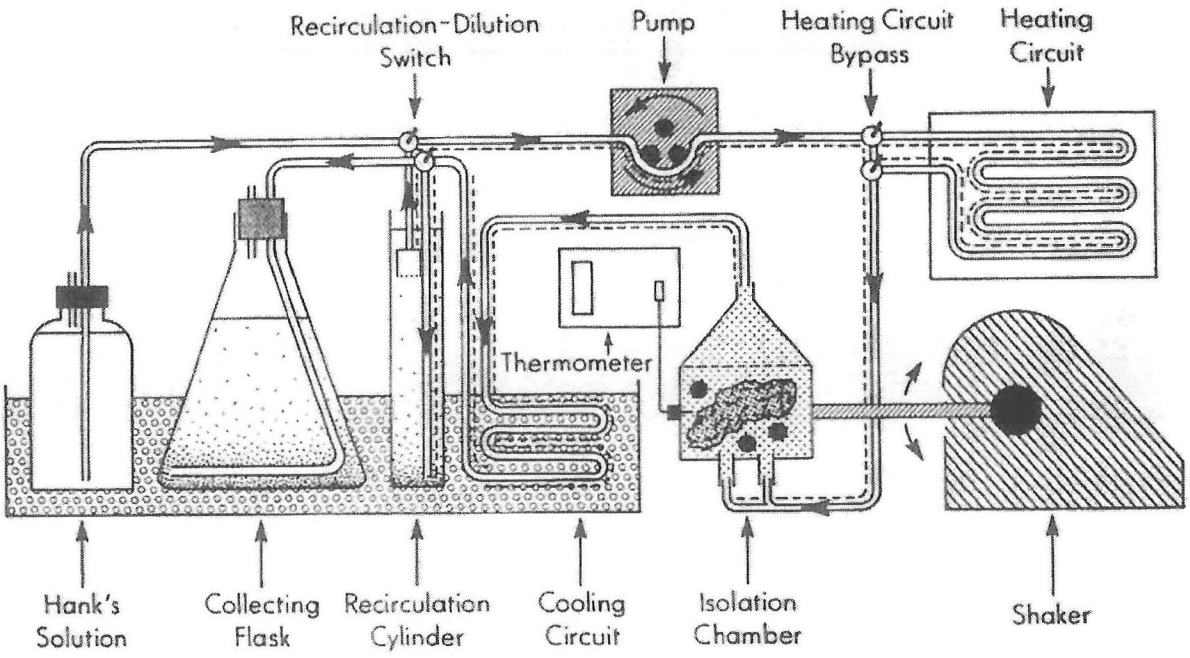


Figure 7: Automated Method for Isolation of Human Pancreas Islets.

Briefly, the human pancreas is dissected from the duodenum from a brain dead multiple organ donor. The main and accessory ducts are identified, clamped and divided. The main pancreatic duct is cannulated and an enzyme blend[9] that includes collagase is infused which

distends the pancreas. The pancreas is then placed in a chamber where a continuous digestion process proceeds to reduce the organ to fragments. A heating circuit activates the enzyme in the chamber while continuous fluid flow through the chamber allows the islets that are progressively released to be collected. Cooling and dilution protects the islets leaving the chamber from further enzymatic destruction. The pancreatic cell clusters are collected in separate containers while the fibrous network of ducts is retained. The final purification step utilizes density gradients to separate the small islet fractures. Recently, specialized cell processors like the COBE 2991 centrifuge have been used for the purification step[10]. With recent improvements the method, approximately 400,000 – 600,000 islets can now be isolated from a single human pancreas. After isolation the purified islets are infused into the portal vein by percutaneous catheterization. In the end, the total volume to be infused into the portal vein should be no more than 5 to 7 mls. Larger volumes of unpurified pancreatic digest when infused into the portal vein or spleen have led to portal hypertension, hepatic or splenic infarction, disseminated intracellular coagulation, splenectomy and even death.

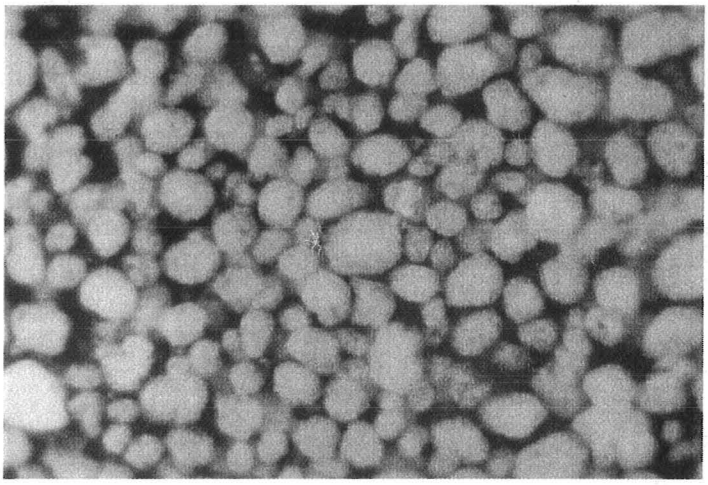


Figure 8: Isolated islets.

