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Results of Pancreas Transplantation with Portal Venous and Enteric Drainage

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Purpose

The standard method for pancreatic transplantation involves drainage of exocrine secretions into the urinary bladder with venous outflow into the systemic circulation. Despite the high success rate associated with this approach, it often leads to complications, including chemical cystitis, reflux pancreatitis, metabolic acidosis, and hyperinsulinemia. The authors developed a new technique of pancreatic transplantation with portal drainage of endocrine secretions and enteric drainage of exocrine secretions (PE), which theoretically should be more physiologic.

Procedures

All patients were insulin-dependent diabetics with end-stage renal disease who underwent combined kidney-pancreas transplantation. Between 1990 and 1994, 19 patients have been transplanted using intraperitoneal placement of the pancreas allograft with exocrine drainage into a Roux-en Y loop and venous drainage into the portal circulations (PE). A comparison group of all patients undergoing standard systemic-bladder (SB) transplantation between April 1989 and March 1993 (n = 28) also was studied. Patient follow-up ranges from 6 months to 5 years for the SB patients (mean = 2.5 years) and 6 months to 4 years for the PE patients (mean = 1.6 years). Routine follow-up includes documentation of the clinical course and detailed endocrine studies.

Findings

Patient and graft actuarial survival at 1 and 3 years is no different for SB and PE patients. Urinary tract infections occurred in 89.3% of the SB patients (2.8/patient) *versus* 26.3% of the PE patients (0.25/patient, $p \leq 0.0001$). None of the PE patients experienced hematuria compared with 53.6% of the SB patients ($p \leq 0.0001$); however, two PE patients had melanotic episodes. The incidence of urinary retention and reflux pancreatitis was 32.1% *versus* 5.3% ($p \leq 0.028$) for SB and PE groups, respectively. Patients in the SB group required sodium bicarbonate therapy (mean = 55 mEq/day) although no PE patient required routine therapy; despite this, SB patients experienced more episodes of acidosis (44 *vs.* 5). Endocrine studies indicate no difference in glycosylated hemoglobin or fasting and stimulated glucose values throughout the follow-up period. In contrast, hyperinsulinemia was evident in both fasting and stimulated tests for the SB patients, with values consistently two- to fivefold higher than those of the PE group.

Conclusions

These results indicate that PE and SB pancreas transplantation are equivalent in terms of patient and graft survival and suggest that the PE approach is associated with a decreased incidence of metabolic and bladder-related complications. In addition, the PE approach eliminates the state of peripheral hyperinsulinemia that characterizes the SB procedure. Continued follow-up will be necessary to determine if long-term outcomes will differ for patients with PE and SB grafts.

Pancreatic transplantation has gained acceptance as a viable treatment option for patients with insulin-dependent diabetes and end-stage renal disease. The International Transplant Registry reports the 1 and 3-year patient survival rates are 90% and 84%, respectively, and the corresponding graft survival rates are 75% and 67%.[1] After successful transplants, patients become normoglycemic, with complete freedom of insulin therapy and experience improvement in the quality of life.[2-6] In addition, improvement in some of the chronic diabetic complications has been reported.[6-9] Therefore, with development of safer immunosuppressive drugs, pancreatic transplantation may become an acceptable therapeutic approach for certain diabetic patients who do not have renal failure.[10-11]

The standard surgical approach to pancreatic transplantation employs drainage of exocrine secretions into the bladder and diversion of venous outflow into the systemic circulation (SB). This technique has been uniformly adopted by most North American transplant centers because of the reported low complication rate[12] and the fact that it diverts pancreatic exocrine secretion into the urinary bladder, thus facilitating monitoring for rejection of the pancreas. Despite its widespread acceptance, the SB procedure has potential surgical and metabolic complications. The surgical drainage of pancreatic exocrine secretion via the urinary bladder provides a constant source of irritation to the bladder mucosa, accentuating the abnormalities associated with autonomic diabetic neuropathy. This environment subsequently leads to chemical cystitis, recurrent hematuria, infection, and repeated episodes of graft pancreatitis.[13,14] In addition, the elimination of pancreatic exocrine secretions in the urine causes loss of bicarbonate, creates electrolyte derangements, and contributes to dehydration, leading to a state of metabolic acidosis.

The systemic diversion of pancreatic venous outflow causes hyperinsulinemia,[15,16] which is thought to contribute to the development of atherosclerosis both directly through stimulation of vascular smooth muscle growth[17] and indirectly through the promotion of hypertension and dyslipidemia.[18,19] Peripheral hyperinsulinemia may lead to insulin resistance because pancreas transplant recipients with systemic venous drainage have been reported to exhibit elevated basal hepatic glucose production and reduced postprandial peripheral glucose disposal.[20] These findings occur in the presence of an elevated proinsulin secretion rate compared with C-peptide secretion rate. Thus, the metabolic status of the SB transplant recipient is characterized by normoglycemia, peripheral hyperinsulinemia, and peripheral insulin resistance.

In an attempt to alleviate these problems, various techniques have been implemented to divert pancreatic venous outflow into the portal circulation and exocrine drainage into the bowel (PE). Most of these trials were associated, however, with technical problems and high morbidity and mortality rates.[21-24] We recently have developed a new technique for pancreas transplantation using portal drainage of endocrine secretions with enteric drainage of exocrine secretions.[25] This report describes the clinical and metabolic data of a series of uremic diabetic patients who received combined kidney/pancreas allografts with the PE technique and a similar group of patients who underwent transplantation with the SB technique.

