PANCREAS TRANSPLANTATION IN DIABETES MELLITUS

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In 1889 Minkowski found that extirpation of the pancreas in dogs resulted in diabetes. Now it is one century later and we are trying to treat diabetes by reversing that operation, transplanting a functional pancreas into patients with diabetes. In this age of transplantation, aided by improved surgical techniques and immunosuppressive drugs, this approach has become a realistic option. However the relative benefits, risks and costs need to be considered in determining the effectiveness of this approach in the management of type I diabetes mellitus.

Since the discovery of insulin in the 1920's, administration of exogenous insulin has been the mainstay of treatment for insulin dependent diabetics. However, despite the best efforts of the patients and physicians caring for them it is often quite difficult to attain control of the blood sugar to a comparable degree as the normal pancreas. Transplantation technology provides a means to provide a cellular source of insulin that would hopefully be regulated and secreted in a physiologic fashion. Presumably this would result in optimal control of fasting and postprandial glucose levels.

PANCREAS TRANSPLANTATION

The first attempt at surgical transplantation of the pancreas was in 1966 at the University of Minnesota (Kelly et al.1967). Two patients were reported with type I diabetes of long duration and renal failure in which simultaneous renal and pancreatic transplants were performed. In the first the body and tail of the donor pancreas were transplanted to the iliac fossa with vascular connections established with the iliac vessels. The pancreatic duct was ligated and the cut end of the pancreas oversewn. The renal graft was never functional; however, blood sugars showed a progressive fall in the absence of insulin for six days to a low of 133 mg/dl. At this point glucose levels began to rise and insulin was needed to control her diabetes. Ultimately the pancreas and kidney transplants were removed. The results of combined renal and pancreas transplantation in the second patient are shown in Figure 1. The entire pancreas and attached duodenum of the donor were transplanted to the iliac fossa with vascular connections to the iliac vessels and the bowel segment was formed into a pouch and exteriorized through a stoma. Following surgery there was a prompt reduction in blood sugars in the absence

of insulin administration. Eleven days later there was an episode of rejection with worsening renal function, increased amylase levels and mildly elevated fasting blood sugars. Increased doses of immunosuppressive agents and radiation helped control this episode and the patient maintained good glucose control without insulin. About two months post-transplant another rejection episode occurred and when increased amounts of steroids were administered the blood sugar rose to 236 mg/dl and insulin therapy was begun. Thus, although both of these patients exhibited apparent function of the pancreas graft, the success was short-lived and ultimately insulin therapy had to be reinstituted in both patients. Unfortunately this experience was similar to those of many institutions in the first decade of pancreas transplants. Of 64 pancreas transplants attempted in this period, none functioned for greater than 1 year. However beyond this point greater success was attained with improvements in immunosuppressive drugs and surgical techniques.

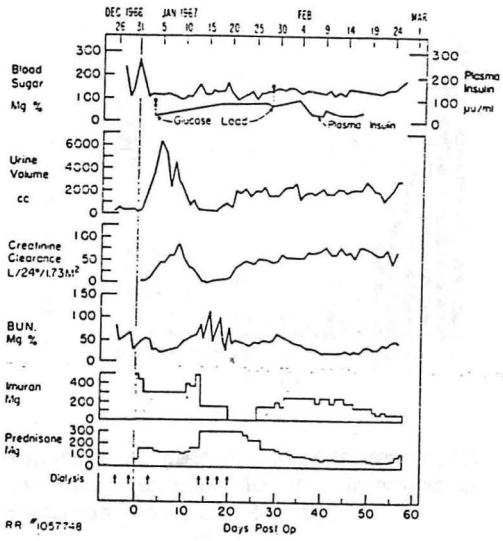

Figure 1 Pancreatic and renal function following simultaneous kidney and pancreas transplantation in patient #2 at the University of Minnesota in 1966.

The results of all centers in the world performing pancreatic transplants is maintained by the International Pancreas Transplant Registry at the University of Minnesota (Sutherland et al.1989; Sutherland and Moudry-Munns, 1990). The number of pancreas transplanted performed per year is shown in Figure 2. In the period from 1966 through 1977 less than 10 pancreas transplants were performed per year and many different institutions attempted the surgery. The experience at any one institution was rather

limited. Beginning in the late 70's there has been a progressive rise in the number of transplants with more than 300 transplants per year having been performed since 1986. The success of these transplants for each era is indicated in Figure 3 where patient and graft functional (insulin-independent) survival rates are shown. In the most recent report of the registry in 1990 (Sutherland and Moudry-Munns, 1990) a total of 2004 transplants were reported. More than one-third of these pancreas transplants had been performed in the last two years. There were 835 grafts functioning at the time. The longest is still functioning after 11 years and 627 have functioned at least

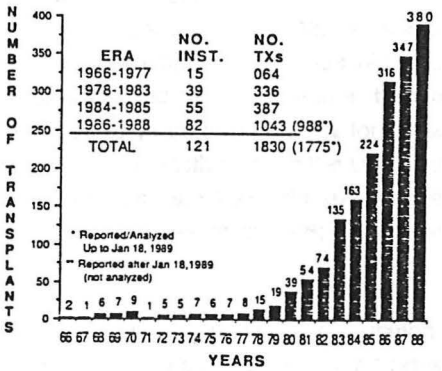

Figure 2 Number of pancreas transplants by year reported to the International Pancreas Transplant Registry.