In 1992 Ricordi, et al[11] reported human islet isolation and allotransplantation in 22 patients. Of these 22 individuals, 6 had diabetes and end stage renal disease and were having a simultaneous kidney transplant as well. Immunosuppression was with FK506 (tacrolimus) plus steroids. Some of the non-diabetic individuals who had undergone complete pancreatectomy for malignancy (6/10) did not require insulin treatment for 5 to greater than16 months. None of the diabetic patients became insulin independent although decreased insulin requirements and stabilization of their diabetes was observed. Subsequently, other groups reported their results using islet transplantation[12,13,14,15].

In July 2000 a "breakthrough" in islet transplantation was reported in the New England Journal of Medicine as well as in the print and electronic media[16]. This paper reported the successful islet transplantation in seven consecutive individuals with Type 1 diabetes with normal renal function. The decision to offer transplantation to these individuals was entirely based on poor glycemic control especially a history of severe and recurrent hypoglycemia. At the time the paper was written, all seven were insulin independent and had remained so for a median follow-up of 11.9 months (4.4-14.9). However, all islet transplant recipients required islets from at least 2 donors and one required three in order to achieve insulin independence.

In this study, islets were isolated by the "Ricordi method" i.e. ductal perfusion with collagase, digested and purified in a xenoprotein free medium and transplanted immediately using a percutaneous transhepatic portal infusion using a gravity feed. The authors made a big deal about the use of a "glucocorticoid-free" immunosuppression regimen consisting of sirolimus, tacrolimus and dacluzimab.

Ryan et al[17] extended the group's observations. In this paper, they reported the results of islet transplantation in 12 individuals with Type 1 diabetes with normal renal function and soon thereafter in 17 patients[18]. In the paper from 2002, the Edmonton group reported the effects of 54 islet transplantation procedures in 30 subjects. Followup was available in 17. All 17 became insulin independent after a minimum of 9,000 islets per kg. The indication for islet transplantation was "brittle" diabetes or problems with hypoglycemia. The choice to transplant was based on poor glycemic control and not because immunosuppression was to be given for some other reason.

Two or three islet infusions were done per patient. After a median of 20.4 months (longest being 34.2 months) all patients had sustainable insulin production. HbA1c decreased from 8.2 ± 0.4% to 6.1 ± 0.8% (Figure 9).

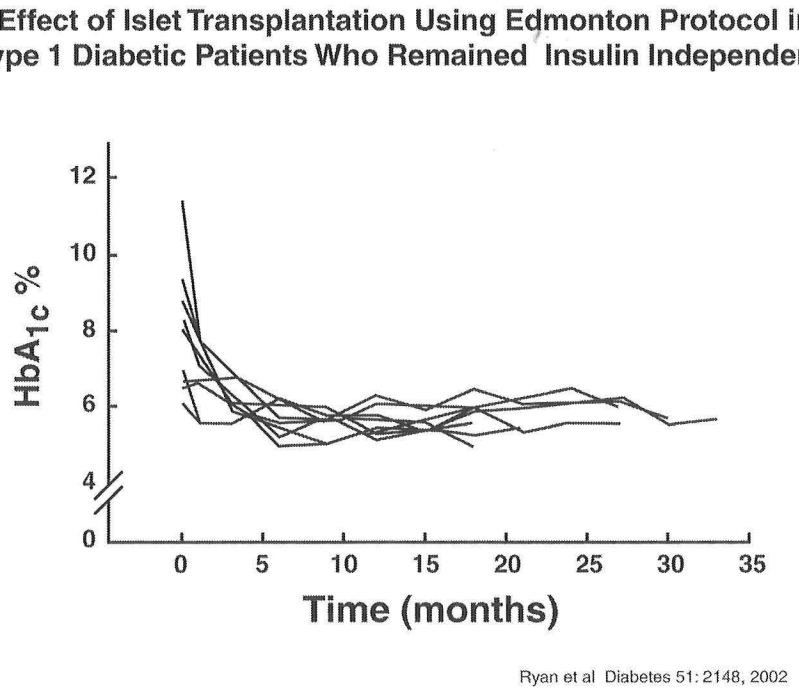
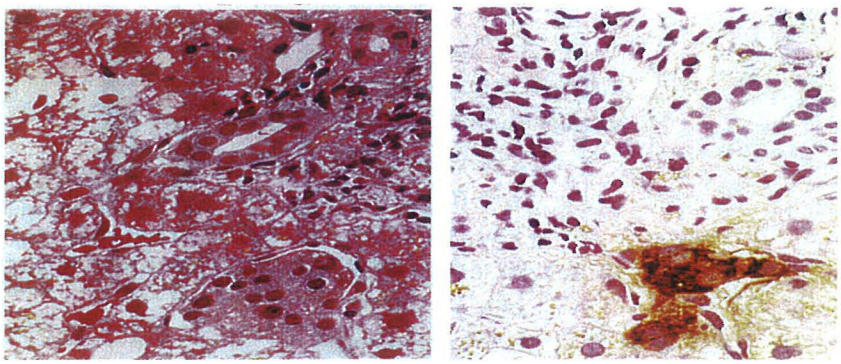


