A 10-Year Experience with 290 Pancreas Transplants at a Single Institution

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Since our report at the 1984 American Surgical Association meeting of 100 pancreas transplants from 1966 through 1983, another 190 have been performed. The current series, begun in 1978, now numbers 276 cases, and includes 133 nonuremic recipients of pancreas transplants alone (PTA), 46 simultaneous pancreas/ kidney transplants (SPK), and 97 pancreas transplants after a kidney transplant (PAK). Duct management techniques used were free intraperitoneal drainage in 44 cases, duct occlusion in 44, enteric drainage in 89, and bladder drainage in 128. The 1-year patient and graft survival rates in the entire cohort of 276 were 91% and 42%. One-year patient survival rates were 88% in the first 100, 91% in the second 100, and 92% in the last 76 cases; corresponding 1-year graft survival rates were 28%, 47%, and 56% ($p < 0.05$). A prospective comparison of bladder drainage (n = 82) *versus* enteric drainage (n = 46) in PAK/PTA cases since November 1, 1984 favored bladder drainage (1-year graft survival rates of 52% *vs.* 41%) because of urinary amylase monitoring. The best results were in recipients of primary SPK bladder-drained transplants (n = 39), with a 1-year pancreas graft survival rate of 75%, kidney graft survival rate of 80%, and patient survival rate of 95%. Logistic regression analysis, with 1-year graft function as the independent variable, showed significant ($p < 0.05$) predictors of success (odds ratio) to be technique: bladder drainage (5.8) *versus* enteric drainage (2.5) *versus* duct injection (1.0); category: SPK (6.0) *versus* PAK from same donor (3.2) *versus* PAK from different donor (1.2) *versus* PTA (1.0); and donor HLA DR mismatch: 0 (5.0) *versus* 1 (2.5) *versus* 2 (1.0) antigens. On April 1, 1989, 90 patients had functioning grafts (60 euglycemic and insulin-free for more than 1 year, 10 for 5 to 10 years); these, along with 24 others whose grafts functioned for 1 to 6 years before failing, are part of an expanding cohort in whom the influence of inducing a euglycemic state on preexisting secondary complications of diabetes is being studied.

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Only preliminary data is available. In regard to neuropathy, at more than 1 year after transplant in patients with functioning grafts, conduction velocities in some nerves were increased over baseline. In regard to retinopathy, deterioration in grade occurred in approximately 30% of the recipients by 3 years, whether the graft functioned continuously or failed early, but thereafter retinopathy in the patients with functioning grafts remained stable. In patients with functioning pancreas grafts, kidney biopsies have shown a decreased glomerular mesangial volume compared to diabetic controls. Pancreas transplantation is increasingly successful in both uremic and nonuremic diabetic patients, and may ameliorate secondary complications of diabetes.

PANCREAS TRANSPLANTS ARE BEING performed with increasing frequency in the management of patients with diabetes mellitus and its associated complications. By the end of 1988, 1830 cases had been reported to the International Pancreas Transplant Registry, and more than 300 were reported for each of the last 2 years.[1] Most pancreas transplants have been performed in uremic diabetic recipients of kidney transplants, but pancreas transplantation to nonuremic diabetic patients with early complications has also been applied, primarily at the University of Minnesota.[2]

The first pancreas transplant was performed at the University of Minnesota in 1966.[3] This case was part of a series of 14 cases that ended in 1973.[4] Only one graft in the early series functioned for more than 1 year.[5] In 1978 pancreas transplants were resumed at the University of Minnesota,[6] and by the end of 1983 a total of 100 had been performed.[7] Between then and March 1989, another 190 pancreas transplants were performed, bringing the total since 1968 to 290 (Fig. 1).

The second series of pancreas transplants, begun in

1978, has now been in progress for more than 10 years, and by the end of March 1989 it included 276 transplants in 222 patients. Three categories of recipients were included in the series: (1) nonuremic, nonkidney transplant patients whose diabetic complications were judged more serious than the side effects of immunosuppression; (2) patients with advanced diabetic nephropathy who received kidney transplants simultaneous with the pancreas; and (3) patients with end-stage diabetic nephropathy who had functioning kidney transplants placed before the pancreas.

This series is unique in that a large number of patients in all three categories have been included. In the initial cases, emphasis was placed on the first and third categories. It was not until 1986 that we began to perform pancreas transplants in the second category.

Another feature of this series is the testing of multiple pancreas graft-duct management techniques, including free intraperitoneal drainage,[6] duct occlusion with synthetic polymers,[8] enteric drainage,[7] and bladder drainage.[9] Other institutions have tended to use one or the other of the techniques exclusively, while we have tested all of the common techniques after their introduction by others.[10,11] Between 1984 and 1987 we performed a prospective study comparing enteric and bladder drainage.[9] Since that time we have used bladder drainage nearly exclusively, except for a few segmental pancreas transplants from living related donors, and for one cadaver donor pancreas transplant to a recipient who also had pancreatic exocrine deficiency and in whom enteric drainage was used to correct this problem as well as the diabetic condition.

The most important feature of our series has been the systematic assessment of the secondary complications of diabetes before and serially after pancreas transplantation. The first case in the initial series established that pancreas transplantation could induce an insulin-independent, normoglycemic state.[3] Numerous studies since that time have confirmed this observation.[12–14] Although minor metabolic perturbations have been described, perhaps secondary to the corticosteroids used to prevent rejection,[15] or, in some cases, to the delivery of insulin *via* the systemic venous system,[16] glycosylated hemoglobin levels in pancreas transplant recipients are normal for as long as the graft functions.[17–19]

Thus pancreas transplantation provides an opportunity to determine whether the induction of a euglycemic state can influence the progression of diabetic complications present at the time of the operation. The results of some of our studies in this regard have been reported in preliminary form.[20–24] The preliminary observations suggest that pancreas transplantation in general has a favorable effect on secondary complications as long as they are not too advanced, but definitive statements will not be possible until long-term observations in a larger number of patients have accumulated.

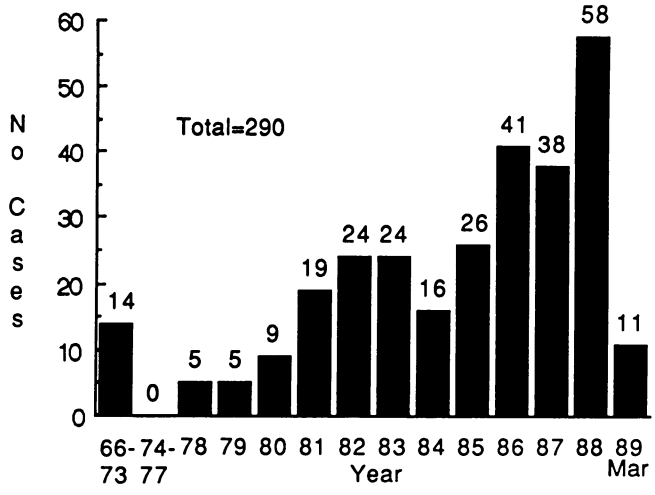


FIG. 1. Number of pancreas transplants by year from December 1966 through March 1989.