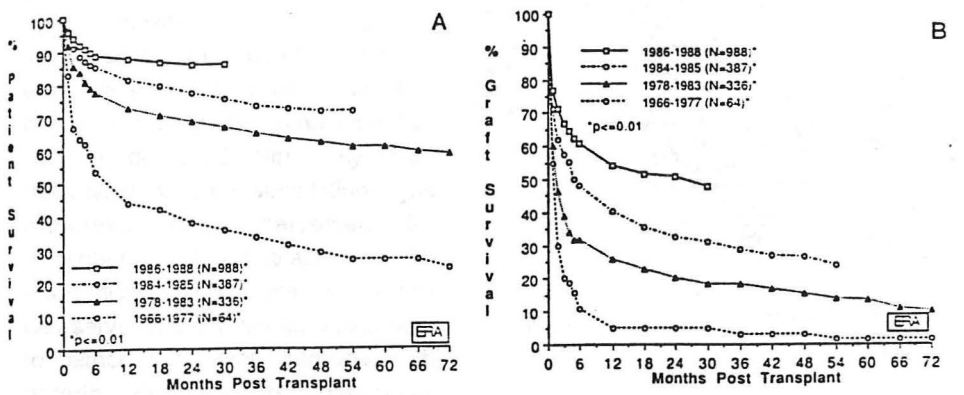

Figure 3 Patient (A) and graft functional (insulin-independent) survival rate curves for pancreas transplant cases.

one year. Analysis of the cases from 1984-1989 (n=1604) shows that the overall 1-year graft function and patient survival rates were 52% and 85%, respectively. Similar rates were observed in transplants performed in North America and Europe. Almost half of the patients receiving pancreas transplants were between 30 and 40 years old and slightly more than half had had diabetes between 30 and 30 years before transplantation. Only 2% had had diabetes less than 10 years and only 1% for more than 40 years. The individual experiences of several different institutions in the U.S. and Europe have also been reported independently and are consistent with the experience reported through the registry (Sutherland et al.1989; Sollinger et al.1988; Cosimi et al.1988; Wright et al.1989)

A variety of different procedures and practices are utilized in pancreatic transplantation. The pancreas can either be transplanted whole or as a segment. Graft survival rates do not differ between these two techniques. Various surgical procedures have been used that differ in the placement site, method of vascular anastomosis and drainage of the exocrine secretions. Although open drainage into the peritoneum was used early on, other procedures are preferred in most transplant centers currently. The pancreatic duct can be occluded with a synthetic polymer prior to transplantation. The pancreas when harvested for transplant is usually attached to the duodenum. This piece of intestine can serve as a conduit for attachment to either the small intestine with enteric drainage of pancreatic secretions or the bladder for urinary drainage. Figure 4 illustrates the

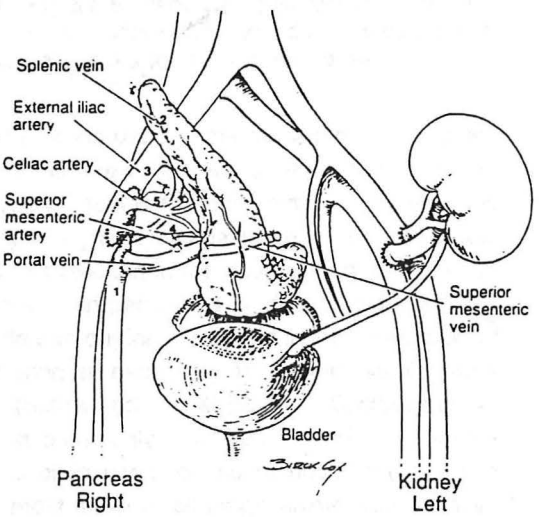

Figure 4 Surgical placement of pancreas and kidney grafts in recipient.

placement of pancreas and kidney grafts in a combined transplant with urinary drainage. At present bladder drainage appears to be the preferred method at most U.S. transplant centers. The urinary drainage of exocrine secretions offers the opportunity to monitor graft function by following urinary amylase. The graft function rate according to duct management categories from the pancreas transplant registry is shown in Figure 5. Preservation time of the graft does not appear to present a problem. Using newer solutions, such as UW solution, preservation times of up to and exceeding 24 hours result in successful grafts.

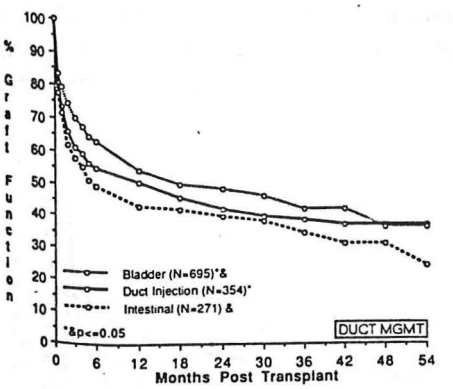

Figure 5 Pancreas graft functional survival rates according to duct management categories for 1984-1988 cases.