MATERIALS AND METHODS

The combined P-K transplantation program at the University of Tennessee-Memphis was started in 1989. The first pancreas transplant using portal enteric drainage was performed in October 1990. Twenty-four of these procedures were performed. Results of the early experience (n = 5) with extraperitoneal pancreas placement and side-to-side duodenoduostomy were reported previously and demonstrated an unacceptably high rate of patient morbidity and mortality.[24] After this initial experience, we modified the portal enteric procedure[25] and performed another 19 transplants. This report compares the surgical and metabolic outcomes of the modified PE transplant procedure with those of the SB procedure.

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Table 1. PATIENT CHARACTERISTICS BEFORE TRANSPLANTATION*

	Portal Enteric (n = 19)	Systemic Bladder (n = 28)
Age	37.6 ± 1.93	39.7 ± 1.43
Sex (M/F)	10/9	11/17
Body mass index (kg/m^2)	24.9 ± 80	23.6 ± .53
Duration of diabetes (yr)	23.9 ± 1.63	24.7 ± .96
Fasting plasma glucose (mg/dL)	143.8 ± 13.03	177.1 ± 22.5
Hemaglobin A_{1c} (%)	8.1 ± .41	6.97 ± 0.24
Hematocrit (%)	31.0 ± 1.39	31.0 ± 1.04

SEM = Standard error of the mean.
* All the comparisons between the two groups were not statistically significant.

Subjects

The study included two groups of patients with insulin-dependent diabetes mellitus and end-stage renal disease who underwent pancreas-kidney transplantation (Table 1). The first group was comprised of all patients who underwent combined pancreas-kidney transplantation using the modified portal-enteric technique at our center between 1990 and 1994. This group included 19 patients (10 men, 19 women) 23 to 53 years of age (mean 37.6 ± 1.93 years). The second group included all 28 patients (11 men, 17 women) 24 to 55 years of age (mean 39.7 ± 1.43 years) who received pancreas and kidney allografts with the SB technique between 1989 and 1993. Both groups represented the first 4 years of our experience with each technique. All patients underwent routine metabolic evaluation at 6, 12, and 24 months posttransplant. Patient follow-up ranges from 6 months to 5 years for the SB group (mean = 2.5 years) and 6 months to 4 years for the PE group (mean = 1.6 years). Pancreas and kidney transplantation and the metabolic study protocols were approved by the institutional review board, and all patients gave informed consent.

Surgical Procedures

The SB technique of pancreas transplantation was performed according to the procedures described by Nghiem et al.[26] Our modified technique for PE transplantation involves an intraperitoneal placement of the pancreatic allograft with exocrine drainage into a Roux-en-Y loop, as described previously.[25] Y-graft, comprising the donor's common, internal, and external iliac arteries, is obtained at the time of organ procurement. The splenic and superior mesenteric arteries arising from the pancreatic allograft are anastomosed to the internal and external iliac branches of the Y-graft, respectively, and the common iliac artery of the Y-graft is anastomosed to the recipient's common iliac artery. The donor's portal vein is anastomosed end to side to a major tributary of the recipient's superior mesenteric vein after minimal dissection in the root of the mesentery. The duodenal segment encompassing the head of the pancreatic allograft is closed superiorly by a double row of staples and inverted with silk sutures. Inferiorly, the duodenal loop is shortened to a 3- to 4-inch segment a and anastomosed end to end to an intestinal Roux-en-Y loop created in the recipient. The pancreas is then wrapped with the omentum to help seal any minor leaks from its surface, and a drain is placed in its proximity. Using standard technique, the kidney graft is placed extraperitoneally based on the left iliac vessels.

Immunosuppression and Monitoring

Immunosuppression was achieved by quadruple sequential therapy, including induction with OKT3 for the first 7 to 10 postoperative days or with ATGAM in patients (n = 5) who were unable to receive OKT3. High-dose methyl prednisolone is given for the first 3 days (500 mg on day 1, 250 mg on day 2, 125 mg on day 3) along with azathioprine (2 mg/kg) daily. Cyclosporine (4–6 mg/kg/day) was started on postoperative days 2 to 7, depending on renal function, and the dose was adjusted to maintain a trough serum level of >250 ng/dL (whole blood-TDX assay). Prednisone was started on the fourth postoperative day at 0.5 mg/kg/day and was tapered to 0.2 mg/kg/day by 3 months. Antilymphocyte therapy was monitored using daily T-subset analysis while on OKT3 or ATGAM therapy. Pancreatic allograft function was monitored by daily measurement of urinary amylase excretion rate in the SB group. In addition, both groups of patients had daily serum anodal trypsinogen measurements to help diagnose pancreas allograft dysfunction. Recently, measurements of the rate of glucose disappearance (k_G) during intravenous venous glucose tolerance testing was introduced to confirm the diagnosis of pancreas rejection.[27] Percutaneous pancreas biopsy[28] has been used to confirm the rejection diagnosis in all SB patients and a few of the PE patients. Confirmed rejection was treated with three daily pulses of high-dose intravenous methylprednisolone (Solu-Medrol, Upjohn, Kalamazoo, MI), followed by treatment with antilymphocyte therapy for 7 to 10 days if the rejection was steroid resistant.