The potential for pancreas transplantation to have an impact on the treatment of diabetes, however, is clear, especially if methods to prevent rejection with fewer side effects than the regimens currently employed are developed. Our results have improved with time, primarily due to the introduction in 1983 of a triple immunosuppressive therapy regimen consisting of cyclosporine, azathioprine, and prednisone,[7] and to the early treatment of pancreas rejection episodes diagnosed by monitoring urinary amylase levels in bladder-drained pancreas transplants.[25] The results of our experience over the past 10 years with the less-than-perfect immunosuppressive regimens available are summarized in this report.

Materials and Methods

Patient Population and Categories of Recipients

Between July 1978 and March 1989, 276 pancreas transplants were performed in 222 recipients (there were 37 second, 15 third, and 2 fourth transplants). Categories of patients included 133 recipients of pancreas transplants alone (PTA), 46 recipients of simultaneous pancreas and kidney transplants (SPK), and 97 recipients of a pancreas after a kidney transplant (PAK). Demographic features, overall and in each of the recipient categories, are shown in Table 1. The number of recipients by category for each year since commencement of the second series is shown in Figure 2. All the SPK transplants have been performed since 1985, and the distribution of pancreas transplants has been nearly equal among the three recipient categories during the past 2 years.

Surgical Techniques and Duct Management Methods

The grafts have been procured from both living related (n = 69) and cadaver (n = 207) donors. Living related

TABLE 1. *Demographic Features of Pancreas Transplant Recipients*

Recipient* Categories (N)	Sex		Mean ± SD (and Range) in Years		
	Male (n)	Female (n)	Age at Onset of Diabetes	Duration of Diabetes	Age at Transplant
Pancreas transplants alone (133)	38	95	11.1 ± 5.9 (<1–32)	20.6 ± 6.6 (1–42)	31.6 ± 6.5 (17–52)
Simultaneous pancreas and kidney txs (46)	19	27	12.0 ± 5.6 (2–26)	23.1 ± 6.4 (12–44)	34.4 ± 6.5 (23–50)
Pancreas after a kidney transplant (97)	49	48	9.2 ± 5.2 (1–33)	24.8 ± 5.6 (11–44)	33.7 ± 5.8 (21–46)
All recipients (276)	106	170	10.5 ± 5.7 (<1–33)	22.5 ± 6.5 (1–44)	32.8 ± 6.4 (17–52)

* All pancreas transplant cases from July 1978 through March 1989; 207 from cadavers and 69 from related donors.
Tx, transplant.

donor grafts were transplanted exclusively to recipients of pancreas transplants alone or a pancreas after a previous kidney, while cadaver donor grafts were transplanted to all three recipient categories, including those who received a simultaneous kidney from the same donor. All of the living related donor grafts were segmental, while 59 of the cadaver donor grafts were segmental and 148 were whole or whole pancreaticoduodenal transplants.

Since 1984 most cadaveric pancreas grafts have been procured from multiple organ donors, including 53 from liver donors. The surgical technique for procuring whole pancreas grafts from liver donors has been previously described.[26] In some cases the celiac axis was retained with the pancreas. In most cases it was not, and either a Y-graft of donor iliac artery was anastomosed to the superior mesenteric and splenic arteries of the graft, or the graft splenic artery was anastomosed directly to the graft superior mesenteric artery before revascularization in the recipient. All but five grafts were revascularized by anastomoses to the iliac vessels of the recipient. In five instances the splenic vessels of segmental grafts were anastomosed to the inferior mesenteric vessels of the recipient.[27]

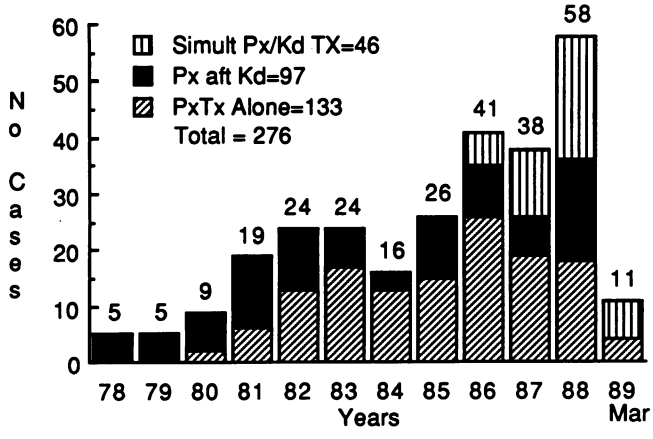


FIG. 2. Annual number of pancreas transplants according to recipient categories from July 1978 through March 1989.

Before 1983, cadaveric pancreases were transplanted immediately after removal from the donor. Since 1983, cadaver donor pancreas grafts have been preserved by cold storage in a silicagel filtered plasma solution (n = 147) or UW solution (n = 23) for periods of time ranging from 4 to 38 hours (mean of 16.3 ± 6.8 hours) before transplantation, solutions shown to be effective in the preservation of canine pancreases for even longer periods.[28,29]

In the entire series since 1978, methods of pancreatic graft duct management in the recipients were free drainage into the peritoneal cavity in 15 cases (open duct), duct occlusion in 44 cases (3 ligations, 36 silicone rubber injected, 4 prolamine injected, and 1 neoprene injected), enteric drainage in 89, and bladder drainage in 128 (Fig. 3). The open duct and duct-occlusion techniques were used in the earliest cases and were than superceded by enteric drainage. Bladder drainage and enteric drainage were performed in nearly equal numbers between 1985 and the first part of 1987. Since then nearly all grafts have been bladder drained.

Bladder drainage was accomplished by ductocytostomy in 11 segmental grafts (5 related, 6 cadaver) of the tail, and *via* a duodenocystostomy in one segmental graft of the head, and in 116 whole pancreaticoduodenal grafts. Of the latter, five were anastomosed to the bladder by the duodenal patch technique described by Sollinger et al.,[11] while 115 were anastomosed to the bladder using a tube of donor duodenum, handsewn in 60 cases as described by Nghiem et al.[30] and by stapling with an EEA device in 51 cases as described by Pescovitz et al.[31]

All the duct management techniques have been used in PTA and KPA recipients, including bladder drainage. In SPK recipients only the bladder drainage technique has been used.