Immunosuppression routines consist of the drugs used in the management of kidney grafts, especially since many of the transplants are combined kidney/pancreas grafts. However, in transplants in patients with type I diabetes mellitus immunosuppression is necessary not only to prevent rejection due to graft incompatibilities, but also to deal with the underlying autoimmune process that resulted in the development of diabetes. When segmental pancreas transplants have been performed in identical twins without the use of immunosuppression, the insulitis that originally resulted in the destruction of the islets is reenacted. Immunosuppression is necessary to prevent autoimmune destruction of the transplanted islets (Sutherland et al.1984). Cyclosporin A, azathioprine and prednisone are the most commonly used regimen with Minnesota Antilymphocyte Globulin (ALG) and OKT3 often used for the management of acute rejection episodes. This regimen is the most effective although animal studies have suggested that cyclosporin can be directly toxic to islets (Hahn et al.1986). HLA mismatches at the A and B loci do not appear to affect graft function survival, a comparable survival rate noted if there were two or fewer mismatches compared to

more than three mismatches. In contrast, mismatches at the HLA DR loci do appear to affect graft survival. With no mismatches at the DR locus 63% of the grafts were functioning at one year whereas two mismatches resulted in only 49% of the grafts functioning after a year (Sutherland and Moudry-Munns, 1990).

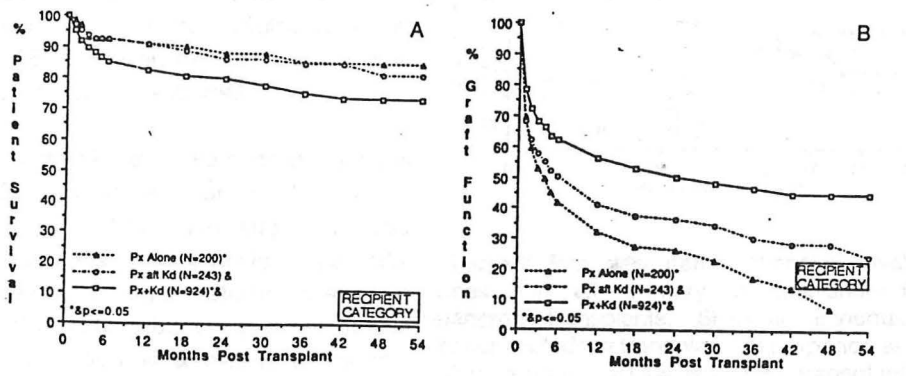

Figure 6 Patient (A) and pancreas graft (B) functional survival rates for 1984-1988 cases, for recipients who received a simultaneous pancreas and kidney transplant, a pancreas after a kidney transplant, or a pancreas transplant alone.

One factor that appears to be important for graft survival is the time of pancreatic transplantation relative to kidney transplantation. Some transplants have been performed in diabetics who do not have transplanted kidneys; however, most of the cases are in subjects who are receiving or have received a kidney in the past. As shown in Figure 6 the patient survival rate for simultaneous kidney and pancreas transplantation is slightly lower than in single organ transplants; however, a substantial difference is noted in the graft functional survival. The one year functional survival rate of pancreas grafts in nonuremic, nonkidney transplant recipients was 32% compared to 56% in grafts transplanted simultaneously with a kidney and 41% in pancreas transplanted to previous kidney graft recipients. Although these data are derived from the accumulation of worldwide experience in the registry, a similar difference is

observed at transplants within a single institution. Figure 7 shows the results of bladder-drained pancreas transplants for the different recipient categories (Sutherland et al.1989). This group has probably the most experience with isolated pancreas transplants in nonuremic patients (Sutherland et al.1988); however, the difference in graft survival was still apparent.

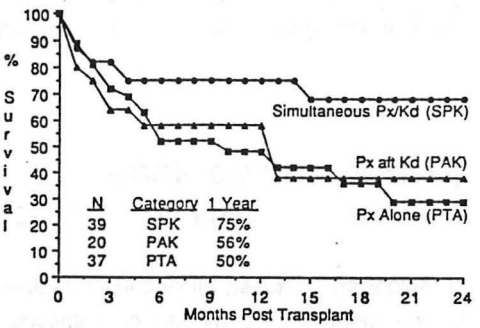

Figure 7 Pancreas graft functional survival rates for all primary bladder-drained pancreas transplants. SPK=simultaneous pancreas/kidney transplant; PAK=pancreas after kidney; PTA=pancreas transplant alone.

The reason for this difference in pancreas graft survival is not entirely clear. Although it has been suggested that simultaneous transplantation may offer some immunologic protection it appears that the primary benefit of simultaneous transplantation is a means to monitor rejection episodes. Monitoring pancreatic function for rejection is relatively insensitive. Hyperglycemia is a late manifestation. In recipients with urinary drainage a fall in urinary amylase excretion can accompany rejection episodes (Brattstrom et al.1989). The best indication is evidence of rejection of a simultaneously transplanted kidney. Therapy can be instituted and hopefully prevent progression of the rejection. In the absence of a simultaneously transplanted kidney it is not possible to use renal function to monitor for rejection. Therapy is instituted later when manifestations of pancreatic rejection are further advanced. This probably results in the greater loss of pancreatic function when only the pancreas is transplanted.