Metabolic Studies

Routine metabolic evaluation was performed at 6 months and annually thereafter with Sustacal (Mead Johnson, Evansville, IN) and intravenous glucose toler-

ance tests. In addition, records of all patients were reviewed for evidence of metabolic acidosis (serum bicarbonate level < 15 mEq/dL), dehydration (defined by the need for intravenous fluid therapy > 1000 mL), and the sodium bicarbonate maintenance dose patients were receiving at the evaluation time points. Because metabolic testing was voluntary, not all patients completed the studies at every measurement point.

1. *Sustacal test.* After a 12-hour overnight fast, an intravenous line was placed in an antecubital vein, a fasting blood sample was drawn, and 6 mL/kg (1 cal/mL) of Sustacal with a maximum dose of 360 mL was given over 5 minutes. Blood samples were collected every 30 minutes for 2 hours for determination of plasma glucose, insulin, and C-peptide concentrations.
2. *Intravenous glucose tolerance test.* After a 12-hour overnight fast, two intravenous lines were placed, one in each antecubital vein. One line was used for injections and the other for collection of blood specimens. Glucose (300 mg/kg) in the form of a 50% solution was administered intravenously over 2 minutes. Blood samples were collected at −15, −10, −5, 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 150, and 180 minutes for determination of plasma glucose, insulin, and C-peptide concentrations.

Biochemical Analyses

Plasma glucose concentrations were measured by the glucose oxidase method with a Beckman Glucose Analyzer (Beckman Instruments, Fullerton, CA). Insulin levels were determined by a double antibody radioimmunoassay using Corning Medical kit (Corning, Bedford, MA). C-peptide concentrations were measured by a double antibody radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA).

Calculations and Statistical Analyses

Survival estimates were calculated using the Kaplan-Meier life test procedure. The trapezoidal rule was used to determine the incremental areas under the curve for glucose, insulin, and C-peptide after the Sustacal administration and for the first phase response during intravenous glucose tolerance testing. Because of the small sample size and large patient-to-patient variability, Sustacal and glucose tolerance areas under the curve were analyzed at each time point using Wilcoxon's rank sum test. The glucose disappearance constant (k_G), representing second-phase response, also was calculated from the results of the intravenous glucose tolerance test. The best linear fit of the natural log of plasma glucose values as a function of time from 10 to 60 minutes was calculated by least-square linear regression. The absolute value of the slope of that line, (in plasma glucose/minute) × 100, is k_G, which is a measure of intravenous glucose tolerance.[26] Between-group differences were determined with repeated measures of analysis of variance, Student's t test, and chi square. Data are presented as means ± SEM.

RESULTS

Patient and Graft Survival

The patient survival rate for all SB patients was 89% at 1 year and 82% at 3 years. The pancreas graft survival, defined as freedom from exogenous insulin, was 75% at 1 year and 63% at 3 years. Kidney allograft survival was 75% at 1 year and 70% at 3 years. In the 19 patients who underwent the modified PE procedure, patient survival was 94% at 6 months and 88% at 12, 24, and 36 months post-transplant. Pancreas graft survival for the PE group was 74% at 6 months and 71% at 12, 24, and 36 months. Neither patient or pancreas graft survival rates were different from those seen in SB group (Fig. 1).

Early loss of pancreas grafts to thrombosis occurred in 3 of 28 SB patients and in 2 of 19 PE patients. An additional pancreas loss occurred in each group, secondary to uncorrectable pancreatic leak (SB) and persistent graft pancreatitis (PE). Two patients died in the PE group, one from disseminated fungal infection that had led to excision of both kidney and pancreas grafts and another from sudden cardiac death (in a patient with functioning grafts). In the SB group, two grafts were lost to irreversible rejection, three patients died with functioning pancreas grafts (two from cardiac causes and one from complications after a subsequent surgical procedure), and two died with disseminated cytomegalovirus and staphylococcal infection. There were no instances of bowel leakage in the group of PE transplant recipients.

Complications

At last follow-up, which ranged from 6 to 42 months, 53.6% of the SB patients required cystoscopic examination to evaluate bleeding, recurrent infections, or intractable urinary symptoms, whereas none of the PE patients experienced symptoms necessitating cystoscopic evaluation. During this time period, 32.1% of the SB patients experienced urinary retention or reflux pancreatitis compared with 5.3% of the PE patients ($p \leq 0.028$). For this study, reflux pancreatitis was defined as elevation of serum amylase and graft tenderness that is associated with increased urinary residual volume requiring catheterization for 24 hours or greater. Eighty-nine percent of the