Recipient Immunosuppression

Before November 1984, only two drugs were used for maintenance immunosuppression in pancreas transplant recipients—either azathioprine and prednisone or cyclo-

sporine and prednisone. Since that time maintenance immunosuppression has been with three drugs, cyclosporine, azathioprine, and prednisone. Antilymphocyte globulin (ALG) has been used for induction immunosuppression, ranging from seven to 14 doses at 20 mg/kg/day. Our current immunosuppressive regimen is depicted in Figure 4. In brief, cyclosporine is given in an initial dose of 8 mg/kg/day, beginning immediately after transplantation to patients who do not receive a simultaneous kidney transplant, and is delayed for five days in those who do. Thereafter the dose is tapered to maintain cyclosporine blood levels at approximately 200 ng/mL in the first 6 months, 150 ng/mL during the second 6 months, and 100 ng/mL thereafter. Azathioprine is given in an initial dose of 5 mg/kg/day and thereafter tapered to 2.5 mg/kg/day and adjusted to maintain a white count of more than 4×10^9 cells/L. The initial prednisone dose is 2 mg/kg/day, and it is then tapered to a dose of 0.5 mg/kg/day by 1 month and 0.2 mg/kg/day by 1 year.

Before the use of bladder drainage, rejection episodes were diagnosed by elevations in plasma glucose levels, and were usually confirmed by biopsy before treatment.[32]

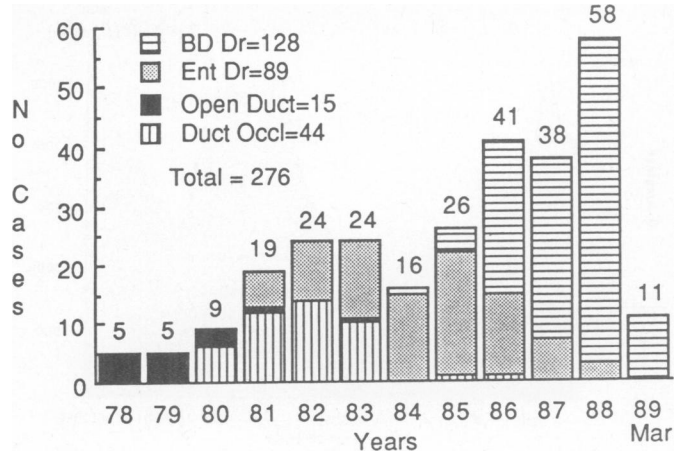


FIG. 3. Annual number of pancreas transplants according to duct management technique from July 1978 through March 1989.

With the introduction of bladder drainage in 1984, urine amylase has been used to monitor for rejection, based on the observations that a decrease in urinary amylase activity precedes hyperglycemia as a manifestation of rejection.[25]

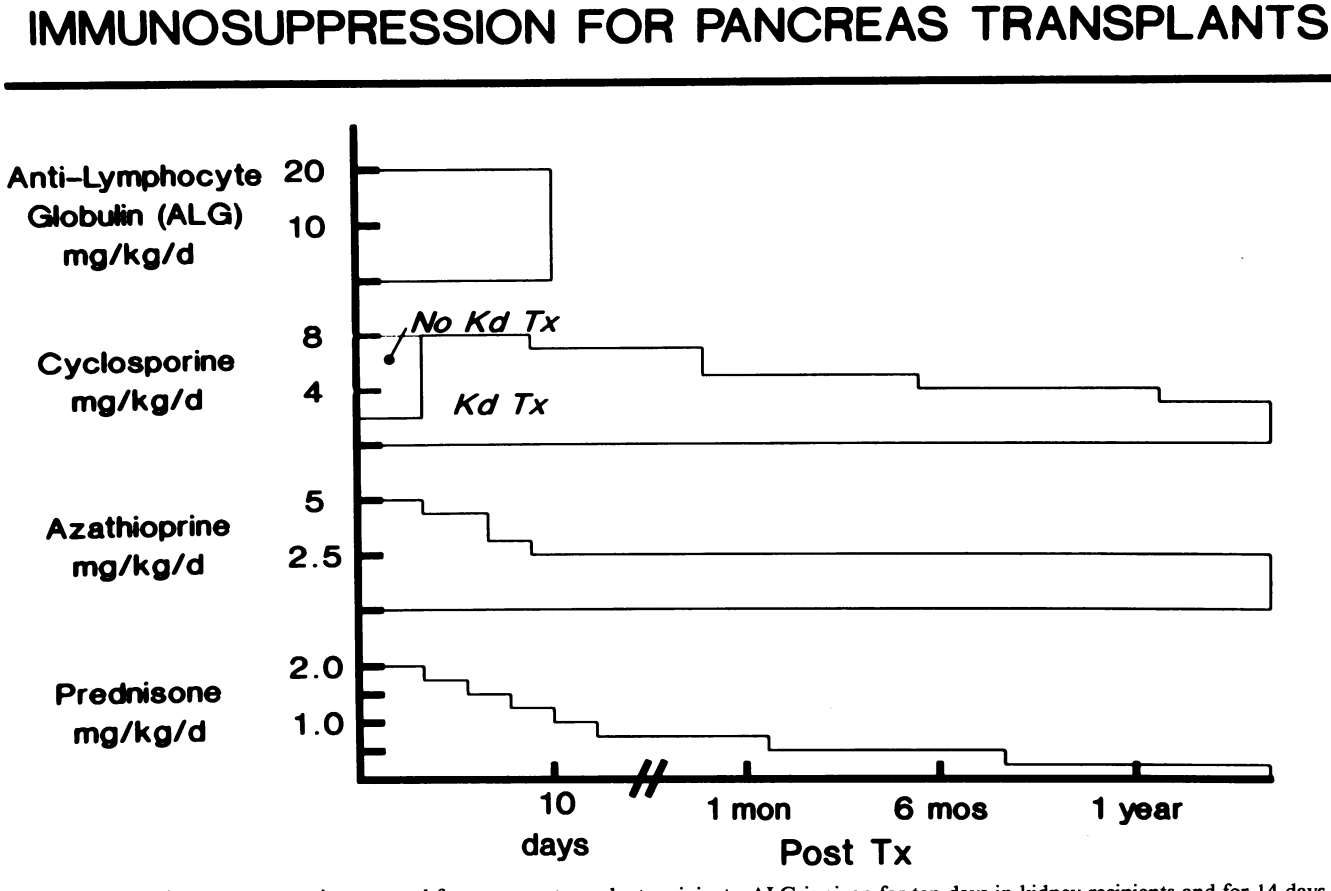


FIG. 4. Current immunosuppressive protocol for pancreas transplant recipients. ALG is given for ten days in kidney recipients and for 14 days in pancreas-only recipients. Recipients of simultaneous kidney transplants are given a lower initial dose of cyclosporine; but otherwise the protocol is similar in recipients of pancreas transplant alone or a pancreas after a kidney.

