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Experience With 500 Simultaneous Pancreas–Kidney Transplants

Hans W. Sollinger, MD, PhD, Jon S. Odorico, MD, Stuart J. Knechtle, MD, Anthony M. D'Alessandro, MD, Munci Kalayoglu, MD, and John D. Pirsch, MD

From the Division of Organ Transplantation, Department of Surgery, University of Wisconsin School of Medicine, Madison, Wisconsin

Methods

From December 1985 to October 1997, 500 simultaneous pancreas–kidney transplants (SPKs) were performed at the University of Wisconsin. Bladder drainage (BD) was used in 388 and enteric drainage (ED) in 112. All pancreas transplants were preserved in UW solution.

Results

Patient survival at 1, 5, and 10 years was 96.4%, 88.6%, and 76.3%; kidney function, 88.6%, 80.3%, and 66.6%; and pancreas function, 87.5%, 78.1%, and 67.2%. Thrombosis of the pancreas occurred in three to four (0.6% to 0.8%) and primary nonfunction in one (0.2%). There was a 4.2% acute tubular necrosis rate for the kidney. Conversion from BD to ED was required in 24% of cases. Primary indications for enteric conversion (EC) were leak (14%), urethritis and extravasation (7%), and chronic hematuria (3%). No graft was lost as a result of EC. There was no difference in 1-year graft survival between ED and BD. Leading causes of pancreas loss were rejection in 45 patients and death with a functioning graft in 27 patients. Since June 1995, mycophenolate mofetil was used for immunosuppression (n = 109). One-year survival rates with mycophenolate mofetil are patient, 98.1%; kidney, 94.2%; and pancreas, 93.1%. Steroid-resistant rejections decreased from 48% to 15%.

Conclusions

This series represents the world's largest experience with SPK, including the longest follow-up for BD pancreatic transplants. Ten-year graft survival rates exceed those of all other transplants, with the exception of HLA-identical living-related grafts. This series confirms that SPK is a highly successful procedure for selected diabetic patients with renal failure.

The first pancreas transplant was performed in 1966 by Kelly et al.[1] at the University of Minnesota. This pioneering effort was followed by a series of pancreas transplants worldwide that were characterized by poor success rates, primarily as a result of technical complications and immunologic rejection. In 1980 the International Pancreas Transplant Registry reported 1-year graft survival of 21% and patient survival of 67%. In addition, the potential beneficial effect of this procedure on secondary diabetic complications was questioned by many. As a result, nephrologists and diabetologists were reluctant to refer patients for pancreas transplantation.

In the 1980s, several developments occurred in pancreas transplantation that contributed to the improved results observed during this era. In 1983, we published the first report on the method of bladder drainage for managing pancreatic exocrine secretions.[2,3] Rapidly, bladder drainage (BD) became the accepted technique for exocrine pancreatic drainage and resulted in a decreased incidence in postsurgical technical complications, in particular a reduction in intra-abdominal sepsis. In the same era, cyclosporine A (Sandimmune, Novartis Pharmaceuticals, Basel, Switzerland) and then somewhat later OKT_3 (Muromonab, Ortho Pharmaceuticals, Raritan, NJ) were added to the immunosuppressive armamentarium; both contributed substantially to the better short-term graft survival by reducing graft loss from refractory rejection. At the same time, the majority of centers switched from segmental to whole pancreaticoduodenal

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Address reprint requests to Hans W. Sollinger, MD. PhD, University of Wisconsin Department of Surgery, 600 Highland Ave., H4/780 CSC, Madison, WI 53792-7375.
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Table 1. GENERAL CRITERIA FOR ACCEPTANCE ON THE SPK WAITING LIST

Renal failure (dialysis dependent or advanced diabetic nephropathy, serum creatinine >3.0)
Low C-peptide
Low cardiac risk (negative thallium stress test, absent or mild coronary artery disease)
No major amputations secondary to diabetic vascular disease
History of compliance
Ability to understand complexity of procedure and willingness to follow posttransplant guidelines

transplantation with improved technical success. In 1987, our group performed the first pancreas transplant preserved with UW solution;[4,5] concomitantly, combined procurement of the liver and pancreas from the same donor was initiated simultaneously by several midwestern centers.[6,7]

As a result of these advances on several fronts, pancreas transplantation made marked gains during this era. Still, long-term success was principally limited by a high (up to 75%) incidence of rejection and frequent complications related to urinary diversion of exocrine secretions. However, in the past 5 years, two immunosuppressants, tacrolimus (Prograf, FK506, Fujisawa USA, Deerfield, IL) and mycophenolate mofetil (MMF) (CellCept, RS-61443, Roche Pharmaceuticals, Nutley, NJ), have significantly reduced the risk of rejection and improved short- and long-term graft function. More recently, daclizumab (Zenapax, Roche), a monoclonal antibody targeted to the IL-2 receptor, holds promise for optimal induction therapy. With the recognition that long-term urinary complications are frequently associated with BD,[8] the enthusiasm for this procedure has diminished in the past 2 years. Consequently, there is now a trend toward performing primary enteric drainage (ED), a more physiologic approach that has also been the procedure of choice at our center for the past 2 years.

Since 1987, there has been a steady rise in 1-year graft survival rates for simultaneous pancreas–kidney allografts (SPKs). The 1-year graft survival for 2387 SPKs performed in the United States between 1994 and 1997 is 82%.[9] Our own series of 500 consecutive SPKs reported here demonstrates that good short-term survival, but also excellent long-term survival, can be achieved in this difficult patient population. With an increasing number of patients available for long-term follow-up, it is now possible to assess the long-term effect of a well-functioning pancreas transplant on secondary diabetic complications.

MATERIALS AND METHODS

Patient Selection

All patients referred to our center were interviewed by a transplant surgeon and a transplant coordinator. General criteria for acceptance on the waiting list are shown in Table 1.

All patients had to undergo a thallium stress test before being placed on the waiting list. If the thallium stress test demonstrated evidence of ischemia, cardiac catheterization was performed. In selected high-risk patients, cardiac catheterization was the initial procedure of choice. Recipient demographics are shown in Table 2.