The source of most pancreas transplants is from cadaver donors. However, segmental transplants from living related donors has been accomplished. The effects of hemipancreatectomy on the donor regarding insulin secretion and glucose tolerance are moderate (Kendall et al.1990). None of the donors developed diabetes. Following an

oral glucose load the glucose response was greater than controls and the insulin response was decreased. The mean 24 hour glucose profile in the donors was slightly greater than controls, but did not exceed the normal range. Thus hemipancreatectomy does have some impact on pancreatic function but in the short term there is no apparent metabolic consequence.

EFFECTS OF PANCREATIC TRANSPLANTATION ON METABOLISM, DIABETIC COMPLICATIONS AND QUALITY OF LIFE

The most striking change observed in response to a successful pancreas transplant is near normalization of the plasma glucose concentration without the administration of exogenous insulin (Sutherland et al.1981; Morel et al.1991; Landgraf et al.1989). Accompanying this is a lowering of glycosylated hemoglobin levels to control levels.

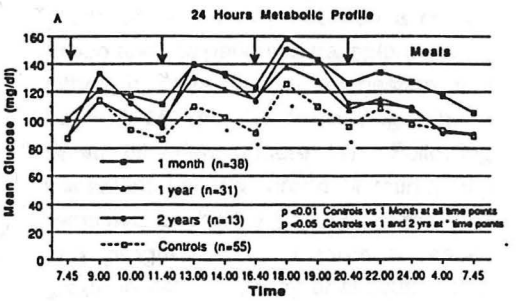

Figure 8 Mean 24-hr plasma glucose levels in recipients of bladder-drained pancreas transplants compared with nondiabetic control individuals.

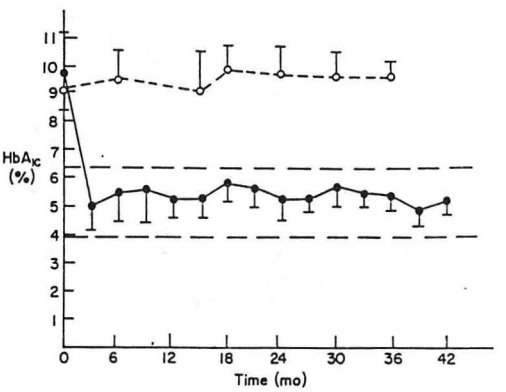

Figure 9 Hemoglobin A_{1c} in recipients of pancreas and kidney transplants (solid line) vs. recipients of kidney transplants (dashed line).

Examples of these patterns are shown in Figures 8 and 9. In most cases the venous drainage of the transplanted pancreas is into the systemic circulation rather than the portal circulation. This results in elevations in basal and stimulated insulin levels, presumably due to decreased clearance of insulin by the liver (Diem et al.1990). Although hyperinsulinemia has been suggested as a risk factor for coronary disease, it is not clear if this change in pancreas transplant recipients is important.

Effects of the long term complications of diabetes have also been examined. Comparing a group of insulin-treated patients neurophysiologic testing of peripheral motor, sensory and autonomic nerves showed a decrease in function over years of time, whereas in the transplanted group the neuropathy tended to remain stable or slightly improve (Figure 10) (Kennedy et al.1990). Symptomatic improvement in neuropathy in these patients does not always correspond to observed changes in nerve conduction velocities and other studies.

Studies examining the effects of transplantation on retinopathy are not entirely clear. No significant difference was noted in changes in visual acuity or grade of retinopathy between a control group and the pancreas transplant group, although there was a suggestion that beyond 36 months there might be a beneficial effect (Figure 11). Following transplantation the grade of retinopathy remained unchanged in 56% of the eyes and progressed to a more advanced grade in 44% (Ramsay et al.1988). In a study of pancreas transplant recipients from Munich, Germany the frequency of vitreous hemorrhage dropped from 69% pretransplant to only 24% after grafting (Landgraf et al.1989).

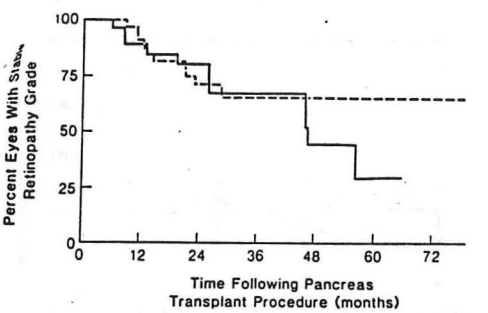

Figure 11 Rate of progression of retinopathy after transplantation in the study group (dashed line) and control group (solid line).

The effects on glomerular structure of transplanted kidneys was investigated in a group of patients with Type I diabetes mellitus who had undergone kidney transplantation and then received pancreas transplants (Bilous et al.1989). They had had diabetes for a mean of 19 years prior to kidney transplantation and the interval between kidney and pancreas transplantation was 1.0 - 7.2 years with a mean of 4.2 ± 2.1 years. Renal biopsies were obtained prior to pancreas transplantation and repeated 23 months to 10 years (mean 4.4 ± 2.4 years) after successful pancreas transplantation. The results are shown in Table I. With diabetic control secondary to secretion from the transplanted pancreas, glycosylated hemoglobins were in the normal range. Following pancreas transplantation there was no significant progression in glomerular volume or basement membrane thickness.