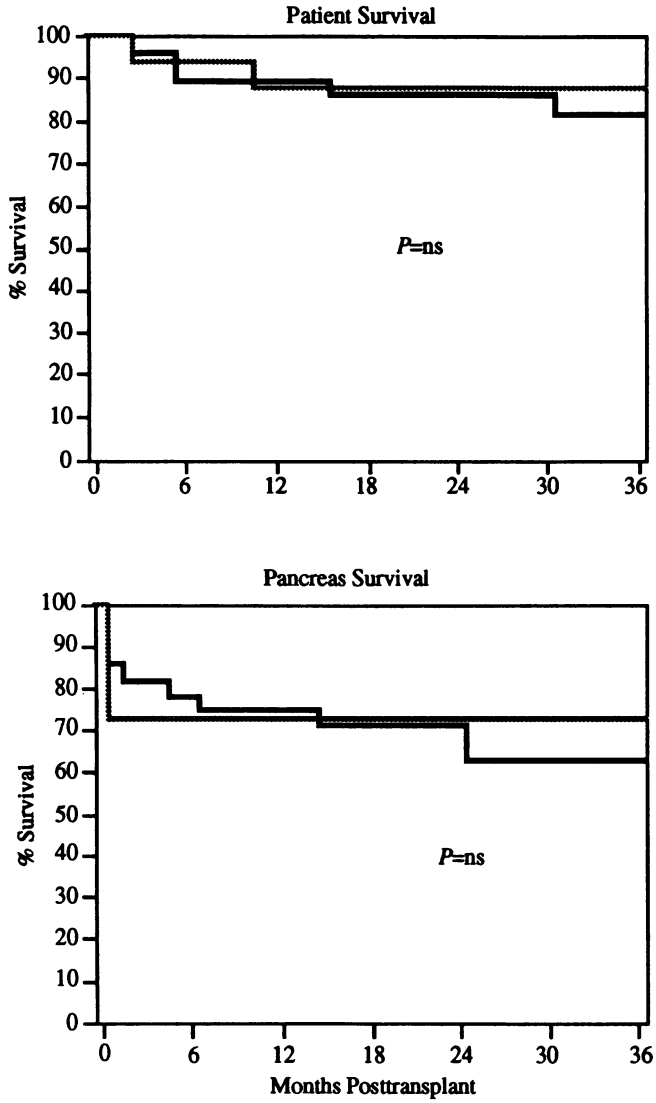

Figure 1. Patient and pancreas survival rates for recipients of systemical-bladder (■) and portal-enteric (▩) drained pancreas allografts.

SB patients experienced at least one urinary tract infection (2.8/patient) compared with 26.3% ($p \leq 0.0001$) of the PE patients (0.25/patient), and 53.6% of the SB patients experienced one episode or more of significant gross hematuria requiring catheter irrigation or cystoscopic evaluation and treatment. In contrast, none of the patients who underwent the PE procedure developed postoperative hematuria. Two patients experienced lower gastrointestinal bleeding, one PE patient had three bleeding episodes in the early postoperative course that required transfusions, whereas the second patient had two bleeding episode 2 years after transplantation. In both cases, the bleeding spontaneously resolved.

Patients in the SB group required an average daily dose of 55 mEq sodium bicarbonate to maintain a normal acid-base balance. Despite this treatment, there were 44 episodes of acidosis (serum bicarbonate < 15 mEq/dL) in the SB patients, 11 of which were associated with dehydration, requiring intravenous replacement therapy. In contrast, none of the PE patients required routine sodium bicarbonate therapy. Five patients in the PE group experienced acidosis associated with rejection episodes or cyclosporine toxicity, but none had dehydration.

Metabolic Evaluation

At the time of the Sustacal and intravenous glucose tolerance testing, both groups of patients were normoglycemic and had normal glycosylated hemoglobin levels while free of exogenous insulin (Table 2). Fasting plasma glucose concentrations in the SB group were 78 to 115 mg/dL (mean = 98.7 ± 3.5) at 6 months and 62 to 104 mg/dL (mean = 88.0 ± 2.5) at 24 months. At the same time points, fasting glucose values for the PE group were 81 to 102 mg/dL (mean 85.5 ± 2.2) and 80 to 152 mg/dL (mean = 98.4 ± 8.0). One PE patient had an abnormal 24-month fasting glucose concentration of 152 mg/dL, but did not require insulin therapy. All other patients had fasting glucose levels less than 116 mg/dL. Fasting plasma insulin levels were found to be higher in the SB group compared with the PE group at 6 months (55.3 ± 9.7 *vs.* 11.0 ± 2.1 μU/mL, $p \leq 0.0002$) and at 24 months (38.8 ± 9.7 *vs.* 7.9 ± 1.8 μU/mL, $p \leq 0.0033$). Fasting C-peptide levels also were found to differ for the SB and PE groups at 6 (2.1 ± 0.21 *vs.* 1.4 ± 0.41 pmol/mL, $p \leq 0.0121$), but not at 24 months (1.8 ± 0.26 *vs.* 1.0 ± 0.18 pmol/mL, $p \leq 0.1370$). The fasting insulin: C-peptide ratio also was different for the two groups at each measurement point (Table 2).

After Sustacal administration, plasma glucose and insulin levels were systematically higher for the SB group at the 6-month evaluation (Figs. 2 and 3). By the 24-month evaluation, glucose profiles were similar in the two groups, whereas insulin levels remained 1.5- to 5-fold higher in the SB group. The insulin area under the curve, significantly different for the two groups at 6 months (3894.2 ± 957.9 *vs.* 2186.9 ± 295.7 μU/mL/minute, $p \leq 0.0214$), was not significantly different at 24 months (2890.3 ± 809.1 *vs.* 3060.2 ± 944.8 μU/mL/minute, $p \leq 0.5800$).

After intravenous glucose administration, and despite identical first-phase glucose profiles and acute C-peptide response, the acute insulin response presented different profiles at 6 and 24 months (Fig. 4). The second-phase glucose response, as determined by the slope (k_G) of glucose decrement (Fig. 5), was found to be similar for the SB and PE groups (1.5 ± .1 *vs.* 1.7 ± 0.1, $p \leq 0.226$).