Organ Procurement and Preservation

The details of organ procurement and preservation were described previously in detail.[7] With the exception of the first 27 transplants, all pancreases were preserved in UW solution (Viaspan, DuPont, Wilmington, DE). In 137 cases, the kidney was cold-stored in Viaspan, and in 363 cases, the kidney was preserved on a Belzer perfusion machine using Belzer-UW perfusate. Characteristics of the pancreas donor and preservation are shown in Table 3. Donor serum amylase and serum glucose levels, if high, were not considered contraindications to pancreas transplantation. If the patient did not have a history of diabetes, judgment about the quality of the graft was based solely on assessment during surgery. Pancreases were not used if there was evidence of pancreatitis, trauma, or severe fibrosis. Moreover, mild saponification and edema of the gland was not considered a

Table 2. DEMOGRAPHICS OF 500 CONSECUTIVE SPK RECIPIENTS

Characteristic	Value or %
Age (yrs)	35 ± 6 (21–51)*
Weight (kg)	69 ± 12 (44–124)
Duration of diabetes (yrs)	16 ± 8 (11–35)
Dialysis pretransplant	
Peritoneal dialysis	26.1%
Hemodialysis	29.8%
Both	5.5%
None	38.7%
Transplant #	
1	96.3%
2	3.5%
3	0.2%
Pancreatic exocrine management	
BD	77.6%
ED w/o Roux-en-Y	22.4%
Pretransplant amputations - total	4.1%
Toe	2.7%
BKA	1.4%
HLA mismatch	
Total HLA match	1.3 ± 0.9 (0–6)
A match (0/1/2)	50%/47%/3%
B match (0/1/2)	73%/26.5%/0.5%
DR match (0/1/2)	56%/41%/3%

* Value ± standard deviation (range).
SPK = Simultaneous Pancreas-Kidney; BD = bladder drainage; ED = enteric drainage; BKA = below knee amputation.

Table 3. DONOR AND PROCUREMENT CHARACTERISTICS

Characteristic	Value or %
Age (yrs)	29 ± 12 (4–60)
Gender	
Male	181 (36.2%)
Female	319 (63.8%)
Weight (kg)	73 ± 18 (17–159)
Serum amylase (SU)	92 ± 175 (2–1512)
Plasma glucose (mg/dl)	194 ± 95 (6–824)
Pancreas cold ischemia (hrs)	16.5 ± 4.1 (4–29)
Cause of Death	
Trauma	64.7%
Aneurysm/intracranial bleed	26.5%
Anoxic brain injury	8.8%
Donor Status	
Heart-beating	96.7%
Nonheart-beating	3.3%
Combined liver-pancreas procurement	395 (79%)
Procured by UW team	480 (96%)

UW = University of Wisconsin.

contraindication to procurement and use of the graft. If significant edema of the pancreas was noted, the donor was resuscitated, primarily with colloids or blood. Vascular anomalies were not considered a contraindication to procurement, and no grafts were discarded because of abnormal blood supply to the liver or pancreas. In 82.3% of cases, combined liver and pancreas procurement was carried out. Instances of isolated pancreas procurement included fatty liver, liver lesions such as large cysts, or severe liver trauma.

The procurement procedure begins with a long midline incision extending from the sternal notch to the pubic symphysis if combined heart and abdominal organ retrieval is planned. Otherwise, the incision starts at the xiphoid and extends to the symphysis pubis. As a first step, the falciform ligament is divided to avoid traction injury to the liver. Next, the distal aorta and vena cava are encircled with umbilical tapes and prepared for cannulation. Next, the blood supply of the liver is evaluated for the presence of a replaced left hepatic artery. If no abnormalities are present, the gastrohepatic ligament is divided. After this, the lesser sac is entered and the short gastric vessels are ligated to mobilize the stomach. A staple line is then placed proximal to the pylorus and the stomach is retracted superiorly. Mobilization of the pancreas is begun by incising the posterior and lateral peritoneal attachments of the spleen. The spleen is then grasped and the dissection is continued posteriorly in a lateral-to-medial direction. The spleen is procured in continuity with the tail of the pancreas. As dissection proceeds, the inferior mesenteric vein is ligated and divided. Diaphragmatic crura and celiac lymphatics are divided along the aorta to expose the celiac axis and superior mesenteric artery. Attention is then turned to the hepatoduodenal ligament. The common bile duct is identified and ligated distally as close to the pancreas as possible. The gallbladder is opened and flushed with normal saline. The portal vein is identified and encircled with an umbilical tape to prepare for cannulation and flushing. The duodenum is mobilized with a Kocher maneuver and the small bowel is divided between staple lines a few centimeters distal to the ligament of Treitz. After this, the mesenteric vessels are ligated with silk ligatures. Once dissection of the organs and cannulation have been completed, the proximal aorta is clamped inferior to the diaphragm and perfusion is begun. Approximately 1000 to 2000 ml of Viaspan are delivered via the aortic cannula, and 500 to 1000 ml are delivered simultaneously through the portal vein. The liver, pancreas, and spleen are then removed *en bloc,* reflushed on the back table, and cold-stored in Viaspan at 4°C.

The procedure for non-heart-beating donors has previously been described by D'Alessandro et al.[10]

Preparation of the pancreatic graft before transplantation is performed on the back table in ice-cold Viaspan solution. The important points include shortening of the duodenal segment and placing staple lines proximally and distally. These staple lines are oversewn with Lembert sutures using 3-0 silk. Splenectomy is performed and lymphatic tissue in the area of the superior mesenteric artery and splenic artery is carefully removed. The portal vein is lengthened by ligating and dividing smaller venous branches. Arterial reconstruction is performed with an iliac artery Y graft (Fig. 1) by connecting the external iliac artery to the superior mesenteric artery and the internal iliac artery to the splenic artery.