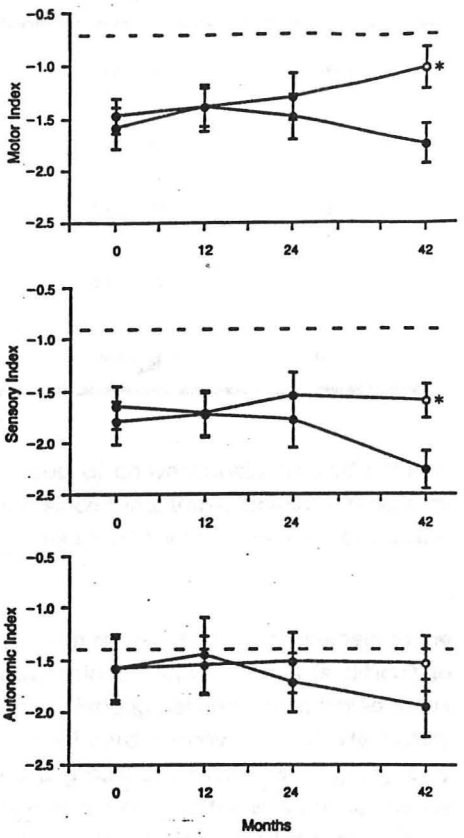

Figure 10 Indexes of motor, sensory and autonomic neuropathy in the study (o) and control (•) groups.

Table I. Analysis of renal biopsy specimens before and after successful pancreas transplantation.

	BASELINE	FOLLOW-UP	P value
Glycosylated Hemoglobin (%)	11.6±1.5	7.0±1.0	0.0003
Creatinine Clearance (ml/sec/1.73 m^2)	1.31±0.32	1.05±0.51	0.01
Mean Glomerular Volume (x 10^6 μm^3)	1.89±0.66	1.80±0.55	0.68
Glomerular Mesangial Volume Fraction ($\mu m^3/\mu m^3$)	0.17±0.05	0.19±0.07	0.38
GBM Thickness (nm)	454±93	499±124	0.07

As shown in Table II, when compared to a group of conventionally treated patients matched with the subjects for the length of time since renal transplantation, recipients of pancreas grafts had significantly smaller glomeruli and less mesangial expansion (Bilous et al.1989).

The most dramatic change described in the literature relates to the improvement in the quality of life in the recipient of a pancreas transplant. Although this is difficult to quantify there is an overall improvement in lifestyle. Among patients transplanted at the MGH in Boston, Nathan reported an across the board improvement in life quality assessment relative to both pretransplant and a group of patients undergoing only kidney transplant, as shown in Figure 11 (Nathan et al.1991). In the Boston experience the pancreas/kidney transplant recipients had a longer length of hospital stay associated with the transplant (18±10 days versus 10±2.8 days for kidney transplants) and required more admissions following transplantation than kidney transplant recipients. The excess admissions following transplantation was attributed to a higher rate of infections and peripheral vascular disease. In contrast, the group at the Karolinska

Table II. ANALYSIS OF RENAL BIOPSY SPECIMENS IN PANCREAS-TRANSPLANT RECIPIENTS AND KIDNEY TRANSPLANT RECIPIENTS RECEIVING CONVENTIONAL INSULIN THERAPY (CIT)

	Pancreas-transplant recipients	Controls CIT	P value
Age at onset of diabetes	8±4	10±4	0.29
Duration of diabetes before kidney transplant	19±3	23±6	0.06
Duration of functioning kidney allograft at time of biopsy (yr)	8.6±2.7	9.8±2.6	0.31
Creatinine Clearance	1.35±0.45	1.13±0.36	0.37
Mean glomerular volume	1.80±0.55	2.47±0.73	0.02
Mesangial-volume fraction	0.19±0.07	0.31±0.10	0.004
GBM thickness (nm)	499±124	545±116	0.17

Institute in Stockholm, Sweden reports the number of lost workdays in pancreas/kidney recipients decreased 44%, whereas there was no change in the number of lost workdays in kidney recipients alone. Although they noted a similar number of patients in each group were able to return to work, 90% of the combined transplant recipients were able to return to their full-time occupation and only 50% of the kidney recipients (Table III) (Nakache et al.1989).

Other less objective parameters of the benefits of pancreas transplantation have also been reported. For instance, four patients from European centers have become pregnant and delivered healthy children. From transplantation to conception was from 10 to 27 months. In all patients glucose control during the pregnancy was no problem; however, in one patient the pancreas graft was lost in acute rejection after delivery despite having functioned normally for three years prior (Tyden et al.1989).

A factor that needs to be considered in pancreatic transplantation at present is the cost. An estimate of the cost by Dr. Ingemar Dawidson is that a successful kidney transplant

alone costs about $50,000. An unsuccessful kidney transplant costs up to $120,000. The transplant of a pancreas simultaneously with the pancreas adds another $25,000-30,000 to the cost. This includes the increased cost of organ procurement and hospitalization. Unfortunately, insurance and other programs usually will not cover the increased cost of pancreas transplantation.