Figure 9: The effect of islet transplantation in type 1 diabetic patients.

As of January 2002, of the 17 subjects 11 remained insulin independent and of these 11 two are on oral hypoglycemic agents.

Figure 10A[17] shows islets in the liver of one of the islet transplant recipient obtained by liver biopsy. Note that the islet is located in close proximity to the portal triad and Figure 10B[17]

shows immunohistochemistry staining with an insulin antibody to confirm the presence of insulin containing cells.



A B

Figure 10: Liver biopsy from a patient following islet transplant

In the case of islet transplantation, more is better. Figure 11 shows the effect of the mass of islets transplanted[18]. The need for exogenous insulin is directly proportional to the mass of islets transplanted. Insulin requirements go down after the second and third transplantation. Thus, the greater the mass of islets transplanted, either by better isolation techniques or by doing second or third transplants, the more likely the patient will become insulin independent.

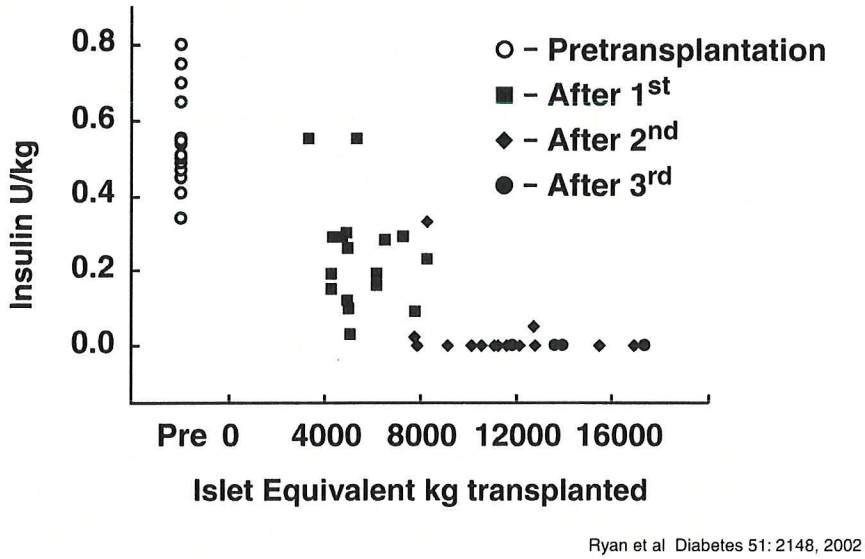


Figure 11: Exogenous insulin use post islet transplantation in relation to the number of islets transplanted.

At the recent Annual Meeting of the American Diabetes Association in June 2003, Dr. Shapiro reported his most recent updated results[19]. To date, they have performed 91 percutaneous transhepatic portal infusions of 378,032 ± 130,000 islets equivalents (IEq) in 48 Type 1 diabetic patients who ranged in age from 24-64 years of age (average 41.5 years). Islets were prepared using controlled perfusion, "Ricordi digestion" and COBE purification.

The "Edmondton Protocol" (steroid free) was used for immunosuppression. The results are as follows:

- Insulin independence
  - 84% at 1 year (n=30)
  - 64% at 2 years (n=15)
- C-peptide sustained in 87.2%
- 4 individuals lost c-peptide secretion
  - 2 to recurrent autoimmunity
  - 1 to rejection
  - 1 to "islet exhaustion"
- In insulin independent subjects
  - HbA1c normalized
  - 8.0% pretreatment
  - 6.0% post treatment
- C-peptide stable for 3 years
  - Fasting - 2.3 ng/ml
  - Stimulated – 5.8 ng/ml

The following adverse effects were noted in Dr. Shapiro's patients: liver bleeds requiring transfusion (11%), hemobilia (2%), severe neutropenia (<500 x 103) (5%), branch portal thrombosis (2%), transient rise in LFT's (49%). Mouth ulceration, diarrhea and elevated cholesterol levels were "common". No deaths, malignancy, or CMV disease was noted. In addition to the adverse effects they reported, no one knows the term consequence of long term islet residence within the liver. Markmann et al,[20] reported the development of periportal hepatic steatosis noted by MRI, apparently induced by the local secretion of insulin with the liver. Apparently this finding was only noted in individuals with a functioning islet graft as measured by insulin independence. The authors feel that using post-transplant MRI may be a way to follow the status of an islet graft. I wonder what effect long term periportal steatosis will have on liver function. Could this, over the years, lead to hepatic cirrhosis?