Table 2. METABOLIC CHARACTERISTICS OF PATIENTS WITH PORTAL-ENTERIC AND SYSTEMIC-BLADDER DRAINED PANCREAS ALLOGRAFTS AT 6 AND 24 MONTHS AFTER TRANSPLANTATION

	Portal-Enteric		Systemic Bladder	
	6 mos	24 mos	6 mos	24 mos
	(n = 19)	(n = 7)	(n = 28)	(n = 17)
Body mass index (kg/m^2)	24.4 ± .78	25.2 ± 1.21	25.1 ± 1.34	24.3 ± 1.17
Hemoglobin A_{IC} (%)	5.9 ± .51	5.7 ± .36	6.0 ± .66	5.6 ± .2
Hematocrit (%)	39.4 ± 2.3	41.8 ± 3.2	40.1 ± 1.67	37.7 ± 1.3
Serum creatinine (mg/dL)	1.5 ± .18	2.8 ± .81	1.9 ± .25	1.8 ± .12
Fasting plasma glucose (mg/dL)	85.5 ± 2.2*	98.4 ± 8.0	98.7 ± 3.5*	88.0 ± 2.5
Fasting plasma insulin (μU/mL)	11.0 ± 2.1†	7.9 ± 1.8†	55.3 ± 9.7†	38.8 ± 9.7†
Fasting plasma C-peptide (pmol/mL)	1.4 ± .41†	1.0 ± .18*	2.1 ± .21†	1.8 ± .26*
Fasting insulin:C-peptide ratio	6.92 ± 1.6†	6.31 ± 1.7*	20.89 ± 2.1†	15.13 ± 2.2*

* $p \leq 0.05$.
† $p \leq 0.01$ between groups at the same time points.
Values are ± SEM.

DISCUSSION

Portal venous and enteric exocrine drainage has been used in early trials of pancreatic transplantation but was abandoned because of technical difficulties and increased morbidity related to the enteric anastomosis.[29] However, technical modifications and progressive experience has made it a safe option for uremic diabetic patients undergoing combined pancreas-kidney transplantation. The results from our series of patients indicate that intraperitoneal portal pancreas transplants with Roux-en-Y drainage is associated with acceptable patient and graft survival outcomes. Concerns related to anastomotic bowel complications have not materialized in this, or other recently reported series,[30,32] and the intraperitoneal Roux-en-Y connection appears to provide adequate drainage for the transplanted pancreas. Establishment of the continued safety of this procedure, however, can only be ascertained with its continued use in larger series of patients.

The PE placement of the pancreas provides distinct practical and theoretical advantages to the patients to justify its continued use. Of practical significance is the elimination of urinary bladder and metabolic complications seen after transplantation. Although the time at risk was somewhat shorter for the PE group because of the more limited post-transplant course, the elimination of recurrent episodes of acidosis and dehydration, and the need for bicarbonate replacement therapy, compared with the widespread occurrence of these problems in the SB group, is noteworthy. More significant was the elimination of recurrent hematuria and the reduction, post-transplant, of bladder dysfunction for the PE patients, compared with the need for repeated cystoscopic examination encountered by the SB patients. By avoiding the duodenocystostomy, the need for prolonged intermittent catheterization also was reduced. The occurrence of urinary retention, reflux pancreatitis, and urinary infections also were markedly reduced for the PE patients. The use of the PE approach also is expected to reduce the need for second operation for enteric conversion of patients undergoing SB transplant, which currently is estimated to be required in 5% to 10% of pancreas transplant recipients.

The PE pancreatic transplant patients had significantly lower insulin levels than patients of the SB group. Hyperinsulinemia in the latter group results from drainage of the pancreatic venous outflow into the systemic circulation, thus bypassing the liver, where approximately 50% of the insulin is degraded during the first pass.[14] Despite the hyperinsulinemia seen in the SB patients, they have been shown to have carbohydrate metabolism similar to that observed in nondiabetic patients receiving the same immunosuppressive doses after kidney transplantation alone, and only minimally different from normal subjects.[33] Similarly, glucose handling appeared to be similar in our patients with either PE or SB pancreas transplants. Although systemic insulin delivery does not appear to significantly impair carbohydrate metabolism, lowering insulin levels could be important because hyperinsulinemia is thought to be atherogenic.[17,19] Insulin may accelerate the development of atherosclerosis through stimulating vascular smooth muscle to undergo hypertrophy or arterial wall lipid deposition.[34] Falholt et al.[35] have reported that dogs rendered hyperinsu-

