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Allogeneic Whole Pancreas Transplantation in Insulin-Dependent Diabetes Mellitus

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A clinical whole organ pancreas transplantation program for patients with insulin-dependent diabetes mellitus complicated by end-stage renal disease was initiated at Henry Ford Hospital in 1987. Five patients have received pancreatic allografts after a previous kidney transplant (phase 1), and six patients had simultaneous pancreas-kidney transplants (phase 2). Ten patients had functioning pancreatic grafts after surgery, and all of them had normal carbohydrate tolerance with appropriate plasma free insulin responses to an oral glucose tolerance test three months after transplantation. As long as 28 months postsurgery six patients remained free of insulin requirements; however, one patient rejected the pancreatic allograft, and three patients died because of cytomegalovirus pneumonia. Two of the latter patients had functioning pancreatic allografts at the time of their demise. These results compare favorably with those of the International Pancreas Transplant Registry which reflects the world experience. Pancreas transplantation is a unique experimental treatment with the potential of restoring euglycemia and improving the prognosis of insulin-dependent diabetic patients. (Henry Ford Hosp Med J 1990;38:246-51)

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The availability of insulin for therapy of diabetes mellitus resulted in a marked prolongation of patient survival after the hormone was discovered in 1921. However, maintaining euglycemia and preventing microvascular complications has been a more elusive goal using conventional insulin therapy. Pancreas transplantation currently offers the only therapeutic intervention for insulin-dependent diabetes mellitus (IDDM) that can provide persistent euglycemia, although continuous immunosuppression is required to prevent graft rejection. The risks attached to the immunosuppressive treatment are considerable and have limited the application of pancreas transplantation to diabetic patients who are previous or simultaneous recipients of kidney grafts. Because such patients frequently present other diabetic complications in addition to their nephropathy, pancreas transplantation has been advocated at a stage in the progression of diabetes earlier than end-stage nephropathy, in the hope that the mortality and serious morbidity associated with advanced neurovascular complications will be prevented (1). In IDDM patients with pancreatic allografts, the long-term effects of euglycemia on the microvascular complications of the disease remain to be established, but preliminary studies have shown encouraging results (2-6).

Whole organ pancreas transplantation in IDDM has been performed worldwide with increasing frequency and improving patient and functional graft survival rates (7). A number of surgical techniques have been used, including duct-injected segmental pancreas allografts, Roux-en-Y jejunostomy enteric drainage with either segmental or whole pancreas transplants, and urinary drainage with whole pancreas allografts. Either the latter approach or whole organ allograft with duodenocystostomy for exocrine diversion combined with a renal transplant (Fig 1) is the currently preferred surgical procedure because of minimal surgical complications (8). The pancreas transplantation program was established at Henry Ford Hospital in May 1987. Phase 1 (pancreas transplantation in patients with functioning kidney allografts) and phase 2 (simultaneous transplantation of kidney and pancreas from a single donor) clinical pancreas transplants have been performed using the surgical technique of urinary bladder diversion of exocrine pancreas secretion. This report presents the results of the pancreas transplantation program at Henry Ford Hospital.

Materials and Methods

Candidates for pancreas transplantation were selected by a multidisciplinary team. Pretransplant evaluation included as-