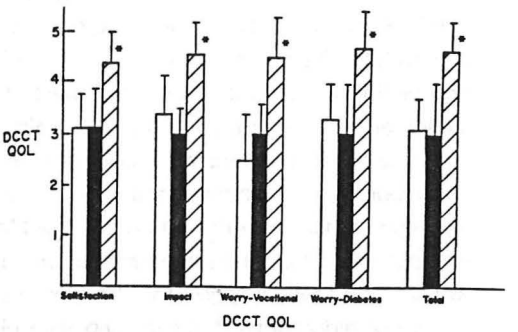

Figure 12 Quality of life assessments pretransplant (open box), 18±11 months after kidney transplant (solid box), and 18±11 months after pancreas/kidney transplant (hatched box).

Table III. Quality of life: Social and role concepts in patients in Stockholm, Sweden.

	Pancreas/kidney transplant	Kidney transplant
Sickness pension	42	62
Preoperative invalidity or sickness pension (%)	28	20
Working patients (%)	65	68
Full-time occupation (%)	90	50
Modification of occupation posttransplantation (%)	7	43
Lost workdays Pre-/posttransplantation	278/155 Decreased 44%	211/213 Unchanged
Nights hospitalized in past 21 mo.	12	25

THE PARKLAND EXPERIENCE

In December, 1990 a kidney-pancreas transplant program was initiated at Parkland Hospital. The progress of this experience has been provided to me by Dr. Luis Ramirez in the Department of Internal Medicine and Dr. Ingemar Dawidson in the Department of Surgery. In the last 9 months eight patients have received simultaneous kidney and pancreas transplants. One patient had an aortic aneurysm that ruptured and the patient died. Another patient is still in the hospital after receiving his transplant, and currently is off insulin with reasonable blood sugar control. Rejection episodes have included the acute rejection of one kidney with the loss of the graft, acute kidney-pancreas rejection adequately treated with OKT3, and one mild pancreas rejection adequately treated with IV steroid boluses. At present 6 patients are home with normoglycemia and off insulin. All of these patients have had a reduction in their glycosylated hemoglobin to normal levels. The program has utilized the procedures discussed above, as well as the use of verapamil to enhance graft survival and reduce cyclosporin renal toxicity and tight glucose control in the immediate postoperative period via a glucose/insulin infusion.

ISLET TRANSPLANTATION

The results of surgical transplantation of the intact pancreas in type I diabetic patients can clearly be effective in the management of diabetes. However, two major obstacles are present for the routine use of this procedure. The first is the need for immunosuppression. As previously mentioned this is needed not only to prevent graft rejection, but also rejection secondary to the autoimmune attack directed at the β cell that initially accounted in the development of type I diabetes. The other obstacle is the availability of sufficient number of pancreata to satisfy the need and the necessity to undergo major surgery for the implantation of the organ. In most of the cases described above the patients already will undergo surgery and immunosuppression for renal transplantation. In this case the inclusion of a pancreas transplant, if possible, seems to be an attractive opportunity. However it would be most desirable to be able to intervene in diabetes and replace functional β cells at an earlier point in the disease process, prior to the development of advanced disease and complications associated

with diabetes. Since the goal of the pancreas transplant is to provide a source of secreted hormone it is not necessary to transplant the entire pancreas. The exocrine portion is not needed. Unfortunately, the endocrine portion of the pancreas is distributed throughout the pancreas in the islets of Langerhans. The islets constitute only about 1% of the volume of the pancreas and are the real organ that needs to be transplanted to reverse diabetes. To this end a variety of investigators over the past two decades have attempted to develop approaches for the purification and transplantation of islets.

Islets can be liberated and purified from the bulk of pancreatic tissue by collagenase digestion and density gradient centrifugation. Using this approach, as outlined in Figure 13, approximately 200,000 - 500,000 islets can be isolated from each pancreas. Several parameters have been tested to eliminate cells that can stimulate rejection. Although these steps have been successful in rodent models of transplantation, in larger animals and man rejection is still a problem (Alejandro et al.1986; Scharp et al.1989). However, purified human islets transplants have been attempted in patients receiving immunosuppression for renal allografts.

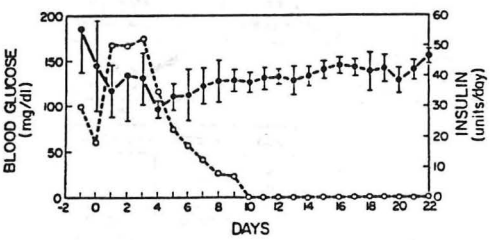

Figure 14 Insulin requirement and glucose levels before and after islet transplantation.

In most cases the islets have been injected into the portal vein to allow implantation in the liver. Substantial numbers of islets also appear to be required for this procedure, usually requiring islets to be isolated from more than one donor pancreas. The requirement for large numbers of islets could reflect the need of a growth factor to support the engraftment of the islets (Tafra et al.1991; Tafra et al.1990). The effects of this procedure on blood glucose levels and the insulin dose in a type I diabetic with an established kidney allograft is shown in Figure 14. No insulin was required within 10

days after transplantation and the blood glucose was reasonably controlled (Warnock et al.1989). Unfortunately, however, the success of these transplants has not been long-lived. In the past 18 months islet transplantation has been performed in six centers: St. Louis; Miami; Pittsburgh; Edmonton,Canada; Milan, Italy; and Paris, France. Insulin independence has been transiently achieved in more than a dozen people. However, only about 20% of the attempted transplants have been successful and only one case was insulin-free for longer than a week. The primary problem accounting for the failure is rejection of the transplanted islets (Keegan et al.1991).