"STEROID FREE" IMMUNOSUPPRESSION

The immunosuppression protocol used by the Edmonton group sounds on the surface as if it is a sort of "soft" immunosuppression given that corticosteroids are not used. But is not! For all of Shapiro's group's islet transplants, immunosuppression was initiated immediately before transplantation. They used daclizumab (Zenapax®) a monoclonal antibody against the interluetin-2 receptor, given at a dose of 1mg/kg every 14 days, sirolimus (Rapamune®) given 0.2 mg/kg as a loading dose followed by 0.1 mg/kg /day to achieve a target trough level of 12-15 ng/ml. The use of sirolimus allowed for a relatively "low dose" of tacrolimus (Prograf®) to be used. Tacrolimus was given at a dose of 2-4 mg BID to achieve a target trough level of 3-5 ng/ml.

The reason given for the choice of the "steroid-free" immunosuppression regimen was that older immunosuppressive regimens using anti-lymphocyte globulin combined with cyclosporine, azothioprine and glucocorticoids when used in previous attempts at islet

transplantation resulted in only 8.2% frequency of insulin independence at one year[21]. This failure of islet transplantation to be successful in terms of resulting in an insulin independent state was blamed on the diabetogenic effects of cyclosporin and glucocorticoids.

It turns out that tacrolimus has considerable effects on the beta cells[22] (Figure 12). These figures show the histological changes in the pancreas of rats that occurs with the administration of tacrolimus. Vacuolation and degranulation of islets can be seen after 10 mg/kg of tacrolimus (Prograf®) (Panel A) or 50 mg/kg cyclosporin (Panel B). With discontinuation of both immunosuppression agents the pathological findings are reversed (Panels C and D).

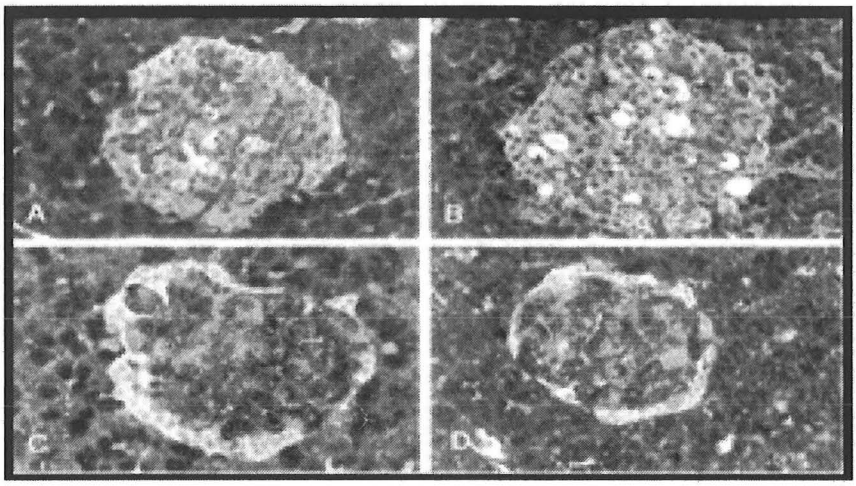


Figure 12: Morphological changes in islet cells in Tacrolimus/Cyclosporin treated rats.

The clinical correlation of the above study in rats was recently published by Cho[23]. They reported the frequency of post renal transplant diabetes in a group of 21 Korean individuals undergoing renal transplantation for non-diabetic renal disease. None had diabetes prior to the transplant. Immunosuppression was tacrolimus based plus additional methyl-prednisolone. Of the 21 individuals, 52.4% had diabetes at 1 month and 57.1% had it by 6 months. When comparisons were made with the individuals who did not develop post transplant diabetes, insulin secretion was markedly suppressed and they also had a greater degree of insulin resistance. The authors of this paper feel the use of tacrolimus was responsible for the high frequency of the development of post-transplant diabetes. Others have found that tacrolimus reduces insulin secretion in pediatric renal transplant recipients, an effect which is reversible by reducing the dose[24]. There seems to be little or no effect on beta-cell function from sirolimus[25] or daclizumab. A more complete discussion of the effects on immunosuppressive agents or glucose and insulin metabolism can be gotten from Dr. Pablo Mora's recent Grand Rounds[26].