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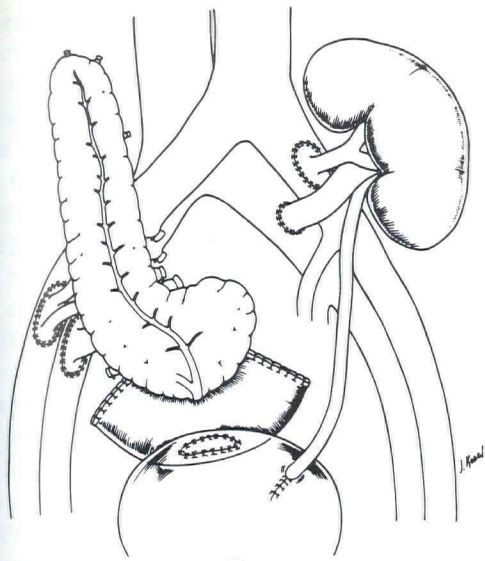orally. The...
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Fig 1—Surgical scheme of the combined kidney-pancreas transplantation with duodenocystostomy for pancreatic exocrine drainage. (From D'Alessandro AM, Stratta RJ, Sollinger HW, Kalayoglu M, Pirsch JD, Belzer FO. Use of UW solution in pancreas transplantation. Diabetes 1989;38[suppl 1]:7-9. Reproduced with permission of the American Diabetes Association, Inc.)
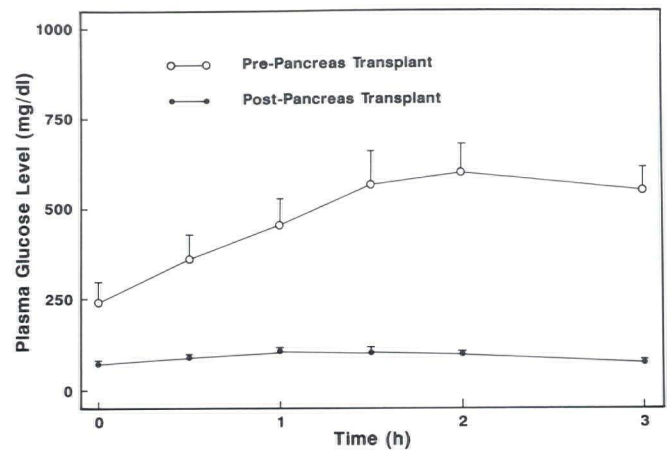

Fig 2—Glycemic profiles in response to an oral glucose tolerance test performed before and three months after a technically successful whole pancreas transplantation in insulin-dependent diabetic patients. Data are shown as mean ± SE (N = 11). Overall differences between glycemic profiles before and after pancreas transplantation were highly significant by a two-tailed, paired Student t test using the Bonferroni adjustment (P < 0.003) (35).

sessments by a psychiatrist, social worker, and chaplain. The candidates were patients with IDDM complicated by diabetic nephropathy and end-stage renal disease who either had a previous, stable kidney allograft or were scheduled to receive a simultaneous kidney and pancreas allograft. Criteria for exclusion were coronary artery disease (angina pectoris and congestive heart failure) and peripheral occlusive vascular disease (intermittent claudication, ischemic foot ulcer and amputation). A total of 11 patients have received pancreas allografts; five patients were former recipients of kidney allografts (phase 1), and six patients received simultaneous pancreas and kidney transplants (phase 2). All patients had oral glucose tolerance tests with assessment of plasma glucose and free insulin levels before and three months after surgery. Plasma free insulin concentrations were measured using a double antibody radioimmunoassay according to Kuzuya et al (9). The pancreas transplantation program was approved by the Institutional Review Board and informed consent was obtained from all patients.

The quadruple immunosuppressive protocol used in the first five patients consisted of Minnesota antilymphoblast globulin 20 mg/kg/day for ten days, cyclosporine A 4 mg/kg/day intravenously followed by 10 mg/kg/day orally, methylprednisolone 0.5 mg/kg/day orally, and azathioprine 1.5 mg/kg/day orally. The subsequent six patients received for immunosuppression an induction with OKT_3 (orthoclone, monoclonal antibody) 5 mg/day for ten days followed by cyclosporine A 10 mg/kg/day orally. These changes in the immunosuppressive protocol were introduced to minimize cyclosporine-related renal toxicity while the kidney graft was recovering from insults related to organ

harvesting, preservation, and reperfusion. Diagnosis of rejection was based on urinary amylase levels, urine pH, and fasting blood glucose measurements. Perfusion scans with ^{99m}technetium, arteriography, and magnetic resonance imaging were utilized to aid in the diagnosis of pancreatic graft rejection. Criteria used for the diagnosis of rejection were a decrease in urinary amylase excretion of 50% or more or an absolute amylase level of 3,000 IU/L. Outpatient surveillance for rejection was done via urine pH testing by a dipstick method. A drop in pH of 1.5 units from previous values was an indication for further evaluation of pancreatic graft dysfunction. Loss of endocrine graft function was established by two consecutive plasma glucose levels of 140 mg/dL or higher (10).