Pancreas and Kidney Transplantation

The surgical technique of SPK using a whole pancreaticoduodenal allograft has been previously described in detail.[8] Three surgical techniques have been used in this series. In the first 17 cases, BD of exocrine secretions using the duodenal button technique was employed.[11] In the sub-

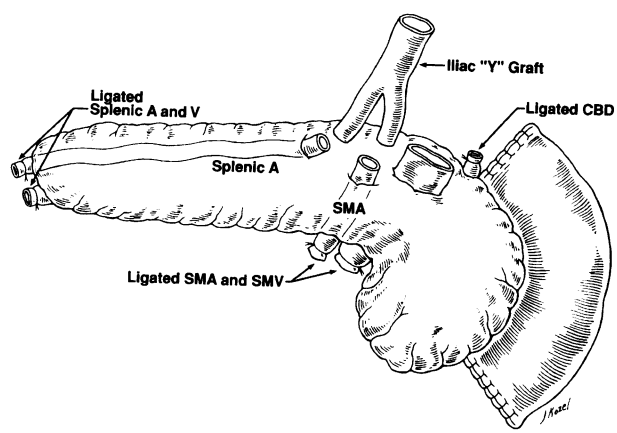

Figure 1. *Ex vivo* reconstruction of pancreaticoduodenal graft.

Table 4. OUTCOMES RELATED TO ORGAN PROCUREMENT AND PRESERVATION

	Overall n = 500 (%)	Enteric Drained n = 112 (%)	Bladder Drained n = 388 (%)
Primary nonfunction*			
Kidney	1 (0.2)	1 (0.9)	0
Pancreas	1 (0.2)	0	1 (0.3)
Graft thrombosis*			
Kidney			
Early	3 (0.6)	2 (1.8)	1 (0.3)
Late	1 (0.2)	0	1 (0.3)
Pancreas			
Early	4 (0.8)	1 (0.9)	3 (0.8)
Late	1 (0.2)	0	1 (0.8)
Acute tubular necrosis†	21 (4.2)	6 (5.4)	15 (3.9)

* Resulting in graft loss.
† As determined by acute dialysis need during primary hospital stay.

sequent 371 cases, BD using a 7- to 10-cm portion of duodenal segment, as first described by Nghiem and Corry,[12] was used. In the last 112 cases, we performed ED using a modification of the Stockholm technique[13] with side-to-side anastomosis of the duodenal segment to the ileum. In the duodenal button technique, the duodenal segment was trimmed to a circular duodenal button surrounding the ampulla of Vater, measuring 3 to 5 cm in diameter. This button was implanted into the bladder with two layers of interrupted sutures. Comparison of the duodenal button technique, as described by D'Alessandro et al,[11] and the duodenal segment technique revealed a high incidence of septic complications; therefore, the duodenal button technique was discarded. In the duodenal segment technique, a side-to-side anastomosis between the antimesenteric border of the duodenal segment and the bladder was performed. Initially, nonabsorbable sutures were used, but later in this series, absorbable sutures (3-0 Maxon) were preferred. In ED grafts, an opening was made in the antimesenteric border of the duodenum measuring 2 to 3 cm long. The site for the anastomosis was the distal ileum approximately 30 to 60 cm proximal to the ileocecal valve. In most instances, a two-layer anastomosis with interrupted silk was used; however, in our recent series, the inner layer was sutured with running 4-0 Maxon. In all other aspects, the recipient operation was similar.

In brief, the abdomen was entered though a long midline incision and the right colon was mobilized by incising the peritoneal reflection, allowing reflection of the right colon cephalad. Right iliac vessels were dissected, and in patients undergoing BD technique, the right iliac vein was completely mobilized by ligating and dividing all posterior branches. This allowed for mobility of the right iliac vein. Exposure of the left iliac system was accomplished by mobilizing the sigmoid colon and reflecting it medially. As on the right side, the iliac vein was mobilized by ligating and dividing the posterior branches. In our later experience, minimal dissection of the vein was performed and the site for the venous anastomosis was the proximal common iliac vein, which was controlled by a side-biting clamp. In all cases, the head of the pancreas and the duodenum were directed toward the pelvis. In BD grafts, the site for the anastomosis was usually the common iliac vein and the common iliac artery. End-to-side anastomosis of the portal vein to the common iliac vein was performed using 6-0 running prolene. No venous extension grafts were used. The iliac bifurcation graft with the common iliac artery was shortened and was implanted in an end-to-side fashion into the common iliac artery. Compared with BD pancreatic allografts, the vascular anastomoses of ED grafts were performed to the more proximal iliac vasculature. Usually, the venous anastomosis was performed in the area of the distal inferior vena cava and the arterial anastomosis was performed to the proximal right common iliac artery. An essential element was the slow release of the vascular clamps after anastomoses were completed. Over the course of several minutes, vascular clamps were removed in the following sequence: proximal venous clamp, distal arterial clamp, proximal arterial clamp, distal venous clamp. After each clamp was removed, careful hemostasis of bleeding vessels on the surface of the pancreas was accomplished before any further clamps were removed. This allowed complete hemostatic control during the reperfusion process. Before removing the vascular clamps, 12.5 g of mannitol and 200 cc of 25% albumin solution were administered intravenously to the recipient. Only after complete hemostasis of the pancreas was obtained was the bladder or enteric anastomosis performed.

The kidney was implanted in the left iliac fossa and a ureteroneocystostomy performed using an anterolateral extravesical Liche technique over a Silastic double-J stent. Midline closure was accomplished with running 1-0 prolene and interrupted 1-0 Ticron sutures.

Enteric Conversion

Patients with significant urologic complications or metabolic acidosis underwent conversion from BD to ED. The technical aspects of this procedure were previously described in detail.[14]

Immunosuppressive Therapy

From 1985 to 1989, our immunosuppressive protocol consisted of a quadruple sequential regimen of azathioprine, prednisone, cyclosporine A, and a 14-day course of Minnesota antilymphocyte globulin (MALG, University of Minnesota ALG Laboratories, Minneapolis, MN). From January 1991, a 14-day course of OKT_3 replaced MALG, a policy that continued until January 1996. From January 1996 until

December 1997, ATGAM (Pharmacia & Upjohn, Kalamazoo, MI) was used for induction therapy, the duration of which varied from 6 to 15 days. In 1995, Neoral (a microemulsified formulation of Sandimmune cyclosporine A, Novartis Pharmaceuticals, East Hanover, NJ) became commercially available, and the use of Sandimmune cyclosporine was abandoned. In May 1995, when MMF became commercially available, this antimetabolite replaced azathioprine at a dosage of 1500 mg twice daily. Nineteen patients in this series received tacrolimus instead of cyclosporine or Neoral.