New strategies have been devised to attempt prevent rejection and provide adequate numbers of cells for transplantation. The first approach is to protect the cells from rejection by masking immunologic determinants. The second approach is to isolate the cells from the immune system so as to prevent their recognition and destruction. This can be accomplished as long as the cells are exposed to ambient glucose concentrations and can release insulin into the bloodstream. Such isolation procedures would allow the use of

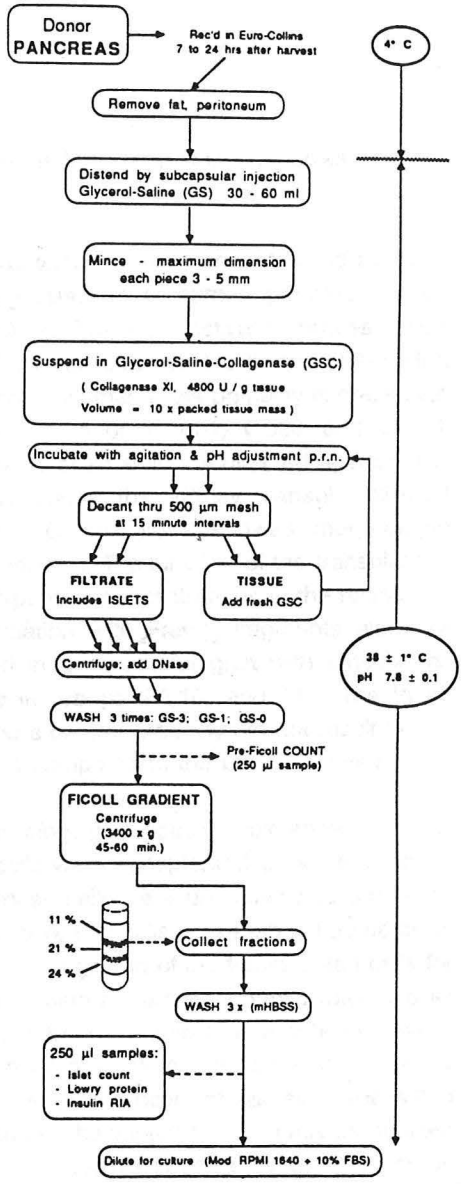

Figure 13 Method for isolating islets from donor pancreas.

foreign cells. This could include xenografts, islets from other animal species, and cell lines capable of acting as artificial β cells.

In a recent paper by Faustman and Coe in *Science* they demonstrated the ability of masking HLA class I antigens in preventing rejection of human pancreatic islets transplanted into mice (Faustman and Coe, 1991). The T cell activation process relies on the association between CD2, CD8 and LFA-1 molecules on T cells and LFA-3, HLA class I, and ICAM-1 molecules on the target cells. Human islets primarily express HLA class I molecules and lack prominent expression of ICAM-1, CD29 and LFA-3. Incubation of human islets with $F(ab')_2$ fragments of an antibody directed against HLA class I molecules prior to transplantation under the kidney capsule allowed transplantation without immunosuppression. Control islets showed morphologic evidence of rejection within 7 days of transplantation. The function of the transplanted islets was monitored by measuring human C-peptide concentrations in the recipients. The results are shown in Figure 15. Incubation with $F(ab')_2$ fragments alone or combined with the control antibody resulted in a successful graft with function as indicated by the increased C-peptide levels in groups 2,3,10, and 11. The intact antibody against the HLA class I molecule and a control antibody did not result in any significant increase in C-peptide concentration compared to the untransplanted mice.

This approach was also successful in allowing graft-specific tolerance of other transplanted tissue. Rat insulinoma (RIN) cells were transplanted under the kidney capsule of nonimmunosuppressed mice. These cells were uniformly rejected when examined after 30 days. In contrast, treatment of RIN cells with $F(ab')_2$ fragments of mouse antibodies to RIN cells allowed survival and growth of the transplanted cells for up to 4 months after transplantation. This treatment apparently induced tolerance as secondary transplants of untreated RIN cells in treated animals were able to survive. This approach suggests that interruption of the initial T cell recognition event can allow xenograft survival of transplanted islets. However, one concern of this technique is that in an autoimmune disease such as type I diabetes the subjects are already immunized against some β cell antigens. Even if islets from another species are used, common and conserved β cell antigens could still serve as a target for rejection.
The second approach is more of a mechanical isolation of the transplanted cells. If a

barrier exists between the transplanted islets that permits the diffusion of small molecules, such as glucose and insulin, but prevents the access of larger molecules, such as immunoglobulins, these cells would be protected from autoimmune attact but still be capable of secreting insulin in response to appropriate stimuli. Two techniques have been described that are being used in islet transplantation. The first is encapsulation. Single islets can be coated with a membrane consisting of alginate-polylysine-alginate. This coating is nonbiodegradable and biocompatible and permits the release of insulin in response to glucose. Implantation of encapsulated islets has been successful in treating diabetic rodents (Sun, 1987; Altman et al.1986); however the limited trials that have been reported in humans have not been encouraging (Wu et al.1989).