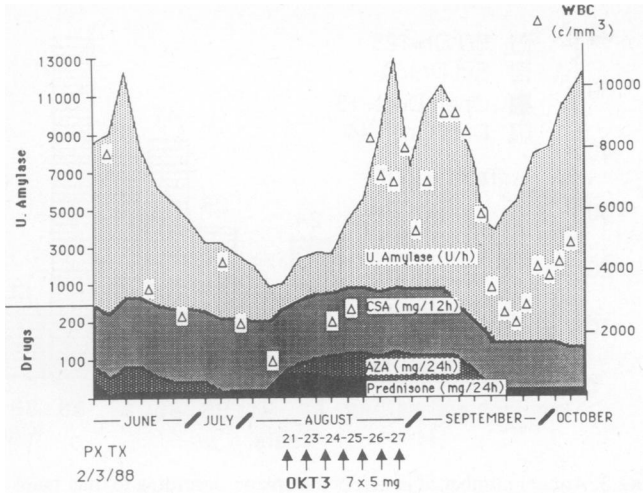


FIG. 5. Urinary amylase levels in relation to antirejection treatment in a nonuremic recipient of a bladder-drained pancreas transplant. The urine amylase declined without a rise in plasma glucose. A pancreas graft biopsy showed rejection. Treatment with anti-OKT3 was followed by an increase in urine amylase and the patient remains normoglycemic.

In recipients of simultaneous kidney transplants from cadaver donors, rejection episodes of the kidney, suspected when there is an increase in serum creatinine, can be confirmed by biopsy, and if present may be a harbinger of pancreas rejection. We have diagnosed rejection episodes of bladder-drained pancreas transplants when there has been a decline in urine amylase, and have not confirmed most of these by biopsies, in contrast to our liberal use of biopsies before the introduction of bladder drainage.[33] However we have done transcystoscopic pancreas graft biopsies in seven bladder-drained transplants, and a decline in urinary amylase activity by more than 50% was associated with histological features of rejection.

Rejection episodes have been treated by a temporary increase in the dose of prednisone, and administration of either ALG (20 mg/kg) or anti-OKT3 monoclonal antibody (5 mg/day) for seven to ten days. Prednisone alone or either ALG or OKT3 alone is used for treatment of rejection episodes judged to be mild based on the magnitude of the decline in urinary amylase and biopsy findings, but most rejection episodes were treated with both prednisone and ALG or OKT3. A typical response to antirejection treatment is shown in Figure 5.

Studies of Secondary Complications

The patients were studied in the Clinical Research Center before and serially after pancreas transplantation. During these admissions the patients underwent metabolic studies, including glycosolyated hemoglobin levels, a 24-hour profile of plasma glucose levels before and 1 and 2 hours after meals, oral and intravenous glucose tolerance tests,[12] islet hormone responses to various secretogues,[16] and detailed studies of nerve,[20,21] eye,[22] and kidney function[34] and morphology.[23,24] In follow-up studies the patients with continuous graft function (more than 1 year) have been compared with those whose grafts failed early (less than 4 months), or to patients who intended to receive pancreas transplants, but who did not for a variety of reasons, such as inability to find a donor to whom they had a negative crossmatch.

Statistical Calculations

Patient and graft survival rates were calculated by the actuarial method, and the significance of differences (p values) were determined by the Gehan test.[35] Logistic regression analysis was used to calculate odds ratios for factors influencing graft survival rates.[36] Student's t test was used to calculate the significance of differences in mean values, and Fishers exact test was used to determine the significance of difference in incidences of events between groups.

Grafts were considered functioning as long as the recipients were insulin independent and euglycemic (plasma glucose < 180 mg/dL). Graft loss was defined as resumption of exogenous insulin for whatever reason, or death with a functioning graft. Graft survival rates were calculated separately for all and for technically successful (TS) cases. A technical failure (TF) was defined as a graft that failed from thrombosis, local infection, bleeding, pancreatitis, or similar problems leading to removal. Patient and graft survival rates were calculate for four eras. The first era, from 1966 to 1973, included the 14 cases in the initial series of Lillehei et al.[5] The second through fourth eras are all in the second series. The second era includes the first 100 cases of the second series from July 1978 through September 1984, the third era includes the second 100 cases from 1984 to 1987, and the fourth era includes the last 76 cases in the second series, performed from September 1987 through March 1988. The last two eras were combined for a separate analysis of outcome according to technique, recipient categories, and other parameters. In both eras triple therapy was used for immunosuppression, and all the bladder-drained and all the simultaneous pancreas/kidney transplants have been performed in this period.

Results

Patient and Graft Survival Rates by Era

Patient and graft survival rates according to era of transplantation are shown in Figure 6. The initial series (1966–1973) was characterized by both low patient and graft survival rates. In the second series, patient survival rates have been high in all three eras (88% for era 1, 91% for era 2, and 92% for era 3). The most frequent cause of death was myocardial infarction, and only a few of the

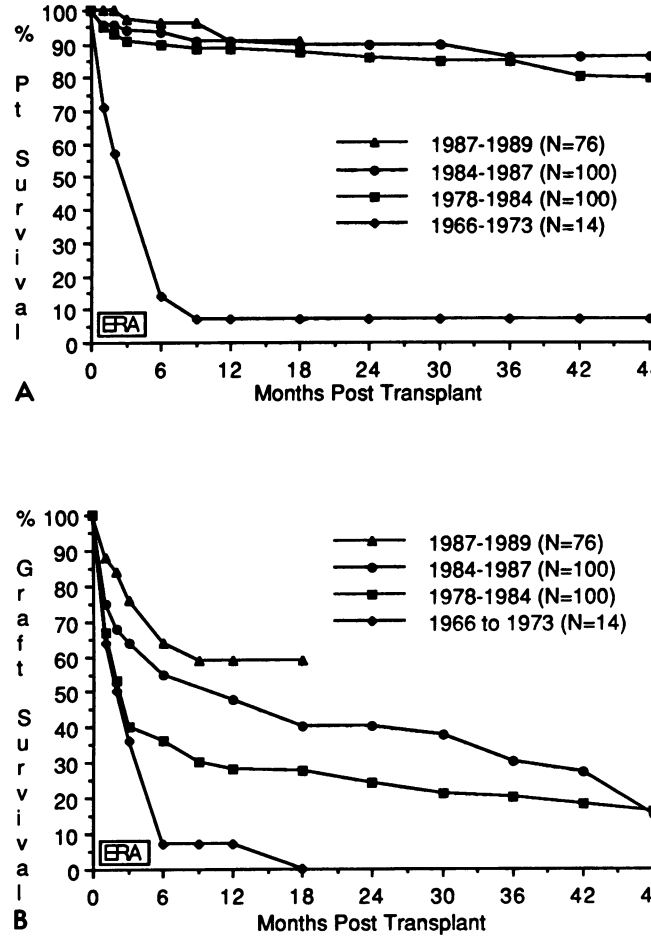
deaths could be attributed directly to the transplant procedure itself or to immunosuppression. Graft survival rates have shown a progressive improvement. In the last era, the overall 1-year pancreas graft survival rate was 55%. The results according to recipient category within each of the last three eras are shown in Table 2. For both the 1984–1987 and 1987–1989 eras the highest pancreas graft survival rates were in recipients of simultaneous kidney transplants.