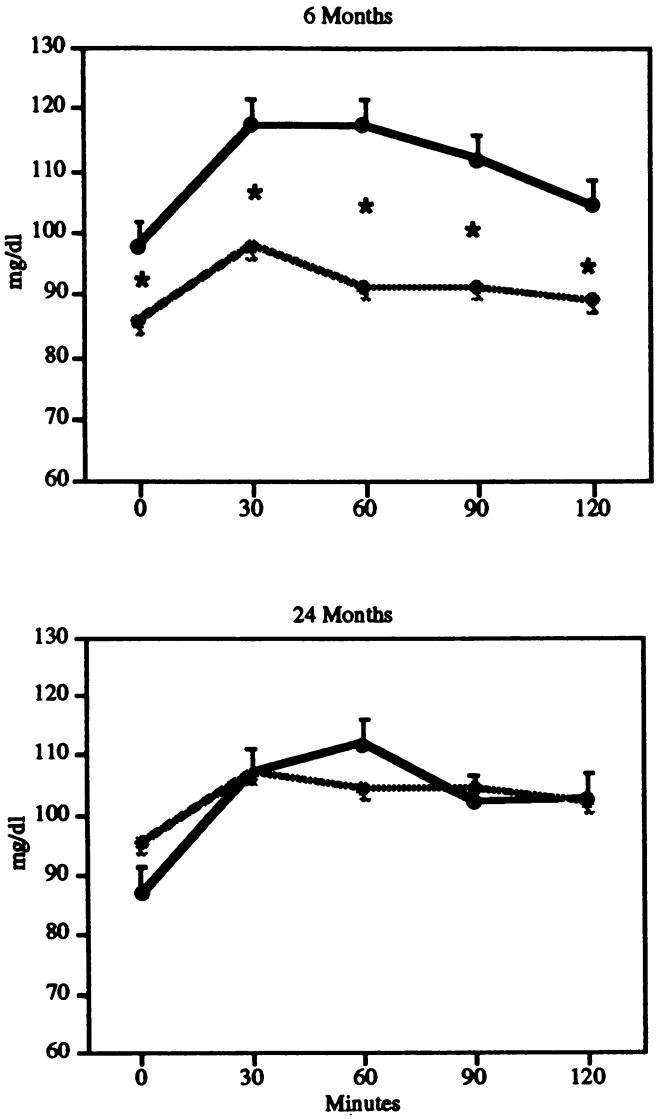

Figure 2. Serum glucose after Sustacal challenge (0 minutes) for patients with systemically (■) and portally (▩) drained pancreas allografts. ($p \leq 0.01$)

linemic by segmental pancreatic transplantation showed increased arterial wall lipid synthesis. Similar findings were demonstrated in pigs with pancreatic allografts placed systemically, but not in those with portally transplanted allografts.[36] Insulin also may lead to atherosclerosis indirectly by promoting the development of hypertension and dyslipidemia. Insulin could contribute to the development of hypertension by stimulating the sympathetic nervous system, promoting renal sodium retention, and affecting cation transport in addition to enhancing vascular smooth muscle hypertrophy.[19] Insulin also could induce dyslipidemia by stimulating hepatic synthesis and secretion of triglycerides with a subsequent increase in the levels of very low-density lipoprotein and decrease in high-density lipoprotein-cholesterol concentrations.[18] Thus, hyperinsulinemia could lead to a lipoprotein profile of higher atherogenic potential. It is possible, therefore, that hyperinsulinemia associated with SB transplantation could accelerate the development of atherosclerosis. Conversely, PE transplantation leads to lower insulin levels, which could have a favorable effect. Long-term follow-up of patients of both groups is needed, however, to determine the impact of both procedures on the development of atherosclerotic cardiovascular disease.

Despite its benefits, the PE approach to pancreatic

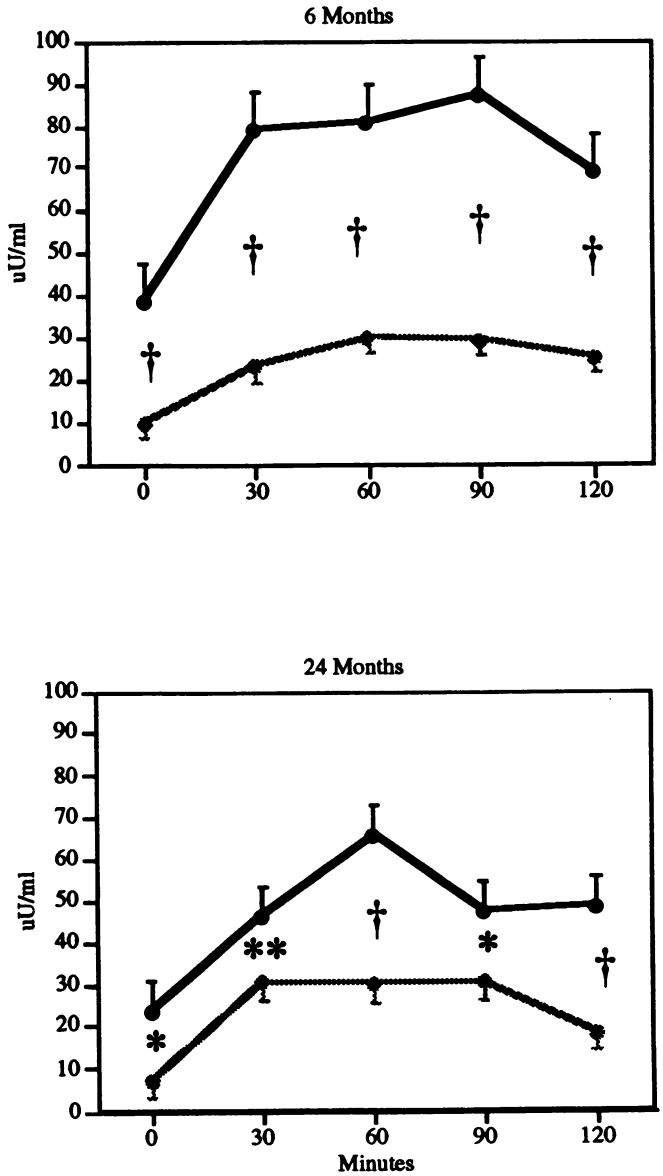

Figure 3. Serum insulin after Sustacal challenge (0 minutes) for patients with systemically (■) and portally (▩) drained pancreas allografts. († = $p \leq 0.0001$, * = $p \leq 0.01$, ** = $p \leq 0.05$)