Rejection episodes, as diagnosed in the majority of cases by renal biopsy, were treated according to severity. Mild to moderate acute cellular rejection was treated with a steroid bolus, whereas severe rejection episodes were treated with a 7- to 14-day course of OKT_3.

Statistical Methods

The rates of events in time such as enteric conversion (EC), infection, complications, rejection, graft failure, and death were estimated with the Kaplan–Meier survival estimator. Comparisons of rates between groups, such as drainage type or immunosuppression, were performed with the log-rank test. All analyses were performed with SAS statistical software.

RESULTS

With the use of Viaspan and the technical principles outlined previously, the overall thrombosis rate for the pancreas was only 0.8% for the entire series (see Table 4). This is the lowest thrombosis rate reported in the literature thus far. Primary nonfunction without thrombosis of the graft occurred in only one pancreatic graft and in one kidney graft. Acute tubular necrosis (ATN), as determined by the requirement for acute dialysis during the first hospital stay, was 3.9% to 4.2% in the entire series. There was a slightly higher ATN rate in our later series of ED grafts, and this may reflect our trend toward accepting more high-risk donors (see Table 3).

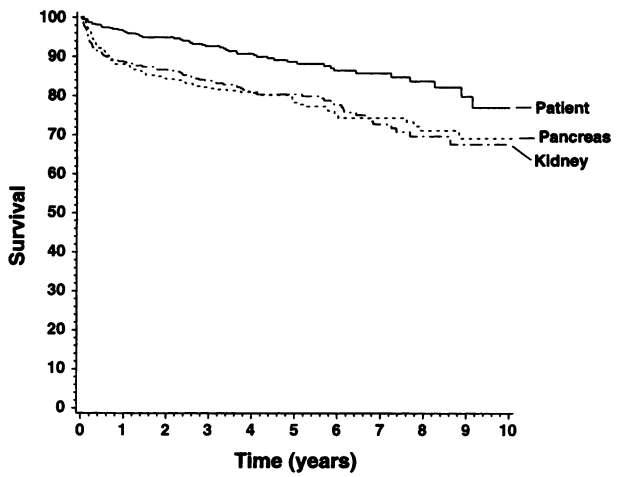

Figure 2. Overall patient, pancreas graft and kidney graft survival—500 consecutive simultaneous pancreas-kidney (SPK) transplants.

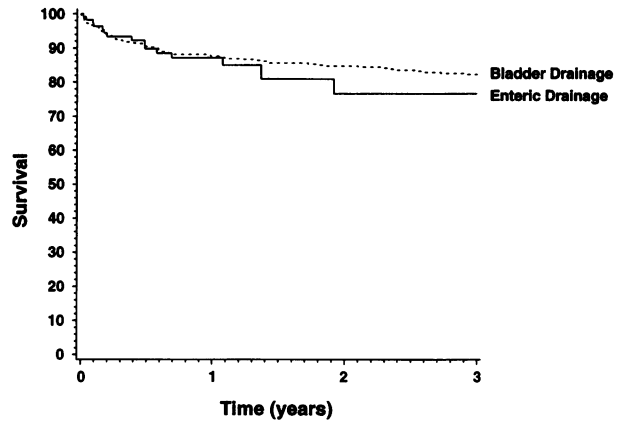

Figure 3. Pancreas graft survival—comparison of bladder drainage *vs.* enteric drainage.

Overall patient, kidney, and pancreas survival rates are shown in Figure 2. Comparison of survival rates between BD and ED do not show a difference at 1 and 3 years (Fig. 3). BD allografts, however, were characterized by significant short- and long-term urologic complications (Table 5). Duodenal segment or bladder leaks occurred at any time after transplantation but were more common in the first 6 months after the transplant. The latest leak in our series occurred 4.8 years after transplantation. Early leaks (<4 weeks) were prominently anastomotic leaks, whereas late leaks occurred most commonly at the duodenal staple lines. Urethral strictures or disruption usually occur months to years after transplantation and are an indication for EC if short-term therapy with Foley catheter drainage for 3 to 4 weeks is unsuccessful, or if recurrence is encountered. Hematuria may be acute or chronic. The etiology of early hematuria is usually bleeding from the suture line, whereas chronic hematuria is caused by ulcers in the duodenal segment or granulation tissue in the area of the anastomosis. In

Table 5. UROLOGICAL COMPLICATIONS IN 388 BLADDER-DRAINED SPK TRANSPLANTS

Complication	n (%)
Urinary tract infection	242 (62.5)
Hematuria	69 (17.7)
Duodenal segment/bladder leak	60 (15.4)
Urethral stricture	11 (2.8)
Urethral disruption	10 (2.5)
Ureteral stricture	4 (1.03)
Ureteral leak	3 (0.77)

SPK = Simultaneous Pancreas-Kidney.

Table 6. TECHNICAL COMPLICATIONS IN THE FIRST YEAR AFTER TRANSPLANTATION IN 500 SPK TRANSPLANTS

Complication	n*	(%)
Enzymatic leak after bladder drainage	60/388	(15.5)
Enzymatic leak after primary enteric drainage	9/112	(8)
Pancreas thrombosis	5	(1)
Kidney thrombosis	4	(0.8)
Ureteral leak	3	(0.6)
Ureteral stricture	4	(0.8)
Intraabdominal abscess	13	(2.6)
Peritonitis and fluid collections	58	(11.6)
Infected pancreatic pseudocyst	2	(0.4)
Wound infection	41	(8.2)
Wound dehiscence	19	(3.8)
Incisional hernia	2	(0.4)
Fasciitis	2	(0.4)

* Denominator of 500 transplants unless otherwise stated.
SPK = Simultaneous Pancreas-Kidney.

serious and persistent cases of chronic hematuria, EC is indicated. Chronic urinary tract infection is by far the most common complication of BD; it can result in chronic complications and frequent readmissions to the hospital, requiring antibiotic therapy.