The improvement in graft survival rates was not due to a decrease in technical complications but rather to the introduction of triple therapy immunosuppression[7] and adaptation of the bladder drainage technique with urine amylase monitoring, allowing early diagnosis and treatment of rejection episodes.[25] Of the first 100 cases in the second series (1978–1984), 29 pancreas grafts failed for technical reasons (29%): 10 from thrombosis (10%), 12 from infection (12%), and 7 from other causes (7%). Of the last 176 cases in the second series (1984–1989), 47 failed for technical reasons (26.8%): 14 from thrombosis (8%), 13 from infection (7.4%), and 20 from other causes (11.4%). For the entire series of 276 cases, the technical failure rate was lower for cadaver donor (50/207, 24.1%) than for related donor grafts (26/69, 37.6%), with thrombosis occurring in 9 cadaver (4.3%) and 15 related (21.7%) donor cases, infection in 16 cadaver (7.7%) and 11 related (13.0%) donor cases, and other complications in 25 cadaver (12.1%) and 2 related (2.9%) donor cases.

Graft Survival Rates According to Duct Management for 1984 to 1989

The results of a prospective study comparing bladder and enteric drainage has been previously reported.[25] Since 1987 almost all transplants have been with the bladder drainage technique. A comparison of graft survival rates was made for transplants performed by bladder drainage and enteric drainge since November 1984. In the analysis of all cases, the 1-year graft survival rate was 56% for bladder (n = 128) and 42% for enteric (n = 46) drainage. The corresponding 1-year graft survival rates for technically successful bladder (n = 99) and enteric (n = 29) drainage cases was 73% and 58%. For primary transplants with bladder (n = 96) and enteric (n = 39) drainage, the 1-year graft survival rates were 60% and 43%. The corresponding 1-year graft survival rates for technically successful primary bladder (n = 77) and enteric (n = 25) drained grafts were 75% and 64% (p = NS).

The ability to use urinary amylase monitoring for rejection, coupled with the higher graft survival rate (even though not statistically significantly), prompted us to switch from enteric to bladder drainage for nearly all cases beginning in 1987. The patient and graft survival rate curves for all bladder-drained pancreas transplants performed since 1984, regardless of recipient category or



FIGS. 6A AND B. (A) Patient and (B) graft survival rates for pancreas transplant recipients according to era.

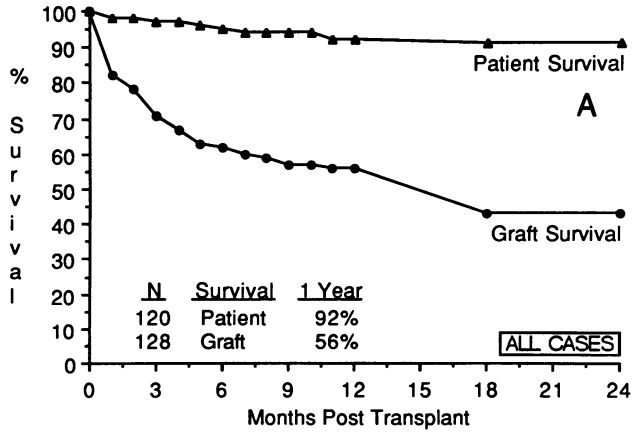
transplant number, are shown in Figure 7A. Although not statistically significant (p = 0.133), the pancreas graft functional survival rate has been higher for first transplants

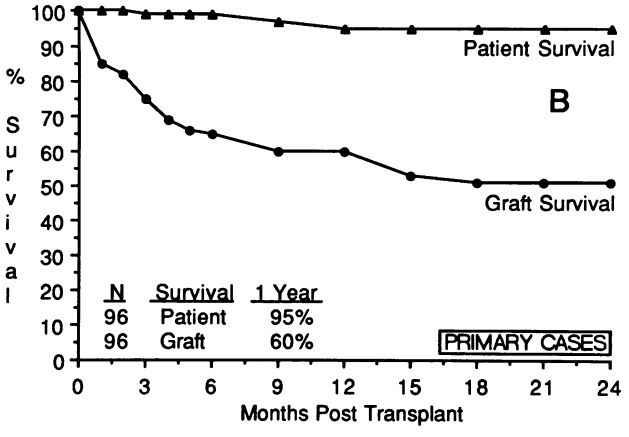
TABLE 2. *Pancreas Graft Survival Rates 1 Year After Transplantation by ERA*

Category (N)*	1978–1984 (N)	1984–1987 (N)	1987–1989 (N)
Px Tx Alone			
All grafts (133)	29% (49)	47% (58)	54% (26)
TS grafts (113)	39% (33)	62% (42)	59% (24)
Simul. px/kid. tx			
All grafts (46)	—	65% (17)	68% (29)
TS grafts (37)	—	79% (14)	89% (23)
Px after kid.			
All grafts (95)	27% (51)	36% (25)	42% (21)
TS grafts (64)	37% (38)	64% (11)	60% (15)
All cases			
All grafts (276)	28% (100)	47% (100)	56% (76)
TS grafts (200)	38% (71)	66% (67)	70% (62)

* Includes all surgical techniques as well as primary and retransplant cases.

Px, pancreas transplant; Tx, transplant.





FIGS. 7A AND B. Patient and graft survival rates for (A) all and (B) primary bladder-drained pancreas transplants performed from November 1984 to March 1989. In (A) 32 of the cases were retransplants, 8 in recipients of previous bladder-drained pancreas transplants, hence the number of patients was 120; the other 24 retransplants were in recipients of previous pancreas transplants managed by techniques other than bladder drainage.

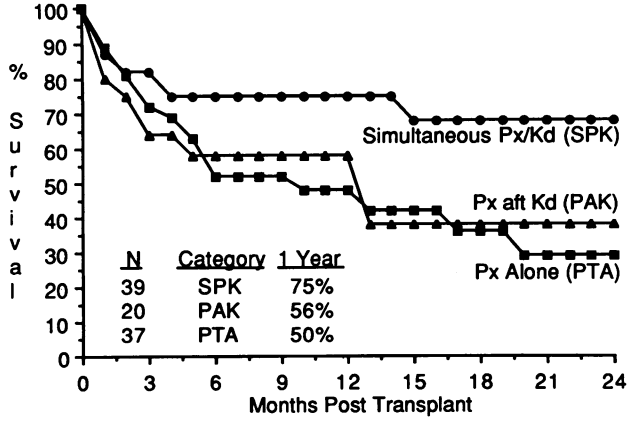


FIG. 8. Pancreas graft functional survival rates for all primary bladder-drained pancreas transplants according to recipient category. PTA = pancreas transplants alone; SPK = simultaneous pancreas/kidney transplants; and PAK = pancreas transplants after a kidney transplant.

than for retransplants, 60% (n = 96) *versus* 46% (n = 32) at 1 year for those with bladder drainage. The overall patient and graft survival rate curves for primary bladder drained pancreas transplants are shown in Figure 7B.