The results of Dr. Shapiro's work have created great interest in islet transplantation as a treatment of Type 1 diabetes. Patients and some physicians have the perception that the diabetes will be miraculously cured. I feel they are under the mistaken belief that there is no danger to either the transplantation procedures or to the life-long immunosuppression regimen that is needed. All that said, Type 1 diabetic patients are lining up for the procedure. There are multiple centers (at least 50) worldwide now attempting islet transplantation with 20 in the United States. Of these 20, 14 have an IND to study islet transplantation and 10 are active. Others are in the process of planning programs.

EFFECT OF PANCREAS TRANSPLANTATION ON THE CHRONIC COMPLICATIONS OF DIABETES

In has been difficult to show changes in diabetic complications as a result of pancreas transplantation. The reason for this should be easily understood. Most individuals who receive pancreas transplants do so in combination with kidney transplantation for chronic renal failure due to diabetic nephropathy. Many of these individuals already have complications of their diabetes and it might be difficult to show improvements. With respect to diabetic retinopathy many individuals who receive kidney and pancreas transplantation already have severe proliferative retinopathy and may have already received laser therapy. It is probably difficult to show improvement after laser treatment. There are some data on the effect of pancreas transplantation on the progression of diabetic retinopathy, however. There are two studies[27,28] that evaluated the progression of diabetic retinopathy after pancreas transplantation. They showed that there was no advantage with respect to progression of diabetic retinopathy from the beneficial euglycemia achieved with pancreas transplantation. They compared retinopathy progression in the pancreas transplant group to that of individuals who received only a kidney transplant[28] or to a control group of Type 1 diabetic individuals whose pancreas graft failed[27]. Schmidt et al[29] actually reported progression of diabetic retinopathy despite the euglycemia achieved by pancreas transplantation.

There are also some data on the effect of pancreas transplantation on the progression of diabetic neuropathy. Kennedy, et al[30] evaluated neurologic function by clinical examination, nerve conduction studies and autonomic function tests in Type 1 diabetic individuals before and after successful pancreas transplantation. Sixty-one subjects were studied before and after 12 months after transplantation, 27 again after 24 months and 11 again after 42 months. A "control group" of Type 1 diabetic individuals treated with exogenous insulin underwent the same studies at similar intervals. Forty-eight were tested before and after 10 months, 21 again after 24 months and 12 again after 24 months. Figure 13 shows the results. In the control group, neuropathy tended to worsen during the followup period. In contrast, in the patients who received a pancreas transplant the neuropathy tended to improve. There was significant improvement in the motor and sensory indices 12 months after transplantation and in the sensory indices 24 months after transplantation. The other measures improved slightly at these times and also at 42 months. The finding of a "non-statistically significant" change at 24 and 42 months may reflect the smaller number of individuals studied at those time points.

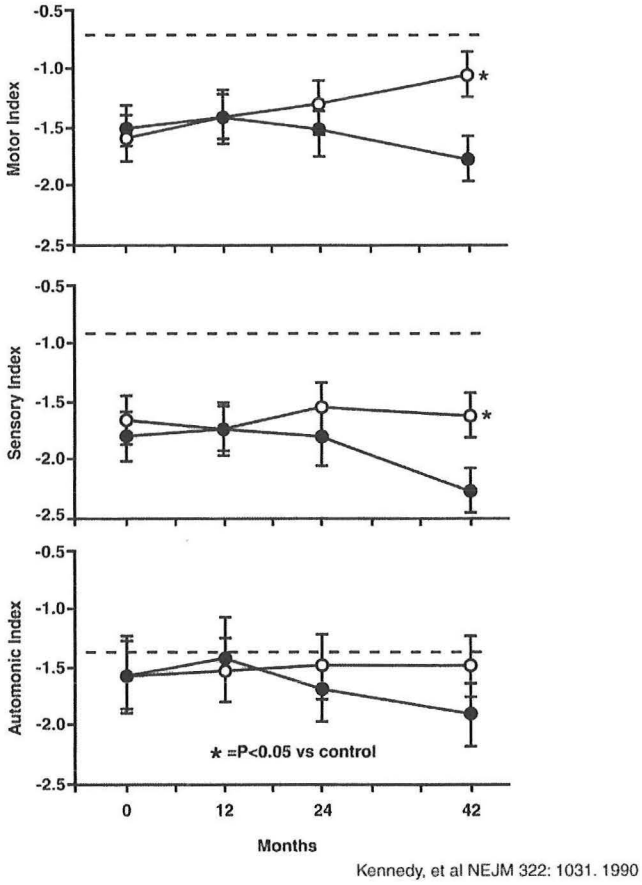


Figure 13: Effect of pancreatic transplantation on diabetic neuropathy.

In another much smaller study, Martinenghi et al[31] studied 5 Type 1 diabetic patients who received a SPK transplantation in whom the pancreas graft failed after 2 years but the kidney graft remained functional for at least 2 additional years. Electrophysiological tests were done over time. Figure 14 shows that nerve conduction velocity improves following pancreas transplantation but deteriorates again once the pancreas graft fails.