In addition to urologic complications, complications that occurred in the first year after transplantation included graft thrombosis, primary nonfunction, intraabdominal abscesses, peritonitis, and infected fluid collections (Table 6).

The majority of wound infections were superficial and did not significantly add to the morbidity rate. Wound dehiscence occurred primarily in patients who had intraabdominal abscesses or peritonitis with large fluid collections. Of these patients, 78% had previously undergone peritoneal dialysis, which suggests that this dialytic modality is a risk factor for subsequent septic intraabdominal complications.

Through March 1998, we performed 111 ECs. By October 1, 1997, when this series concluded, 95 ECs had been performed. The indications for EC are shown in Table 7. EC was performed at a mean time of 1.3 years (median 0.6, range 0.1 to 7.6 years after transplantation). In 85 cases, anastomosis was performed to the distal ileum and in 7 cases to the jejunum; in 3 cases an Roux-en-Y limb diversion procedure was performed. Men had a higher incidence of EC (24%) than women (16%) because of a greater frequency of urologic complications, predominantly related to urethritis. To calculate the true incidence of EC, a Kaplan–Meier graph was generated, plotting the percentage of SPK patients undergoing EC *versus* time (Fig. 4). This revealed a 5-year EC rate of 23.8%. Complications after EC that required surgical intervention occurred in 23 patients (24%). The most common surgical complication was an anastomotic leak (eight patients [8.4%]). Management of leaks, unless small and asymptomatic, involved a secondary drainage and diversion procedure. Other surgical complications included incisional hernia (seven), intraabdominal abscess (two), small bowel obstruction (one), negative exploration (one), dehiscence (one), postsurgical hemorrhage (one), and enterovesical fistula (one). Only one graft was lost within 2 months of EC, a kidney that failed from renal artery stenosis 40 days after EC.

Table 7. INDICATIONS FOR ENTERIC CONVERSION IN 388 BLADDER-DRAINED PANCREAS TRANSPLANTS

Indication	n (%)
Leak	42 (44)
Urethral complication	22 (23)
Hematuria	18 (19)
Recurrent UTI	10 (11)
Other	3 (3)

UTI = urinary tract infection.

To examine the risk of neoplastic changes resulting from the exposure of bladder epithelium to pancreatic exocrine secretions, a rim of bladder mucosa was obtained for pathologic review in 48 patients at the time of EC. Of these, one patient exhibited reactive atypia of the bladder epithelium after 8 months. No other patients have developed evidence of bladder neoplasia.

Because of the high incidence of urologic complications and the frequent need for EC, we investigated the use of ED in sporadic instances since 1989 and switched permanently to this drainage technique soon after the commercial release of MMF in June 1995. The majority of ED procedures were

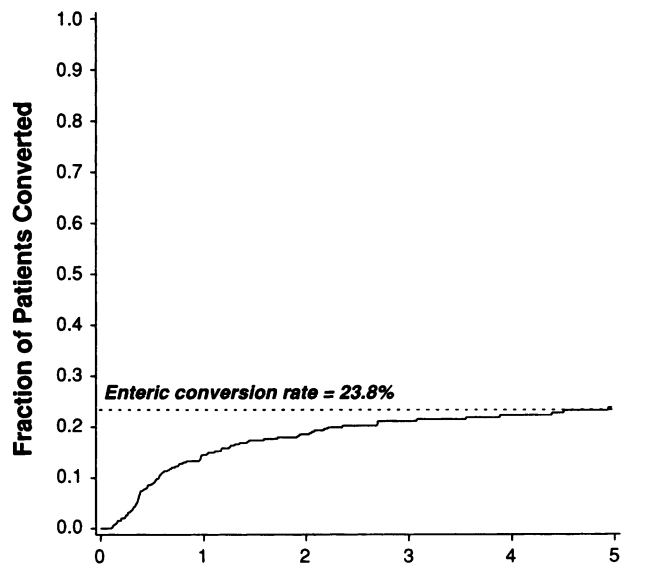

Figure 4. Time to enteric conversion. (Bottom line represents time in years.)

Table 8. ENTERIC DRAINAGE *VS.* BLADDER DRAINAGE

	BD n = 388 (%)	ED n = 112 (%)	p
1-year patient survival	96.1	97.7	NS
1-year kidney survival	88.9	87.5	NS
1-year pancreas survival	87.6	87.1	NS
Intraabdominal infection in 1st year	14.2	12.9	NS
Incidence of infections in 1st year	75.0	55.6	NS
Incidence of UTIs in 1st year	62.5	11.7	p = 0.0001
CMV infections in 1st year	10.9	7.9	p = 0.03
Fungal infections in 1st year	16.7	7.3	p = 0.03
Anastamotic leaks in 1st year	16.7	5.3	NS

BD = bladder drainage; ED = enteric drainage; UTI = urinary tract infection; CMV = cytomegalovirus.

performed during the past 2 years. There was no difference in 1-year patient and graft survival rates between BD and ED (Table 8). There was also no significant difference between the rate of intraabdominal infections and the overall incidence of infections in the first year; however, there was a trend toward fewer infections in the ED group. Most notable is the highly significant decrease in urinary tract infections in the first year, as well as fungal infections. Surprisingly, the incidence of cytomegalovirus infections was also decreased; however, this could be attributed to superior prophylaxis for cytomegalovirus during the past 2 years. The incidence of enzymatic leaks after ED was 5.3%, whereas the incidence of leaks in BD allografts was 15.5% (see Table 6). As a result of enzymatic leakage, one patient and two pancreas transplants were lost. An ongoing analysis demonstrates that readmissions for ED patients are significantly less than for BD patients.

In the entire series, the major reason for pancreas graft loss was rejection, predominantly recalcitrant acute cellular rejection (Table 9). This was followed in frequency by death with a functioning graft (Table 10). Graft loss from technical complications such as enzymatic leak or bleeding was rare. As for pancreas graft loss, kidney graft loss in the majority of cases was the result of acute and chronic rejection, with no difference between ED and BD allografts (Table 11).