Pancreas Graft Survival Rates According to Recipient Category

As shown in Table 2, pancreas graft survival rates were highest in recipients of simultaneous kidney transplants and lowest in recipients of a pancreas after a kidney, with recipients of a pancreas transplant alone being intermediate. In all recipient categories, graft survival rates were highest with bladder drainage (Fig. 8). The 1-year actuarial patient and graft functional survival rates for all and for primary pancreas transplants performed since 1984 with bladder drainage are shown in Table 3. The pancreas graft survival rates at 1 year were over 50% for pancreas transplants alone and 65% for all recipients of simultaneous pancreas/kidney transplants. In recipients of primary pancreas and primary kidney transplants, the 1-year pancreas graft survival rate was 75%, the 1-year kidney graft survival rate was 80% and the 1-year patient survival rate was 95% (Fig. 9). The patient and kidney graft survival rates in SPK recipients were not significantly different than those in 43 concurrent diabetic recipients of primary cadaver kidney transplants alone (KTA). The 1-year patient and kidney survival rates were 90% and 85%, respectively, in KTA recipients.

The incidence of pancreas graft rejection episodes was higher in PTA than in SPK recipients. Conversely the incidence of kidney graft rejection episodes was higher in SPK than in KTA recipients. In recipients of technically successful primary pancreas transplants with at least 6 months follow-up, during the first 6 months after transplant pancreas rejection episodes occurred in 22/24 (92%) of PTA *versus* 12/23 (52%) of SPK recipients ($p < 0.003$). In recipients of technically successful primary cdaver kidney transplants, during the first 6 months after transplant kidney rejection episodes occurred in 19/27 (70%) SPK *versus* 15/36 (42%) KTA recipients ($p < 0.03$). During the first 6 months after transplant, 27 SPK recipients had 12 first rejection episodes that clinically involved the kidney only, 7 of the pancreas and kidney together, and 3 of the pancreas only.

Effect of HLA Matching and Other Variables on Pancreas Graft Survival Rates

HLA matching has been difficult to apply in pancreas transplantation because of the limitations of graft preservation. The duration of preservation tolerated by a pancreas has increased with the introduction of the new preservation solutions.[37-39] It might be possible to apply HLA matching prospectively if matching was shown to make

TABLE 3. *One-Year Actuarial Patient and Graft Functional Survival Rates for All Cases and for Primary Pancreas Transplants with Bladder Drainage*

	Graft Survival—All Cases		Graft Survival—Primary Cases		Patient Survival	
	All Txs (N)	TS Txs* (N)	All Txs (N)	TS Txs* (N)	All Cases (W)	Primary Cases (N)
Pancreas txs alone	53% (50)	66% (42)	50% (37)	58% (32)	97% (50)	96% (37)
Simultaneous panc./kid. txs	65% (46)	82% (37)	75% (39)	93% (32)	87% (46)	95% (39)
Pancreas txs after a kid.	48% (32)	66% (20)	56% (20)	75% (13)	91% (32)	95% (20)
All cases	56% (128)	73% (99)	60% (96)	75% (77)	92% (128)	95% (96)

TS = Technically successful transplants (excludes technical failures from thrombosis, local infection, etc.).
Txs, transplants.

a difference in pancreas graft survival rates. Such an effect has been seen in analysis of pancreas transplant registry data.[1,40] Thus, we analyzed cadaver donor graft survival rates according to number of HLA A, B, and DR antigens matched and mismatched between the donors and recipients in the entire second series.

We found no significant effect of matching for A and B antigens, with those matched for 0 to 2 antigens (n = 136) having a 1-year graft survival rate of 50% *versus* 67% for those matched for 3 to 4 antigens (n = 9); the corresponding graft survival rates for technically successful cases were 66% (102) and 75% (n = 8). When analyzed according to number of A and B antigens mismatched, the outcome was the same, with 0 to 2 AB mismatches (n = 53) being associated with a 1-year graft survival rate of 54% and 3 to 4 mismatches (n = 92) with a 1-year graft survival rate of 49%; corresponding 1-year graft survival rates for technically successful cases were 66% (n = 42) and 67% (n = 68).

However, matching at the DR loci did appear to improve graft survival rates; at 1-year the rate was 39% for those matched for 0 (n = 82), 67% for those matched for 1 (n = 54), and 75% for those matched for 2 (n = 8) antigens ($p < 0.05$ for the 1 and 2 antigen-matched groups *versus* the 0 antigen-matched group). When technically successful cases only were analyzed, 1-year graft survival rates were 55% for those matched for 0 (n = 60), 84% for those matched for 1 (n = 41), and 75% for those matched for 2 (n = 8) DR antigens; in these subgroups the differences between a 0 and a 1 antigen match were significant. When the one and two antigen-match groups were combined, in both the analyses of all cases (n = 62) and of technically successful cases (n = 49), the 1-year graft survival rates were significantly higher than for the 0 antigen-matched groups (66% for all and 82% for technically successful cases matched for ≥ 1 DR antigen *versus* 39% for all and 55% for the technically successful 0 DR matched subgroup). When analyzed according to number of DR antigens mismatched, the same trend was seen for all cases and the statistical significance was reached for technically successful cases. For all cases, grafts matched for 0 DR antigens (n = 16) had a 1-year graft survival rate of 65%, *versus* 56% for those mismatched for 1 (n = 73) and 42% for those mismatched for 2 DR (n = 55) antigens ($p = 0.06$ for the 0 *versus* the 2 DR antigen mismatches). When technically successful cases were analyzed, the 1-year graft survival rate was 75% for those mismatched for 0 antigens (n = 14), 76% for those mismatched for 1 (n = 52), and 54% for those mismatched for 2 (n = 43) antigens ($p < 0.05$ for both the 0 and the 1 antigen mismatched group *versus* the 2 antigen mismatched group).