Results and Discussion

Pretransplant characteristics of the recipients are listed in Table 1, and donor information is given in Table 2. The organ recipients (three men and eight women) ranged in age from 17 to 44 years, and their mean duration of diabetes was 22.2 years. Metabolic control in most patients was suboptimal prior to surgery, and they all had significant diabetic microvascular complications, some very severe. Organ donors ranged in age from 13 to 44 years (mean 26.8 years). All but one of the transplanted pancreatic allografts had good initial function, and no insulin was required postsurgery in any patient. Table 3 shows the results and complications after a follow-up to 28 months. The mean glycemic profile during oral glucose tolerance tests performed before and three months after pancreas transplantation is given in Fig 2. Carbohydrate tolerance was normalized by the functioning grafts. Free insulin levels corresponding to these studies (Fig 3) rose markedly in response to the oral glucose

Table 1
Pretransplant Characteristics of Diabetic Patients

Patient No/Age/Sex	Duration of Diabetes (yrs)	Insulin Dosage (U/d)	Hb A$_{1C}$ (%)	Secondary Complications
1/35/M	33	52	11.2	S retinopathy, right eye blind, S polyneuropathy, ESRD S/P LRT 12/83
2/33/F	23	33	14.1	S gastroparesis, S polyneuropathy, S retinopathy, ESRD S/P LRT 5/75
3/44/F	22	52		S gastroparesis, S polyneuropathy, S retinopathy, pancreatic insufficiency, ESRD S/P CAD Tx 3/86
4/31/F	24	25	11.8	M retinopathy, M polyneuropathy, ESRD S/P LRT 11/82
5/31/F	21	35	9.5	S retinopathy, S gastroparesis, S polyneuropathy, ESRD, on dialysis
6/27/F	20	40	13.9	M retinopathy, M polyneuropathy, osteomyelitis, ESRD, on dialysis
7/31/F	24	30	11.9	M retinopathy, S gastroparesis, M polyneuropathy, osteomyelitis, ESRD, on dialysis
8/27/M	21	38	11.4	M retinopathy, M polyneuropathy, S gastroparesis, ESRD S/P LRT 4/87
9/24/M	20	64	8.4	Blindness, M polyneuropathy, ESRD on dialysis
10/31/F	19	30	15.0	M retinopathy, S polyneuropathy osteomyelitis, ESRD, on dialysis
11/17/F	17	62	10.6	Mild polyneuropathy, blindness, mild gastroparesis, approaching ESRD

Hb A$_{1C}$ = hemoglobin A$_{1C}$, S = severe, M ≈ moderate, ESRD = end-stage renal disease, S/P = spleen/pancreas, LRT = living related (renal) transplant, CAD Tx = cadaver (renal) transplant.

Table 2
Pancreas Donor and Transplantation

	Donor Information				Transplantation					
Patient No	Donor Age	Cause of Death	CIT (hrs)	Pres Solution	Liv/Pan Harvest	Pancreas Only	P+K	Immediate Function	Hospital Stay (days)	Complications
1	23	MVA	2.5	Belzer's	No	V		Yes	23	Rejection episode, UTI/pancreatitis
2	28	GSW	3.0	Belzer's	No	V		Yes	103	Rejection episode, CMV pneumonia, chronic rejection
3	26	MVA	4.0	Belzer's	No	V		Yes	28	Orthostatic hypotension
4	42	CVA	3.0	Belzer's	No	V		Yes	24	Rejection episode, seizure, clot retention
5	44	MVA	4.0	Belzer's	No		V	Yes	23	HUS, clot retention
6	24	MVA	5.0	Belzer's	No		V	Yes	44	Rejection episode, transplant nephrectomy
7	17	MVA	4.5	Belzer's	Yes		V	Yes	26	Rejection episode
8	28	CVA	6.0	Belzer's	Yes	V		Yes	30	Rejection episode, UTI
9	26	CVA	5.0	Belzer's	No		V	Yes	21	Clot retention
10	24	GSW	5.6	Belzer's	Yes		V	Yes	29	Clot retention, metabolic acidosis
11	13	MVA	5.0	UW	Yes		V	No	41	Vascular thrombosis

CIT = cold ischemia time, Pres = preservation, Liv/Pan = liver/pancreas, P+K = pancreas and kidney, MVA = motor vehicle accident, GSW = gunshot wound, CVA = cerebrovascular accident, UW = preservation solution UW, V = check mark on type of performed surgery, UTI = urinary tract infection, CMV = cytomegalovirus, HUS = hemolytic uremic syndrome.

challenge. Such a response is expected in patients with functioning pancreatic allografts who have a degree of insulin resistance secondary to the steroids used for immunosuppression. Normalization of metabolic control during the same posttransplantation period is further demonstrated by normal hemoglobin A_{1c} levels (Fig 4). Of the 11 whole organ pancreas transplants performed with the duodenocystostomy technique described by Sollinger et al (11), ten of the procedures were technically successful (indicated by postoperative functioning grafts) and one graft was lost by chronic rejection after the patient acquired cytomegalovirus (CMV) pneumonia and immunosuppressive therapy was withdrawn. Two recipients who succumbed from CMV infection at three and 16 months, respectively, had normally functioning pancreatic allografts.