Causes of death over a 12-year period are shown in Table 10. Cardiovascular events, including myocardial infarction, cardiac arrest of unknown etiology, and arrhythmia, were the leading causes of death, followed by infection, malignancy, and cerebrovascular accidents. In 11%, patients died at home and no autopsy was performed.

Over the length of our pancreas transplant program, we have made a continuous effort to improve the immunosuppressive regimen because it was demonstrated (see Tables 9 and 11) that rejection was the leading cause of graft loss. Further, the incidence of acute rejection episodes at our

Table 9. REASON FOR PANCREAS GRAFT LOSS

	Overall* 102/500 (%)	Enteric Drained 18/112 (%)	Bladder Drained 84/388 (%)
Rejection	45/102 (44.1)	7/18 (38.9)	38/84 (45.2)
Death with functioning graft	27/102 (26.5)	3/18 (16.7)	24/84 (28.6)
Enzymatic leak	4/102 (3.9)	3/18 (16.7)	1/84 (1.2)
Bleeding	4/102 (3.9)	0	4/84 (4.7)
Graft thrombosis			
Early	4/102 (3.9)	1/18 (5.6)	3/84 (3.6)
Late	1/102 (1.0)	0	1/84 (1.2)
Primary nonfunction	1/102 (0.9)	0	1/84 (1.2)
Infection	3/102 (2.9)	0	3/84 (3.6)
Pancreatitis	3/102 (2.9)	1/18 (5.5)	2/84 (2.4)
Recurrent diabetes	2/102 (2.0)	0	2/84 (2.4)
Chronic graft loss, etiology undetermined	2/102 (2.0)	1/18 (5.5)	1/84 (1.2)
Hemolytic uremic syndrome	1/102 (0.9)	1/18 (5.5)	0
Noncompliance	1/102 (0.9)	0	1/84 (1.2)
Other	2/102 (2.0)	0	2/84 (2.4)
Unknown	2/102 (2.0)	1/18 (5.5)	1/84 (1.2)

* Overall 102 of 500 pancreas allografts failed.

Table 10. CAUSE OF DEATH AFTER SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

Cardiac	20/53 (38%)
MI (12)	
Cardiac arrest (5)	
Arrhythmias (2)	
Cardiac, not MI or pericarditis (1)	
Infection	9/53 (17%)
Sepsis, bacterial (2)	
Sepsis, fungal (1)	
Sepsis, type not specified (1)	
Infection, other (3)	
Infection, pulmonary (1)	
Infection, viral (1)	
Malignancy	5/53 (9%)
PTLD (2)	
Lymphatic (1)	
CNS	3/53 (5.5%)
CVA (2)	
Anoxic brain damage (1)	
Withdrawal from dialysis	3/53 (5.5%)
Respiratory	2/53 (4%)
PE (1)	
Other respiratory, not infection (1)	
Drug overdose, not suicide	2/53 (4%)
Other	2/53 (4%)
Suicide	1/53 (2%)
Unknown	6/53 (11%)

n = 53.
MI = myocardial infarction; PTLD = posttransplant lymphoproliferative disorder; CNS = central nervous system; CVA = cerebrovascular accident; PE = pulmonary embolus.

center (75% at 1 year) was significantly higher than the rejection episodes encountered after kidney transplantation alone (47%). In our initial series, MALG was used in the initial phase of our program. However, after the production of this very potent antilymphocyte serum was discontinued, we switched to induction therapy with OKT_3. Retrospective analysis by Melzer et al. from our group[15] demonstrated that graft and patient survival rates at 1 year did not differ between the two induction regimens. However, there were fewer steroid-refractory rejections in the OKT_3 group. Our initial experience with OKT_3 was favorable as far as side effects were concerned. Later in this series, one patient died as a result of an OKT_3-induced cytokine release syndrome, and two patients developed near-fatal episodes of adult respiratory distress syndrome. For this reason, we abandoned the use of OKT_3 and switched to ATGAM induction.

In June 1995, MMF was introduced commercially, and we retrospectively analyzed our experience with 109 patients receiving MMF maintenance therapy *versus* 249 patients receiving azathioprine maintenance therapy, both groups in combination with cyclosporine and prednisone. In all patients, MMF therapy was initiated at a dosage of 1500 mg twice daily, reduced only if side effects specific for this drug (*e.g.*, diarrhea, neutropenia, or cytomegaloviral syndrome) occurred. As demonstrated in Table 12, with the use of MMF there was a significant reduction in the incidence of rejection episodes for kidney as well as pancreas during the first year. Equally important was the significant reduction in steroid-refractory rejection episodes requiring either OKT_3 or other antilymphocyte preparations for rescue therapy. Kidney and pancreas survival rates at 2 years were significantly better in the MMF group.

DISCUSSION

One of the key elements of a successful pancreas transplant program is the selection criteria for patients undergoing this procedure. We believe that the guidelines outlined in Table 1 provide a reasonable starting point as far as

Table 11. REASONS FOR KIDNEY GRAFT LOSS

	Overall 99/500 (%)	Enteric Drained 15/112 (%)	Bladder Drained 84/388 (%)
Acute rejection	31/99 (31.3)	4/15 (26.7)	27/84 (32.1)
Chronic rejection	29/99 (29.3)	4/15 (26.7)	25/84 (29.8)
Death with functioning graft	25/99 (25.3)	3/15 (20.0)	22/84 (26.2)
Transplant vascular thrombosis			
Early	3/99 (3.0)	2/15 (13.3)*	1/84 (1.2)†
Late	1/99 (1.0)		1/84 (1.2)‡
Primary nonfunction	1/99 (1.0)	1/15 (6.7)	0
Renal artery stenosis	1/99 (1.0)	0	1/84 (1.2)
Infection	2/99 (2.0)	0	2/84 (2.4)
Hemolytic uremic syndrome	2/99 (2.0)	1/15 (6.7)	1/84 (1.2)
Noncompliance	1/99 (1.0)	0	1/84 (1.2)
Other	3/99 (3.0)	0	3/84 (3.6)

* Includes one renal artery thrombosis and one renal vein thrombosis.
† Renal vein thrombosis.
‡ Renal artery thrombosis.