To determine if the influence of HLA matching seen in the univariate analysis was a true effect or an artifact of other factors that could influence the results, logistic regression analysis was carried out on 163 pancreas transplants performed between July 1978 and October 1987. Thus every recipient had at least 1-year follow-up. One-year graft function was the independent variable; year of

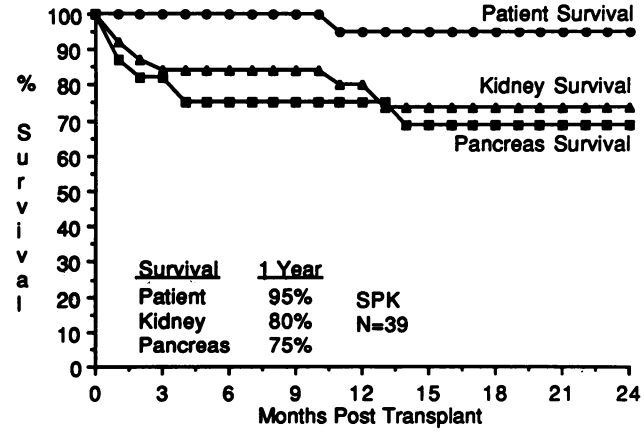


FIG. 9. Patient survival and kidney and pancreas graft survival rates in diabetic recipients of bladder-drained simultaneous primary pancreas and primary kidney transplants from cadaver donors performed from July 1986 through March 1989.

transplant, age, sex, donor source, recipient category, type of graft, duct management technique, immunosuppressive regimens, and preservation time were the independent variables. The only significant ($p < 0.05$) predictors of success (odds ratio) were duct management technique, recipient category, and HLA-DR match. In regard to duct management, the odds ratio for bladder drainage *versus* enteric drainage was 2.2 and *versus* duct occlusion was 6.2, while that for enteric drainage *versus* duct injection was 2.8. In regard to recipient category with PTA as the baseline (1.0), the odds for success were 6.0 for SPK, 3.2 for PAK from the same living donor as the kidney, and 1.2 for PAK from a donor different than the kidney. HLA-DR remained significant in the logistic regression analysis with 0 DR mismatch being superior to a 1 DR mismatch, and both to a 2 antigen mismatch (respective odd ratios 5.0, 2.5, and 1.0).

Metabolic Studies in Pancreas Transplant Recipients

The results of simple metabolic profiles and oral and intravenous glucose tolerance tests in our pancreas transplant recipients have been reported previously.[7,12] The results in the patients treated with triple therapy since 1984 are similar to those previously reported and are not reiterated here. Patients with functioning grafts usually have normal fasting and postprandial values and most have glucose tolerance test results that are within the broad range of normal. The glycosolyated hemoglobin levels obtained every year when the patients return to the Clinical Research Center for follow-up studies have been tabulated. The normal values in our laboratory for glycosylated Al hemoglobin (HbA1) is 5.4% to 7.4% of total hemoglobin. In a nontransplanted diabetic control population (n = 18), mean (± SD) HbA1 was 10.2% ± 1.7%. In pancreas transplant patients followed for 2 years with functioning pancreas grafts, baseline HbA1 was 11.2% ± 2.0% and the values at 1 and 2 years were 6.6% ± 0.9% and 6.4% ± 0.7% ($p < 0.05$ compared to baseline), with 82% of the values at 1 year being < 7.4% and 95% of the values at 2 years being < 7.4%. In contrast, patients followed for 1 and 2 years after early failure of a pancreas transplant had mean values of 12.1% ± 2.1% and 11.2% ± 2.9%, not significantly different from the baseline mean value of 13.4% ± 2.7%, and none of the values were below 7.4%. Thus, a successful pancreas transplant restores glycoslyated hemoglobin levels to normal or nearly normal. The minor elevations in a few pancreas transplant patients may reflect the use of steroids, as this is also seen in some nondiabetic recipients of kidney transplants alone.[19]

Studies of Secondary Complications

Preliminary observations on the course of retinopathy, neuropathy and, nephropathy following pancreas transplantation have been reported,[20–24] and the definitive studies will be reported elsewhere. The preliminary reports show that 1 and 2 years after pancreas transplantation, conduction velocities increase in some nerves and evoked muscle action potentials remain stable in patients with functioning pancreas grafts, while in control patients and in recipients of grafts that fail soon after transplantation, conduction velocities do not change and evoked muscle action potential continue to deteriorate.[20,21] In regard to retinopathy, almost all of the patients have had advanced disease, and progressive deterioration occurred in approximately 30% of the recipients of successful grafts in the first 3 years after transplant, a percentage no different than that observed in patients with failed grafts.[22] However, thereafter the patients with functioning grafts remained stable while deterioration continued in those with failed grafts. Although not statistically significant, this divergence at 3 years between the two groups suggests that euglycemia may stabilize retinopathy in the long term. In regard to nephropathy, preliminary observations have been made on the mesangial matrix volume in biospies of native kidneys in recipients of pancreas transplants alone[23] and in kidney grafts after a pancreas transplant.[24] In native kidneys at more than 2 years after transplant, there was a statistically significant decrease in glomerular mesangial volume compared to baseline biopsies.[23] In the group who received pancreas transplants after a kidney transplant, the follow-up biopsies show a lower mesangial volume in the kidney grafts of pancreas transplant recipients than in a group of diabetic recipients of kidney transplants alone biopsied at comparable times after kidney transplant.[24] Again these results are consistent with an ameliorating effect of pancreas transplantation on diabetic nephropathy, but the number of patients studied is small, and the follow-up is relatively short.

Discussion

Two series of pancreas transplants at the University of Minnesota, one in the late 1960s and early 1970s,[5] and the other beginning in the late 1970s[7] and continuing to the present, were both initiated with the intention of improving the lot of diabetic patients. Because immunosuppression itself has side effects, which in some diabetic patients could be more serious than the complications destined to evolve from their diabetes, pancreas transplantation has been applied to selected diabetic patients and not to the diabetic population at large.

Most groups have limited pancreas transplants to uremic diabetic recipients of simultaneous kidney transplants, patients who are already obligated to immunosuppression.[18,41–45] In our own series, more than three fourths of the recipients of simultaneous primary pancreas and primary kidney transplants were insulin independent 1 year after transplant, and patient and kidney graft survival rates

were similar to those of diabetic recipients of kidney transplants alone. This outcome is in accordance with those reported by others,[18,41–45] and pancreas transplantation is rapidly becoming a routine addition to a kidney transplant in uremic diabetic patients who do not have advanced coronary artery disease and in whom the risk of an extended operation is low. SPK recipients enjoy the benefit of insulin independence in addition to being dialysis free, recurrence of diabetic nephropathy appears to be prevented in the transplanted kidney,[24,46,47] and at least the potential for a salutary effect on other pre-existing secondary complications of diabetes exists.