Effect of Pancreas Transplantation on Diabetic Neuropathy

	Baseline	2 years post transplant	Pancreas graft failure	2 years post pancreas graft failure
	M/sec			
Sural Nerve	37.6 ± 2.9	39.8 ± 4.0	39.4 ± 6.6	38.0 ± 7.8
Peroneal Nerve	31.2 ± 8.7	37.3 ± 8.3	39.0 ± 8.1	37.2 ± 5.8
Ulnar Nerve	49.1 ± 4.9	52.1 ± 5.9	51.9 ± 7.0	49.0 ± 8.7

Martinenghi, et al Diabetologia 40: 1110, 1997

Figure 14: Effect of pancreatic transplantation on diabetic neuropathy.

Others have seen similar beneficial effects on diabetic neuropathy following pancreas transplantation[32,33,34,35].

Dr. Dawidson has had considerable experience in pancreas transplantation at UT Southwestern during his previous tenure here.[35,36,37] I feel fortunate to have been a part of the transplant team. These pancreas transplants were almost all done in combination with kidney transplantation although Dr. Dawidson also attempted fetal islet transplantation[38].

One of the most noticeable results to me of successful pancreas transplantation was the improved quality of life in those individuals made insulin independent by pancreas transplantation that I helped care for and whom I saw in follow-up. Gross and Zehner[39] studied health states and quality of life outcomes of 131 patients who were 1 to11 years post transplant. Patients were compared based on the current status of their pancreas graft, i.e., whether or not their grafts were successful in maintaining an insulin independent state. For this study, quality of life was defined as these individuals perception of well being and the ability to function in six areas; physical and mental health, social function, role (work and home) function, overall health perception and physical pain. Patient self-report questions from the medical outcome study were used to provide a score scaled from 0-100. Health states were assessed by sick days, hospitalization and emergency room visits. Patients with a successful graft (n = 65) reported significantly more positive health perception (51.9 vs. 28.9), less pain, (33.9 vs. 45.3) and a greater ability to function socially (84.9 vs. 71.3) than did patients whose grafts were not successful (n = 64). In addition, patients with successful grafts rated their ability to perform routine activities as nearer to normal and were more likely to view themselves healthier since the pancreas transplant than were patients whose pancreas grafts were not successful. Others have seen similar positive outcomes on quality of life following successful pancreas transplantation[40].

EFFECT OF ISLET TRANSPLANTAION ON THE CHRONIC COMPLICATIONS OF DIABETES

There are a few data on the effects of islet transplantation on the chronic complications of diabetes. Fiorina, et al[41] studied the effect of islet transplantation on patient survival and diabetic vascular complications. Thirty-seven Type 1 diabetic kidney transplant patients underwent islet transplantation (KI). Diabetic kidney-pancreas (KP) transplant patients (n=162), diabetic kidney only transplant patients (KD) (n=44) and 196 uremic diabetic individuals on hemodialysis (HD+DM) constituted the control groups. Patient survival was similar in the kidney islet and kidney pancreas group and higher than in the hemodialysis patients. Patients experience long-term islet function (n=24) showed a better survival (100%, 100%, 90%) than those who lost islet function (n=13) (84%, 75%, 40%) at 1, 4, and 7 years respectively (Figure 15). The cardiovascular death rate for the kidney islet group (18%) was the same as the kidney transplant alone (19%) but when only the individuals whose islet grafts were still functioning were considered it was lower (5%).

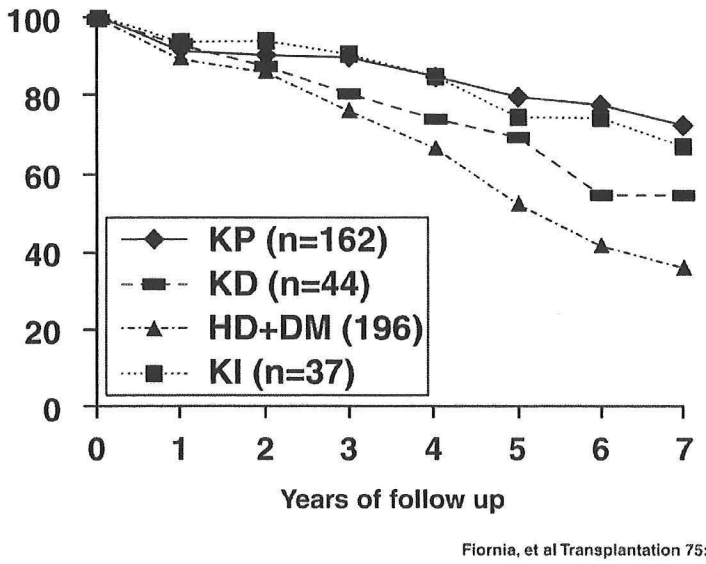


Figure 15: Patient survival in four groups of diabetic patients (KP – kidney-pancreas transplantation; KD – Diabetic kidney-only transplantation; HD+DM – diabetic individuals on hemodialysis; KI – kidney-islet transplantation).