Table 12. COMPARISON BETWEEN MYCOPHENOLATE AND AZATHIOPRINE IMMUNOSUPPRESSION

	MMF (n = 109)	AZA (n = 249)	p value
Acute kidney rejection in first year	34 (31%)	187 (75%)	0.001
Acute pancreas rejection in first year	8 (7%)	62 (24%)	0.003
Steroid-refractory rejection in first year	16 (15%)	133 (52%)	0.01
2-Year Survival			
Patient	99%	95%	NS
Kidney	95%	86%	0.02
Pancreas	95%	83%	0.016

MMF = mycophenolate mofetil; AZA = azathioprine; NS = not significant.

patient selection is concerned; however, personal evaluation by the transplant surgeon is always necessary for individual selection. In addition to the specific points already mentioned, the selection of patients for SPK was guided by the fact that pancreas transplantation was considered a therapy that should provide long-term improvement in quality of life and possible stabilization or improvement of secondary diabetic complications. In our view, it seems to be a waste of donor organs as well as to the disadvantage of our patients to select patients for this procedure who have a limited life expectancy secondary to advanced cardiovascular disease or other advanced diabetic complications such as cerebrovascular or peripheral vascular disease. Unfortunately, screening for coronary artery disease using thallium stress testing, or even cardiac catheterization, does not eliminate the risk for cardiac events; careful follow-up of these patients and thallium stress testing or cardiac catheterizations at regular intervals after transplantation might be necessary. We have recently instituted such a protocol at the University of Wisconsin and hope to decrease the incidence of cardiac deaths in this patient population.

One of the most interesting aspects of the experience described here is the unusually low incidence of immediate posttransplant graft failure secondary to organ-procurement or organ-preservation problems. The characteristics of our donor population, as well as the preservation times, are within the national average range. The incidence of vascular thrombosis of the pancreas is extremely low, possibly lower than any other reported series. We have previously outlined possible reasons for these results.[16] We believe that pancreas retrieval must be performed by a team highly trained and experienced in this procedure. Also, the liver and pancreas were always retrieved by the same team. Clearly, the use of Viaspan has reduced the incidence of postsurgical reperfusion-related pancreatitis, as well as vascular thrombosis. We believe that the use of a venous extension graft for the portal vein enhances the incidence of vascular thrombosis, so it was never used in this series.

In 388 patients, we used BD, in 371 using the duodenal segment technique. This technique was associated with fewer immediate postsurgical complications than other drainage techniques used at that time.[17]

In most centers that adopted this technique, survival rates for pancreas transplantation improved, and centers performing more pancreas transplants alone used urinary amylase monitoring to detect rejection episodes. Over time, however, it became obvious that BD is associated in the long term with significant urologic complications (see Table 5). Duodenal segment or bladder leaks do not always require surgical repair. On occasion they can be treated with Foley catheter drainage, but in most cases definitive surgical repair is required. In our center, we prefer immediate EC if a leak cannot be treated conservatively. Similarly, urethral strictures and disruption, as well as serious cases of chronic hematuria, are best treated by immediate EC. Although the incidence of EC at our center seems higher than at others, this may be solely related to the longer follow-up of BD patients at the University of Wisconsin. Clearly, the high incidence of urinary tract infections—in particular recurrent urinary tract infections—was of major concern. For this reason, as early as 1989 we made attempts to use primary ED. However, several of these patients developed early duodenal segment leaks that resulted in serious septic complications. Analysis of the pancreaticoduodenal grafts after pancreatectomy revealed that anastomotic leaks were always associated with histologic evidence of duodenal rejection. For this reason, we considered it premature to use ED in the majority of our patients until improved immunosuppressive therapy was available. We therefore continued to use BD until June 1995, when MMF became commercially available, and after we had already experienced a significant reduction in rejection episodes during a trial in recipients with cadaver renal allografts.[18]

As of October 1997, 112 primary ED pancreas transplants had been performed. Although there was no difference in patient and graft survival rates, the incidence of urinary tract infections, as well as opportunistic infections, was significantly lower in the ED group. Further, there was no need for EC, and there was a significantly lower incidence of readmissions for urologic problems. For these reasons, ED has now become our drainage procedure of choice, and we will continue to use this technique and further analyze its long-term outcome.

Immunosuppressive therapy has continually evolved over the 12-year time span of this series. Although no prospec-

tively randomized series exists at our center, the use of induction therapy was thought to provide superior outcomes. MALG, OKT_3, or ATGAM was used for induction. There were no differences in graft and patient survival rates between MALG/ATGAM *versus* OKT_3. However, the disturbing side effects caused by the OKT_3-induced cytokine release syndrome prompted us to abandon OKT_3 for induction and to use ATGAM in the later part of our series. Also, over time, and particularly after the introduction of MMF, the course of ATGAM therapy was shortened from 12 to 14 days to 4 to 8 days. Most recently, our center has switched to the use of Zenapax, a monoclonal antibody targeted against the IL-2 receptor, for induction therapy; however, these patients were not included in the present series. Our preliminary data using this monoclonal antibody have been extremely favorable as far as the incidence of rejection and side effects are concerned. Since June 1995, when MMF was released commercially, this antimetabolite was used to substitute for azathioprine. As previously demonstrated in a prospectively randomized trial in recipients of cadaveric renal allografts, marked reduction in the incidence of acute rejections within the first year was noted, as well as in the incidence of steroid-refractory rejection (see Table 12). Two-year kidney and pancreas survival rates are statistically significantly superior to azathioprine maintenance therapy in our retrospective analysis. Also, MMF use allows for more aggressive steroid tapering.