In regard to nonuremic diabetic patients, the main dilemma is how to select those patients who are at high risk for developing diabetic complications that are more morbid than the side effects of the antirejection drugs or of chronic immunosuppression in general. The dilemma is further compounded by the fact that the probability of success is not as high with pancreas transplants alone in nonuremic individuals as with pancreas transplants performed simultaneously with a kidney in uremic individuals. Uremia itself is immunosuppressive,[48] and may blunt the rejection response to an allograft. Nevertheless, nonuremic, diabetic patients have more potential to benefit because their diabetic complications are less advanced than those whose kidneys have already failed from diabetic nephropathy. In our own series of bladder-drained pancreas transplants, the current long-term success rate approaches 50%.

Criteria for selection of pancreas transplant recipients before end-stage diabetic nephropathy have been proposed.[49] Albuminuria, an indicator that early nephropathy will otherwise inevitably progress,[50] along with a creatinine clearance above 50 mL/minute so cyclosporine nephrotoxicity will be tolerated,[34] has been our main criteria along with difficulty with diabetic control.[2] If the ongoing observations of the effect of pancreas transplantation on secondary complications continue to show stabilization or improvement,[20–23] and if immunosuppressive regimens with fewer side effects evolve, the criteria for selection will be redefined and application to nonuremic diabetic patients will certainly increase.

The results in our series continue to support the use of bladder drainage for management of the pancreatic duct exocrine secretions. The main advantage is the ability to monitor pancreas graft rejection independent of plasma glucose levels, essential for recipients of pancreas transplants alone, and an adjunct to that of monitoring kidney rejection in SPK recipients. In recipients of pancreas transplants alone, if bladder dranage is not done the only alternative for monitoring rejection independent of plasma glucose has been to leave a catheter in the pancreatic duct for external drainage, and these devices are only temporary.[51,52] For pancreas transplants performed simultaneously with the kidney, the kidney can be used as a monitor for rejection episodes that affect both organs simultaneously, but rejection can also occur independently in each organ, even when they are from the same donor.[52,53]

We believe that urinary drainage is the current method of choice for management of pancreas graft exocrine secretions. The concept was introduced by Gliedman in the early 1970s[54] and was made practical by Sollinger et al.[55] by using the recipient bladder for direct anastamosis to the graft duct or the graft duodenum as a conduit. Our prospective trial comparing bladder and enteric drainage showed superior pancreas graft survival rates with bladder drainage.[9] The only other prospective trial comparing two techniques was that of the Lyon group.[56] They did not include bladder drainage and found no difference in outcome for enteric drainage *versus* polymer injection in SPK recipients.

Another means of reducing the incidence of graft loss from rejection is to use living related donors.[57] Living related donor pancreas transplants are difficult, as attested by our higher technical failure rate, compared to cadaver donor transplants, but this is offset by a lower incidence of rejection. Metabolic studies in the living related donors have shown that if first-phase insulin release during intravenous glucose tolerance testing pretransplant is above the 30th percentile of normal, the donors will remain normal metabolically thereafter.[58] We use the living related donor option for families that are highly motivated and for recipients who have a high percentage of cytotoxic antibodies to the panel, making it difficult to find a cadaver donor, but who have a negative crossmatch against their relative.

Diabetes (type I) is an autoimmune disease in which the beta cells are selectively destroyed.[59] Recurrence of autoimmune isletitis has been described in identical twin and other related donor pancreas grafts following transplantation to non- or minimally immunosuppressed recipients.[8,60,61] Fortunately, recurrence of disease can be prevented by administration of adequate immunosuppression.[62] Because the rejection rate is lower, if the technical failure rate with pancreas transplants from living related donors can be lowered, it would be as attractive as living related kidney donation is now, particularly if the number of transplants increases to the point in which the number of cadaver donors available is a limiting factor.

Another approach to reducing the graft loss from rejection is to use HLA matching. The positive effect of minimizing mismatches for DR antigens between the donor and recipient we found in our series is in accordance with observations also made in an analysis of registry data.[40] Prospective matching for DR antigens should be possible with the increase in pancreas graft preservation time now possible with cold-storage solutions.[37–39]

The ultimate prospects for widespread application of pancreas (or eventually, islet) transplantation as a treatment for diabetes are excellent. The progressive improvement in pancreas graft survival rates even with imperfect immunosuppressive regimens, coupled with the preliminary evidence of an apparent favorable impact on secondary complications, are a stimulus in this direction and the impetus will be even greater when better antirejection strategies are available. Meanwhile, pancreas transplants should be performed in most uremic diabetic recipients of kidney transplants, and are applicable to selected noruremic patients with other diabetic complications.[63]

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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): Dr. Sutherland, you and President Najarian are to be congratulated on this series that describes the largest and best-studied single center experience. The results are excellent and it is gratifying that they continue to improve.

This series is in agreement with many other smaller ones, including our own, in pointing out that there are subgroups of patients in whom current results are particularly good, such as those patients in whom the pancreas transplant is drained into the bladder, especially when a kidney transplant is done simultaneously.

It would be of great interest to know why the latter technique is so advantageous. Is it only the opportunity for monitoring the function of the kidney as a sensitive index for diagnosing simultaneous rejection of the two organs that leads to this improvement, or does the kidney transplant actually have an immunodepressive or enhancing effect? Perhaps Dr. Starzl in his report tomorrow on cluster transplants will comment on whether a similar improvement might be expected with simultaneous pancreas and liver transplants.

The size of the Minnesota series and the unique perspective of long follow-up of this pioneering series allow several unique observations. The first concerns the impact of successful pancreas transplantation on the complications of diabetes. It is very important for us to know that in contrast to the results of an earlier report by the Minnesota group in the *New England Journal of Medicine*,(1988; 318:208–214) it is apparent that diabetic retinopathy is ameliorated, or at least stabilized, if the pancreas transplant functions for 3 years or more. Another important observation possible because of the meticulous follow-up of these patients, which includes serial biopsies of the concomitant kidney allografts, is that the expected development of diabetic nephropathy in the new kidney is prevented by a functioning pancreas transplant.

Another valuable aspect of the report of particular interest to me was the beneficial influence histocompatibility had on the outcome of the pancreas transplants. While this result may not seem surprising because it is a general law of transplantation, in an autoimmune disease such as diabetes one might actually have predicted the opposite outcome. On the basis of the immunological principle of major histocompatibility complex restriction, recurrence of diabetes in the transplanted pancreas might be most likely to occur in a closely matched patient. That this was not the case could be the result of the immunosuppression overriding both recurrence and rejection. I wonder if Dr. Sutherland thinks that the possibility of recurrence of diabetes in human pancreas transplants would be similar to that which Dr. Naji and our group have found in the rat, *i.e.*, that there is MHC restriction of recurrent autoimmune insulitis. If so, recurrent disease will be more likely in well-matched transplants such as those with twin- and other family-donor transplants.

DR. PAUL S. RUSSELL (Boston, Massachusetts): It is a pleasure to see this marvelous progress from Minnesota that continues to be very valuable