transplantation is not without shortcomings. Enteric drainage does not allow the monitoring of urinary amylase as a marker of rejection episodes and makes the pancreas less accessible to percutaneous biopsy. The inability to follow urinary amylase determinations represents a particular problem in recognizing isolated pancreas rejection episodes in the combined transplant recipient and obviates the use of this procedure for pancreas transplantation alone. To circumvent this, we have used both serum anodal trypsinogen and measurement of glucose disappearance rate (k_G) for monitoring of pancreas allograft function. Although serum anodal trypsinogen has been reported to be a reliable marker for pancreatic allograft dysfunction,[37,38] we have found the glucose disappearance rate calculated from intravenous glucose tolerance testing to be a more specific indicator.[27] Similarly, Henry[39] has reported using first-phase insulin response for detection of pancreas allograft rejection. The availability of these techniques has helped in the successful monitoring of pancreas function in our patients and has helped us achieve equivalent graft survival rates for the PE and SB transplants. To further aid in the diagnosis of rejection, we have in more recent cases affixed the pancreatic tail to the anterior abdominal wall, thus allowing successful percutaneous biopsy of the pancreas.[28]

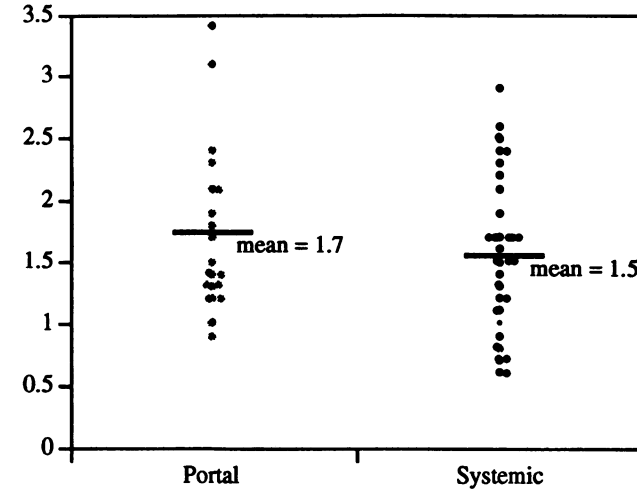

Figure 5. Post-transplant glucose decrement (k_G) of pancreas transplant recipients with portal and systemic venous drainage during stable graft function.

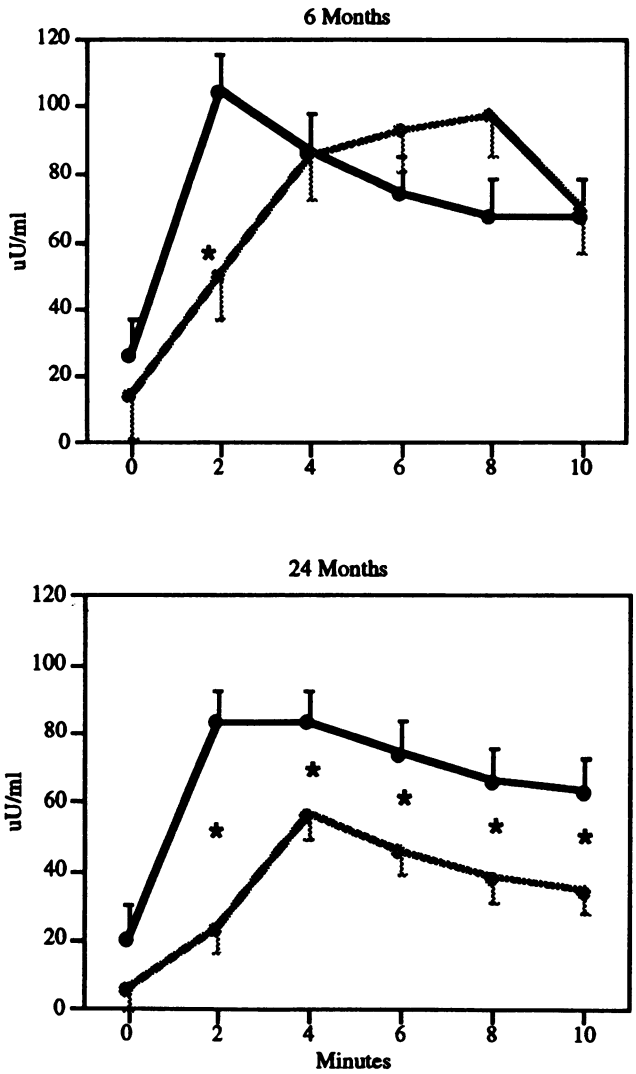

Figure 4. First-phase insulin response during intravenous glucose tolerance testing of panreas-kidney transplant recipients with systemic (■) and portal (▨) venous drainage of the pancreas allograft. ($p \leq 0.01$)

Another complication of the PE technique is the potential for bleeding from the duodenal segment, a problem that was suspected in 2 of our 19 patients. Although both episodes of bleeding stopped spontaneously and were not severe, they still demonstrate the potential risk of complication from the enteric placement of the duodenal segment.