In a companion paper Fiorina, et al[42] showed considerable differences in outcomes between the successful islet-kidney transplantation and the unsuccessful ones. Those with successful grafts had better endothelial dependent dilution, higher basal nitric oxide levels, lower levels of von Willabrand factors and d-dimer fragments. These authors concluded that successful islet transplantation improves survival, cardiovascular and endothelial function in Type 1 diabetic kidney transplant patients.

Meyer et al[43] showed that successful intraportal islet transplantation does not restore hypoglycemia-induced glucagon secretion, but does improve the response of other counterregulatory hormones and hypoglycemic warning symptoms even in long standing Type 1 diabetes.

OTHER BETA CELL REPLACEMENT THERAPY

It is clear that the use of either pancreas or islet transplantation as a viable treatment for Type 1 diabetes is limited. There are millions of Type 1 diabetic individuals worldwide. In the case of pancreas transplantation there can be only one recipient for every donor. In the case of islet transplantation it takes at least two donors for each recipient and sometimes three. This is a "supply side problem". Thus, other means of islet replacement therapy must be developed.

To me, one of the most interesting attempts at islet replacement therapy is the use of gene therapy to induce islet neogenesis. Kojima and his colleagues at Baylor University Medical Center in Houston[44] attempted to induce islet neogenesis in the liver as a strategy for the treatment of diabetes in mice. They first attempted to use helper-dependent adenovirus (HDAD) to deliver the pancreatic duodenal homeobox-1 gene *Ipf-1* also known as *Pdx-1* to streptozotocin

treated diabetic mice. The homeobox-1 gene is required for normal pancreatic and foregut development. Administration of HDAD-*Ipf*-1 partially reverses the diabetes in these mice, but they developed fulminant hepatitis. The diabetes of streptozotocin mice was partially reversed by HDAD mediated transfer of *Neurod* also known of Beta-2. *Neurod* is a basic helix-loop-helix transcription factor down stream of *Ipf*-1. *Neurod* is required for proper morphogenesis of pancreatic islets, and mice lacking *neurod* die of severe diabetic ketoacidosis shortly after birth. The diabetes in these mice was completely reversed when a B-cell stimulating hormone, betacellulin (*btc*), was added to the gene construct (i.e. HDAD *neurod-btc)* without producing hepatitis. Treated mice were healthy and normoglycemic for 120 days, the duration of the experiment (Figure 16). Within the liver of animals transfected with this gene construct, insulin and other islet specific transcripts can be found. Immunochemistry detected the presence of insulin, glucagon, pancreatic polypeptide and somatostatin producing cells organized into islet clusters. Immunoelectron microscopy showed typical insulin containing granules (Figure 17).

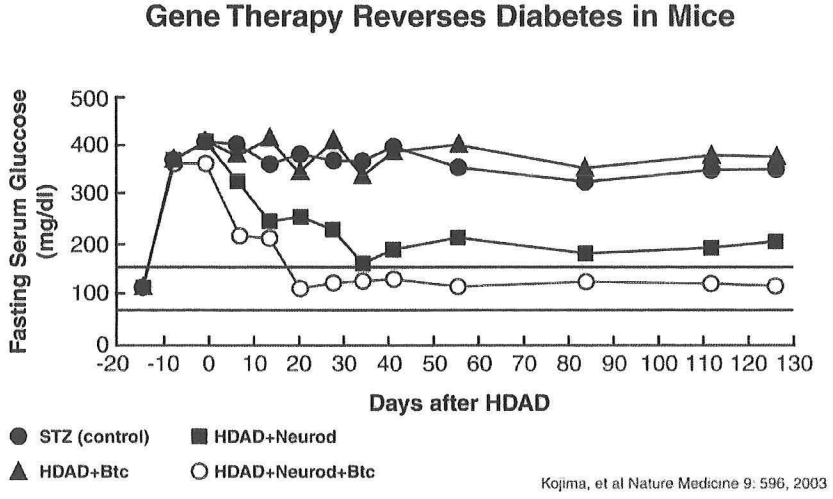


Figure 16: Results of gene therapy in diabetic mice.