Another strategy for immunoisolation is the used of a chamber to contain islets or cells, separated from blood by a semipermeable membrane (Sullivan et al.1991; Maki et al.1991; Altman et al.1988). A schematic diagram of a "biohybrid artificial pancreas" for implantation of islets is shown in Figure

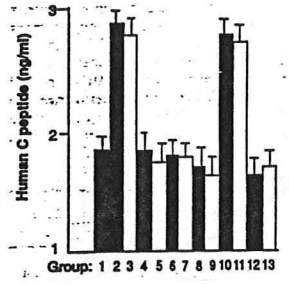

Figure 15 Function of human xenografts evaluated by human C peptide concentrations.

Group treatment:

1	Untransplanted mice	
2	HLA Class 1 $F(ab')_2$	day 30
3	HLA Class 1 $F(ab')_2$	day 200
4	HLA Class 1 antibody	day 30
5	HLA Class 1 antibody	day 200
6	Control $F(ab')_2$	day 30
7	Control $F(ab')_2$	day 200
8	Control antibody	day 30
9	Control antibody	day 200
10	HLA Class 1 and control $F(ab')_2$	day 30
11	HLA Class 1 and control $F(ab')_2$	day 200
12	untreated islets	day 30
13	untreated islets	day 200

16. Injection ports allow the introduction of islets into the islet chamber. Vascular access allows diffusion of nutrients from the blood into the space surrounding the islets, but prevents antibodies and cells from gaining access to the islets. Implantation of this device has been accomplished in dogs with reasonable success. Thrombosis is prevented by administration of aspirin. When two of these devices were seeded with approximately 160,000 canine islets per device and implanted into dogs with streptozotocin-induced diabetes exogenous insulin therapy was able to be discontinued. In these animals glucose control was maintained for up to 157 days. An example of the results of implantation is shown in Figure 17.

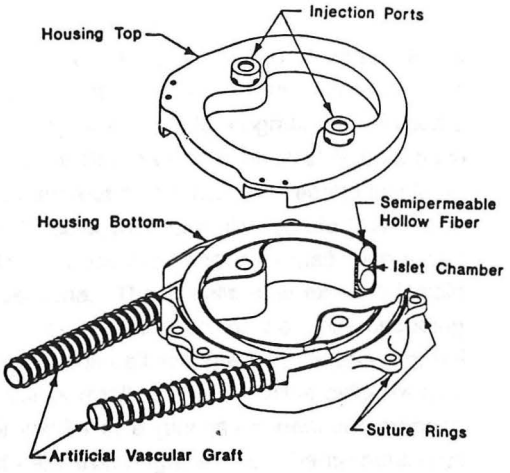

Figure 16 Schematic of biohybrid artificial pancreas.

ARTIFICIAL β-CELLS

All of the previous approaches have relied on the use of β cells already programmed for the synthesis of insulin and its release in response to appropriate stimuli. However, an alternate approach is to design a cell capable of insulin release by genetic engineering techniques. Such a cell needs to be able to sense changes in glucose concentrations and other stimuli to

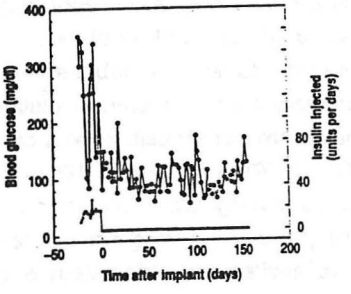

Figure 17 Exogenous insulin requirements and fasting glucose concentrations before and after device implantation.

appropriately release the insulin. Potentially such a cell would not display β-cell antigens involved in the autoimmune destruction of the β cell. Thus, immunologic masking techniques as described above might allow successful engraftment of such a cell. Recently, Dr. Newgard and his colleagues at Southwestern Medical School have made progress in the development of a non-pancreatic cell that can secrete insulin in response to glucose. A pituitary cell line, AtT-20 cells, that normally secrete ACTH have had synthetic genes encoding insulin and the glucose transporter normally expressed in the β cell (GLUT2) introduced into their genome. These cells now express insulin which they package in secretory granules. The introduction of the DNA encoding GLUT2 permits the cells to transport glucose into the cell at a greater rate then normal and over the concentration range that the β cell normally senses. These cells are now capable of releasing significant amounts of insulin in a glucose-dependent manner. These cells provide an alternative source of cells that might escape the immunologic attack in type I diabetes, but would be capable of alleviating the insulin deficiency resulting from the destruction of the β cell.

CONCLUSIONS

Pancreas transplantation combined with kidney transplantation is relatively successful in the management of type I diabetes. However, in these recipients they are already committed to the use of immunosuppression. The long term ability to reverse complications is uncertain, although it appears to prevent deterioration of renal function and clearly the perceived quality of life is substantially improved. The transplant of a pancreas alone in a patient with type I diabetes without renal disease is a more complex issue (Grundfest-Broniatowski, 1990; Sutherland, 1991; Robertson, 1991). One is committing these patients to immunosuppression and its risks. Although with careful HA DR matching and early treatment of rejection episodes the graft survival rate may be improved. The long term would hope to provide reasonable alternatives to β cell replacement therapy. These would involve approaches that protect the transplanted islets or even utilize cells that functionally replace the β cells, but are not recognized as β cells by the autoimmunity of type I diabetes.

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