Our overall experience demonstrates that PE transplantation is technically feasible and is associated with good patient and graft survival outcomes. Marked improvement in bladder-related complications and normalization of physiologic parameters are immediate benefits of the new approach. Obviating the risk of hyperinsulinemia continues to be the major stimulus for using the PE procedure. Determining whether the theoretical benefits of reduced hyperinsulinemia outweigh the potential risks of the procedure will require the continued judicious use of the new procedure in deciding where detailed outcome studies are performed.

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Discussion

DR. JOHN C. MCDONALD (Shreveport, Louisiana): I am pleased to have the opportunity to comment upon this latest contribution of the University of Tennessee group to transplantation and, specifically, pancreatic transplantation. For several years, this group has been engaged diligently in careful studies of patients with pancreatic transplantation in an effort to establish that the pancreatic transplant will improve the quality of life of these patients, as well as to determine whether or not complications of diabetes, such as gastroparesis, cardiac disease, and neuropathy improve following pancreatic transplantation.

In my view, these are some of the more scholarly and important papers in this particular field of study. In this paper, they have tested whether or not venous drainage of the pancreas by the portal system and exocrine drainage by the gastrointestinal tract provides an operative procedure that is less morbid than the standard procedure of the day, which is to establish venous drainage into the systemic venous system and exocrine drainage into the bladder. They have convincingly shown, I believe, that it does, and I think these conclusions will be rapidly accepted.

The reason that this procedure has not been adopted before, however, has been due to the increased morbidity and technical complications of this obviously more complex implant in the intra-abdominal position associated with bowel anastomoses. In this series, that was not the case—i.e., there was no increased morbidity by this more complex technical procedure. But I think a larger study will be required to convince most students of the problem that such a procedure can be widely applied with similar results.

One of the disturbing aspects of pancreatic transplantation is that with current practice, almost all patients receive a kidney and pancreas simultaneously. The national allocation system allows such patients high priority for organs; therefore, the kidney goes with the pancreas. By this policy, diabetic patients get the very finest kidneys available. And yet in this series, as in others, there is a 70% to 75% 1-year graft survival of the kidney which, were it implanted in the absence of the pancreas, would be expected to be at least 85%, if not 90%.

Thus the question remains, does a pancreatic transplant improve patient survival and general health sufficiently to justify a kidney transplant survival 10% to 15% less than would be obtained if it were implanted without the pancreas?

I wonder if Dr. Britt or Gaber would comment upon this dilemma.

Thank you for the opportunity to comment on this paper.

DR. JOHN B. HANKS (Charlottesville, Virginia): Dr. McDonald, Dr. Copeland, thank you for allowing me the time to comment on this paper. I rise to congratulate the authors on an excellent presentation on pancreas transplantation.

This presentation analyzes the judicious application of a difficult technical procedure (pancreas transplantation) to the complicated Type I diabetic. Additionally, long-term metabolism studies that the authors outline so elegantly in their presentation allow understanding not only of the pathophysiology of the insulin deficient stage of diabetes, but also give us some understanding of the relevance of the normal anatomy and enteropancreatic relationships, which are not clearly understood, even in the normal circumstance.

There are several remarkable aspects to this paper for which the authors are to be congratulated. First, their survival statistics in this chronically ill group are excellent. Everyone knows that the long-term survival of patients with complicated Type I diabetes is altered by the disease process, as Dr. Britt so nicely showed by his green-line curve. Therefore, a paper that reports successful pancreas transplantation, with patient and pancreas graft survival approaching 90% and 80%, respectively, for 1 year is really excellent.

Secondly, the authors have given us insight into an important question, the delivery of insulin by the systemic or portal route and whether or not this has long-term metabolic consequence. Hyperinsulinemia after pancreas transplantation has been well documented in the literature, and its cause is by no means clear. It is easy to say that hyperinsulinemia after systemic drainage of the pancreas might be due to the bypassing of first pass hepatic extraction, and I agree, to a certain extent. There is an intriguing second explanation, i.e., that insulin hypersecretion may occur after denervation of the transplanted gland. In any event, despite the etiology of hyperinsulinemia, concern has and will continue to exist concerning the relationship of hyperinsulinemia to long-term atherogenesis.

Encouraging literature has recently occurred in the October issue of *Transplantation,* where Foger's group has reported the effect of pancreas transplantation on lipoprotein metabolism. They studied 11 healthy controls and compared them with 11 Type I diabetics who had received pancreas/kidney transplants and demonstrated distinctly elevated high-density lipoprotein cholesterol in the pancreas transplant recipients. These patients had low postprandial triglyceride levels resulting from a high activity of lipoprotein lipase. Thus, this group uniquely and importantly reports that the hyperinsulinemia and the resultant high-density lipoprotein cholesterol was the very opposite circumstance to Type II diabetics with high triglyceride and low high-density humidity cholesterol. They felt that the post-transplant high high-density lipoprotein cholesterol showed a very favorable plasma lipid profile and hypothesized that their hyperinsulinemia might not lead to the risk of atherogenesis as previously thought, thereby, allaying a lot of concerns of multiple groups dealing with hyperinsulinemia after pancreas transplantation.

With this information, I have just a few questions for the authors. The data that they present compared two post-transplant groups. I think that an important group would have been a set of normal controls. In our series of systemic *versus* portal transplants at the University of Virginia several years ago, we noted that the portal vein transplant patients also had lower insulin levels in the basal and stimulated state compared with the systemically drained transplants. However, the portal