Gene Therapy Reverses Diabetes in Mice

Density Distribution of Insulin-Positive Cells in the Liver

Treatment	Single Insulin-Positive Cells	Islet-Like Clusters	
	Cells/mm2	Clusters/mm2	Insulin-Positive Cells per cluster
STZ	0.08+0.03	ND	—
STZ+Btc	0.12+0.01	ND	—
STZ+Neurod	5.10+1.32*	0.0670+0.0150*	30.6+8.6
STZ+Neurod-Btc	5.23+1.05*	0.1100+0.0120*	49.2+6.1

* = p<0.05 vs STZ

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Figure 17: Distribution of insulin-positive cells in the liver after gene therapy in diabetic mice.

A more complete discussion of gene therapy as a potential treatment for diabetes with all of its nuances may be found in the review by Xu, et[45].

A complete description of potential other sources for Beta-cell replacement therapy is outside the scope of this discussion. Several excellent reviews may be found[46,47,48]. Briefly, other sources include the use of non-human Beta-cell or xenotransplantation, non-beta cells engineered to perform beta-cell function, islet regeneration from residual endogenous endocrine tissue or from sub-therapeutic islet or fetal islet transplants. There are regenerative factors that can induce endocrine cell development in vivo (also in vitro). Such candidate regeneration factors include products of the *reg* gene family[49], islet associated neogenesis protein (INGAP)[50], augmenter of liver regeneration (ALR)[51] and glucagon-like peptide-1[52]. In addition, there are multiple growth factors that are being studied such as epidermal growth factor (EGF)[53] insulin like growth factors-1 (IGF-1)[54] transforming growth factor-α (TGFα)[55] and many others[56]. Other potential sources could come from stem cells induced to differentiate into beta cells, the in vivo expansion of primary beta cell cultures or a expansion of fetal islet and islet-like clusters with culture techniques. Of interest, much of the leading work done with respect to the manipulation of non-beta cells into insulin secreting cells has been done by Dr. Christopher Newgard, who recently left UT to continue his work at Duke. Dr. Newgard was the recipient of the Lilly Award in 2002[56].

CONCLUSIONS

Pancreas transplantation is now an accepted form of medical therapy in Type 1 diabetic patients, especially when immunosuppression is required for some other life saving procedure. This is the case when SPK or PAK transplantation is done. What, in my opinion, remains most contentious is PTA. In these circumstances, the surgical procedure and subsequent life-long immunosuppression are considered a better treatment alternative for Type 1 diabetes than what we already have. The treatment of diabetes has advanced in recent years with the development of insulin pumps, insulin analogues, and many new and accurate methods of monitoring blood glucose levels, either intermittently or even on a continuous basis. Type 1 diabetes is a manageable affliction, although to be honest, in some Type 1 diabetic individuals the treatment is difficult. It is a 24 hour a day process often punctuated with frequent severe and usually unexpected hypoglycemic episodes.

All of this said, I am still not certain that the risk of a major surgical procedure and of immunosuppression are less onerous than the present treatment for the disease. The following very interesting study, illustrates my concerns for the transplantation of the pancreas in the absence of any other need for immunosuppression. Venstrom et al[57] compared the risk of post-pancreas transplant death relative to that of patients still on the "transplant wait list". They felt that the "transplant wait list" group approximates those given a transplant since cadaveric pancreas allocation is based primarily on blood type and wait list time and not disease severity. They analyzed the United Network for Organ Sharing (UNOS) database from January 1, 1995 through December 31, 2000, during which time 11,926 individuals were listed for a pancreas transplant and 6402 received a transplant. Patients were subdivided by anticipated procedure:

PTA, PAK, and SPK. The results were striking. They found that SPK results in a long-term patient survival advantage as compared to those waiting for the transplant. The overall transplant recipient mortality, relative to patients awaiting the same procedure over 4 years, was 2.4 for those receiving a PTA and 1.6 for PAK recipients. These data suggest that while the relative risk of dying decreases after the immediate post-transplant period, it appears that mortality is higher for those receiving either PTA or PAK as compared to Type 1 diabetic individuals awaiting these same procedures. Transplant patients' survival rates at 1 and 4 years were 95.8% and 84.0% for PTA and 95.7% and 82.5% for PAK. Simultaneous "transplant wait list" patient survival rates were 98.5% and 95.9%. I agree with these authors' conclusions that in diabetic patients with normal renal function more work is needed to identify individuals who are appropriate for pancreas transplantation.

In most cases all islet transplantation has been done in diabetic individuals with normal renal function, although some patients have received an islet transplant after receiving a successful kidney transplant. Most islet transplants are now done in an attempt to obtain insulin independence and euglycemia in individuals with difficult to manage Type I diabetes. Despite my feelings about Type 1 diabetes being a treatable disease, for the most part all islet transplants are now being done as part of an experimental protocol. Thus, most islet transplantations are done in order to advance science rather than only as a treatment for Type 1 diabetes. Clearly, this work must continue. More importantly, work to find alternative sources of insulin secreting tissue must go forward given the logistical problem of using human tissue for such purposes.

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