Ten-year patient and graft survival rates for SPK recipients in this series are 77% for patient survival and 67% for kidney and pancreas survival. At our center, these survival rates are superior to those of diabetic recipients who receive an HLA-identical live donor kidney, a haplotype-matched live donor kidney, or a cadaver kidney transplant. Clearly, diabetic recipients of cadaver kidneys are older than SPK recipients and have more risk factors, explaining the statistically significantly inferior outcome. However, recipients of live donor grafts were well matched for age and risk factors. It is possible that the long-term beneficial effect of a well-functioning pancreatic transplant, providing perfect blood glucose control, has a beneficial effect on long-term outcome. It will be of great interest to follow this group of patients for 15 to 20 years because the beneficial effect of the pancreas transplant should become even more pronounced during long-term follow-up.

Because a well-functioning pancreas transplant has a significant impact on the quality of life,[19] improvement of neuropathy,[20] stabilization of retinopathy,[21] and prevention of recurrence of diabetic nephropathy in the transplanted kidney,[22] this procedure is justified and is clearly the procedure of choice in well-selected uremic patients with type 1 diabetes.

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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): This is an altogether remarkable paper describing one of the world's largest and most successful series of pancreas transplants. It is ironic that Dr. Sollinger's group, which was responsible for popularizing the bladder drainage technique, have experienced at least as great incidence of late complications from this procedure as others who followed their lead.

Although development of this method was a contribution in the evolution of pancreas transplantation, since it was safe and facilitated recognition of rejection, the Wisconsin group are now changing to the bowel drainage technique, as I think most other groups are doing. The overall results of graft survival in their series, which includes patients transplanted as long as 12 years ago are about 5% better than the current overall U.S. results and about 15% better than earlier results of others during the time comparable to this series.

One wonders what factors were responsible for the superiority of the Wisconsin experiences. The manuscript suggests several possible reasons about which I would like to ask Dr. Sollinger: Is his recipient selection unusually careful, excluding high-risk patients who might be accepted for transplantation by others leading to poorer outcome? Does their unusually low rate of acute tubular necrosis of the kidney (only 4%) favor the pancreas and the kidney?

Mentioned in their manuscript is an aggressive protocol employed in donors who they believe results in an observable decrease in donor pancreas edema. Is this a factor in the remarkably low incidence experienced by the Wisconsin group of pancreas allograft vascular thrombosis (less than 1%, no more than their incidence of thrombosis of the kidney transplant vessels). This is approximately 12 times lower than the incidence of complication reported by others over the time during which their series was compiled. Can Dr. Sollinger tell us how he avoids this catastrophic complication which is so commonly encountered by others?

Finally, it is of considerable interest that although they see acute rejection crisis in about 75% of their simultaneous kidney-pancreas patients, as compared with only 47% in the kidney alone patients, the eventual kidney allograft survival is actually better in the simultaneous kidney-pancreas recipients than in kidney alone, even those with related donors.

Is it conceivable that the greater antigen load of the double transplant or the large number of passenger leukocytes derived from lymphoid rich pancreaticoduodenal component of the double allograft actually provide an advantage over the kidney alone transplants? This would add further support to Dr. Starzl's contention that the lymphoid cell chimerism resulting from solid organ allografts is importance in their acceptance.

DR. HANS W. SOLLINGER (Madison, Wisconsin): Thank you, Dr. Barker. First of all, I do not know of any scientific evidence exploring why kidney-pancreas transplants, despite the high incidence of rejections, fare better than kidneys which have about half the incidence of rejection episodes. As far as antigen load is concerned, I hope that Dr. Starzl can shed some light on this issue.

As far as the preservation characteristics are concerned and why we do so well as compared with other series, obviously having been trained by Dr. Fred Belzer has helped us to understand how to preserve organs very well.

The low thrombosis rate has even surprised me. But we have trained a number of fellows over the years, and after they went out and started their own programs, they also had very low thrombosis rates. So there might be something about the technical aspects which we use in our procedure which leads to low thrombosis rates. Some of the critical points have been outlined in an editorial in *The Journal of the American College of Surgeons* a year ago. So I refer you to my editorial, which lists several points about how to address the low incidence of thrombotic complications.

DR. THOMAS E. STARZL (Pittsburgh, Pennsylvania): Dr. Robb Corry, a pioneer of pancreas transplantation at the University of Iowa, asked me to pay tribute to this landmark paper of Hans Sollinger, and also to the late Richard Lillehei, who was the first to perform whole pancreas transplantation 31 years ago. Under azathioprine-based immunosuppression, the procedure had such a high mortality that it was abandoned world-wide in 1971 for about a dozen years. After the advent of cyclosporine, we reintroduced the Lillehei procedure in Pittsburgh, with the modification of exocrine drainage through a duodenal bubble which was anastomosed to the host jejunum (Starzl et al., *Surg Gynecol Obstet* 1984;159:265–272. Sollinger at Wisconsin and Corry at Iowa further modified the operation by anastomosing the bubble to the bladder instead of bowel. This allowed monitoring of rejection with urinary amylase determinations, but with the urologic and metabolic complications that are well known.

By the time Dr. Corry joined the Pittsburgh faculty, the more potent drug, tacrolimus, was available. In agreement with what Dr. Sollinger has said, secondary reforms were possible with the more reliable control of rejection. First, the perioperative induction therapy with ALG and OKT3 that had become standard with cyclosporine-based therapy was no longer necessary. In addition, the more physiologic enteric drainage procedure could be performed safely. We have almost exclusively used the original enteric drainage procedure described in 1984, which also has become Sollinger's preferred technique.

This slide shows Dr. Corry's results with 110 cases after he joined our Pittsburgh faculty in 1994. You can see the very high 2-year survival of patients, 98%; kidneys, 94%, and pancreas grafts, 81%. In connection with Dr. Barker's comments, these patients were not highly selected. There were many who had had previous amputations, were blind, and had other complications. Thus, it is a procedure that is applicable across the board. Incidentally, as Dr. Barker implied, the better survival of kidneys in the Wisconsin double organ recipients *versus* that of kidneys alone probably is due to the greater dose of donor leukocytes and consequent augmented chimerism under the former circumstances.

I think what we have heard today is an announcement, and a far-reaching one, from Dr. Sollinger, who is a very important figure in the field, that the day of pancreas transplantation as a legitimate, cost-effective, and efficient service has arrived. All we can say is thank you for what you have done.