The International Pancreas Transplant Registry recorded 1,394 pancreas transplants performed from December 1966 to March 1988 (12). These data reveal progressive improvement in graft functional survival rates, with a one-year average survival rate of 61% of the technically successful pancreas transplants performed from 1983 to 1988. Combined use of cyclosporine A and azathioprine was more effective than any single immunosuppressive protocol in maintaining pancreatic allograft function. One-year functional graft survival rate for simultaneous pancreas-kidney transplants (53%) was better than for those with a preceding kidney transplant (40%) or no kidney transplant at all (32%). Corresponding one-year patient survival rates were 90%, 88%, and 77%.

Our experience with the first 11 pancreas transplants compares favorably with the results listed in the International Pancreas Transplant Registry, but CMV infection remains a major concern for the recipients. Recommended measures to reduce the ominous complication of CMV infection include matching CMV antibody-negative donors with CMV antibody-negative recipients, the use of CMV-negative blood products, and the prophylactic administration of anti-CMV immunoglobulin.

The immunosuppression protocols currently in use have been optimized only to prevent pancreas allograft rejection as indicated by parameters such as urinary amylase or pH and may be less effective in arresting pancreatic beta cell autoimmunity. The postulated autoimmune pathogenesis of IDDM (13-15) is likely to continue operating after a pancreas transplant and may lead to progressive loss of both beta cells and insulin secretory reserve in the pancreas allografts. Thus, recurrence of IDDM has been observed in recipients of segmental pancreas grafts from a monozygotic twin donor (16,17). The possible impact of currently used immunosuppressive protocols on the autoimmune destruction of pancreatic beta cells is unknown. However, attempts to arrest pancreatic beta cell loss in newly diagnosed IDDM patients have been only partially and transiently successful (18-20). Further studies are needed in the context of preserving pancreas graft function and preventing graft immunological rejection.

Islet cell transplantation and transfection of spliced insulin-coding segments of the genome into nonbeta cells are potential alternative approaches for restoring adequate insulin secretion in IDDM. The former intervention requires the availability of a sufficient mass of pancreatic islets and the need to prevent the immunologic rejection. Utilizing multiple pancreases from inbred animal donors has permitted successful isografting of isolated pancreatic islets in animal models, but for obvious reasons this is not feasible in human diabetics. Transplantation of dispersed pancreatic preparations without islet purification has resulted in increased yields of islet tissue and reversion of IDDM in dogs (21,22). Success in applying this procedure to patients—

Table 3
Results of Phase 1 and Phase 2 Pancreas Transplants

Patient No	Follow-up (months)	FBS (mg/dL)	SCr (mg/dL)	U Amylase (U/L)	U pH	Complications	Outcome
1	28	92	1.5	104,500	7.5	Urinary retention	Well
2	6	173	0.9	16	6.5	CMV pneumonia, chronic rejection	Died 25 months posttransplant
3	23	72	1.1	94,736	8.0	BKA	Well
4	16	79	1.2	93,700	7.0	Osteomyelitis, UTI, pseudomembranous colitis, CMV infection	Died 16 months posttransplant
5	3	107	6.0	65,900	7.5	HUS, CMV pneumonia	Died 3 months posttransplant
6	11	85	12.4	62,400	8.5	Transplant nephrectomy, CVA	Well
7	7	84	0.9	38,000	7.0	Osteomyelitis, trans-metatarsal amputation, urine leakage, transplant pancreatectomy	Diabetic
8	6	103	1.4	57,702	7.0	Rejection episode	Well
9	5	92	2.1	46,852	7.5	Clot retention	Well
10	4	85	1.1	258,816	8.0	Metabolic acidosis	Well
11	1	135	2.2	0	5.5	Thrombosis of vessels	Diabetic

FBS = fasting blood sugar, SCr = serum creatinine, U = urine, BKA = below-knee amputation, UTI = urinary tract infection, CMV = cytomegalovirus, CVA = cerebral vascular accident.
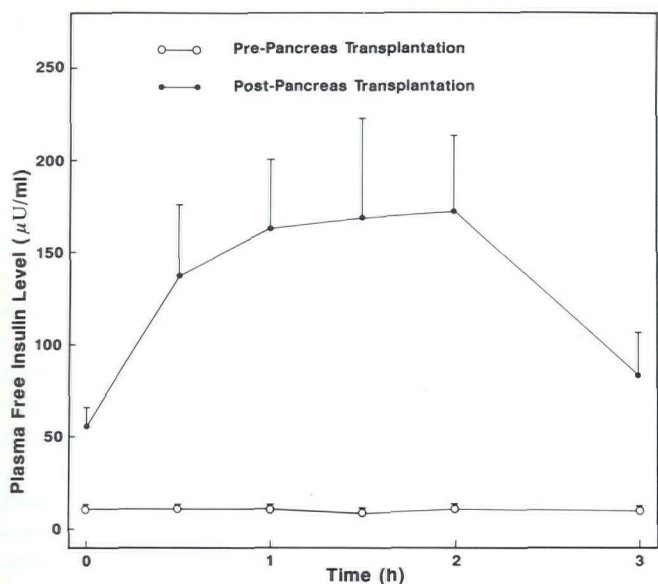
Fig 3—Mean plasma free insulin concentrations corresponding to the oral glucose tolerance tests summarized in Fig 2. Data are shown as mean ± SE (N = 11). Statistical analysis performed as described in the caption to Fig 2 revealed highly significant differences between the curves describing the plasma free insulin responses to an oral glucose challenge before and after pancreas transplantation (P < 0.006).

Fig 4—Comparison of mean hemoglobin A_{1c} levels before and three months after technically successful whole pancreas transplantation (N = 10).

autotransplantation of islet cells after a near-total pancreatectomy for intractable pain of chronic pancreatitis—has been limited by low islet yields from fibrotic pancreatic tissue (23-26) and autoimmune recurrence of the diabetic state (27). An interesting new attempt to obtain insulin-secreting cells is the transfection of total genomic DNA or spliced DNA fragments containing the insulin coding gene(s) and regulatory elements into nonbeta cells (28,29), but these approaches have been limited by problems with inefficient transfection rates and instability of the genetic constructs. Further research into these areas may help solve the problems of insufficient yields of insulin-secreting cells and immune rejection by converting in vitro nonbeta cells of the recipient into insulin-secretory cells through transfection of insulin genes prior to grafting.

Development of new immunosuppressive drugs, many currently at different stages of clinical trials, is an encouraging step toward improved prevention of allograft rejection. These drugs include FK506 and monoclonal antibodies to the interleukin-2 receptor. FK506 has a mechanism of action similar to that of cyclosporine A but has much greater immunosuppressive potency and no nephrotoxicity (30). Cyclosporine A and FK506 produce immunosuppression by inhibiting transcription of early T-cell activation genes (e.g., interleukins-2, -3, and -4, interferon-γ, and granulocyte-macrophage colony stimulating factor) (31). These two therapeutic agents also bind to proteins that are peptidyl-prolyl-cis-trans-isomerases (rotamases), thereby inhibiting their catalytic activity (32). Elucidation of these mechanisms may help in the design of more potent immunosuppres-
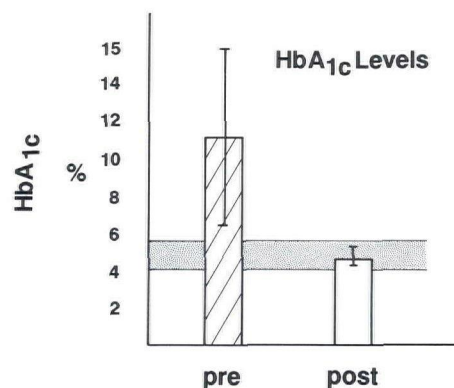
sive agents. Antibodies against the interleukin-2 receptor block the binding of interleukin-2, preventing the proliferation of T cells that participate in allograft rejection and in certain autoimmune diseases (33). Anti-interleukin-2-receptor therapy is effective in preventing rejection of renal grafts (34).

In conclusion, the results of the pancreas transplantation program at Henry Ford Hospital compare favorably to those of the world experience recorded in the International Pancreas Transplant Registry. Combined renal and pancreas transplantation from a single donor is the currently preferred procedure. The significant improvement in the results of whole organ and segmental pancreas transplantation, in terms of both patient and functional graft survival, indicates that this approach, although still experimental, represents a potential cure of IDDM.

Acknowledgments

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