Diabetologia (1981) 20: 435–450

Diabetologia

Review Articles

Pancreas and Islet Transplantation*

II. Clinical Trials

D. E. R. Sutherland

Department of Surgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota, USA

Contents

* Part I appeared in Diabetologia (1981) 20 (3): 161–185. Reference numbers follow sequentially from Part I

V. Clinical Transplantation of Immediately Vascularized Pancreatic Grafts

A. Pancreas Transplant Registry

The American College of Surgeons/National Institutes of Health Organ Transplant Registry recorded 57 pancreas transplant in 55 diabetic patients from December 17, 1966 until the registry closed on June 30, 1977 [295]. Only two patients were independent of insulin for more than one year, one a patient of Lillehei et al. [296] with a pancreaticoduodenal graft, and one a patient of Gliedman et al. [297] with a segmental graft; both died with functioning

Table 1. Human pancreas transplants reported to the American College of Surgeons/National Institutes of Health Organ Transplant Registry and to the New Pancreas Transplant Registry According to type of graft

ACS/NIH Transplant Registry Dec. 17, 1966 to June 30, 1977		New Pancreas Transplant Registry	
		Feb. 3, 1976 to Nov. 19, 1976	July 1, 1977 to Oct. 31, 1980
Pancreaticoduodenal alone	6		
Pancreaticoduodenal plus kidney	20		1
Pancreas alone (whole organ)	1		
Pancreas alone (segmental)	23[a]	2*	41[b]
Pancreas (segmental) plus kidney	7	1	26
Total	57[c]	3	68[d]

TOTAL number of known pancreas transplants: 128 in 118 patients[e]

[a] 6 patients subsequently received a renal allograft
[b] 17 patients had received renal allografts before 18 of the pancreas transplants
[c] 55 patients in ACS/NIH Registry and [d] 67 (63 new) in New Registry
[e] Ten patients had second transplants after the first failed; 2 had both recorded in ACS/NIH Registry, 4 had one recorded in each Registry (includes 2 patients* retransplanted before June 30, 1977, but missed by the old registry), and 4 had both recorded in the New Registry

0012-186X/81/0020/0435/$03.20

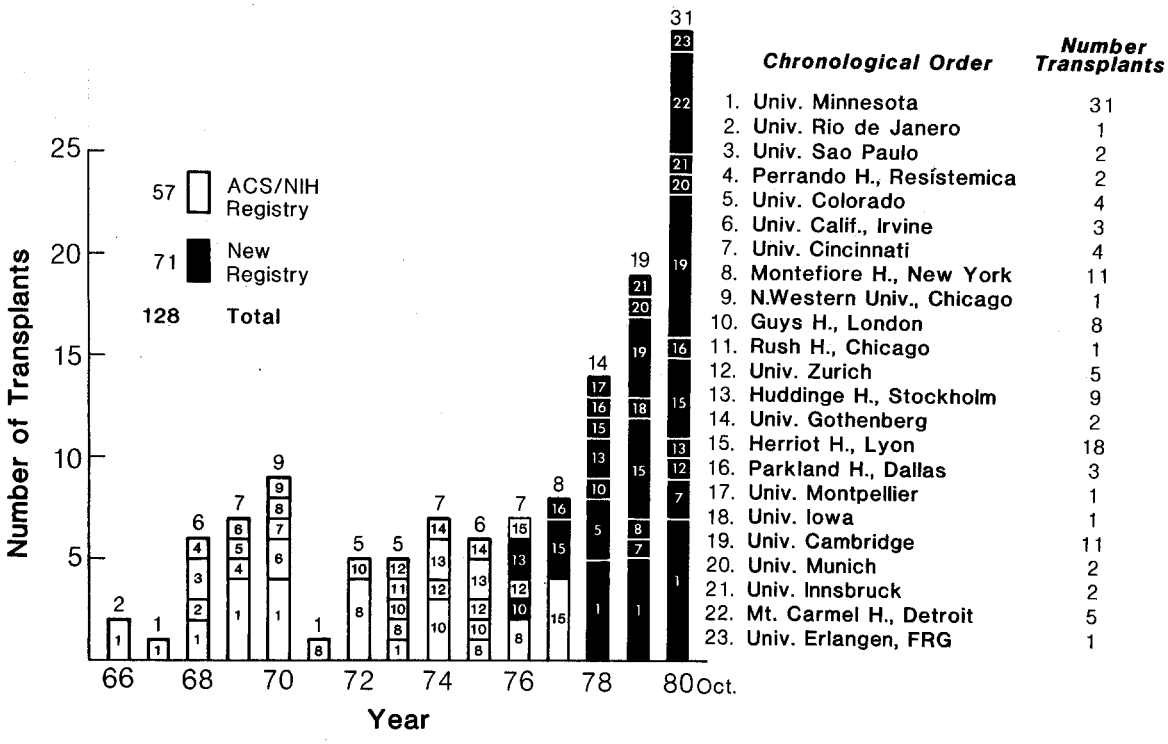

Fig. 1. Number of pancreas transplants performed in the world according to year and institution. Each institutions is assigned a number according to the chronological order by which they did their first transplant

grafts at 12 [296] and 49 months [297], respectively. Nearly half of the transplants reported to the ACS/NIH Registry were pancreaticoduodenal (Table 1).

A new Human Pancreas and Islet Transplant Registry has recently been formed [298]. Seventy-one transplants in 67 (63 new) patients were reported to the new Registry by October 31, 1980 (Table 1). Three transplants performed before July 1, 1977 (includes 2 retransplants) were missed by the old registry and are included in the new Registry. All but one of the transplants reported to the new Registry were segmental [301].

Ten patients have had a second pancreas transplant after their first grafts failed; two patients had both grafts recorded by the ACS/NIH Registry; four patients, three of Groth et al. [299] and one of Traeger et al. [300], had their first transplants recorded by the ACS/NIH Registry and their second by the new Registry; four patients had both grafts recorded by the new Registry. Thus a total of 128 pancreas transplants in 118 patients are known to have been performed [301].

Most of the patients who have received pancreas transplants had diabetic nephropathy [301]. A kidney transplant was performed either before (18 cases), simultaneous (55 cases) or after (6 cases) the pancreas transplant in 78 patients (Table 1).

The number of transplants performed in the world according to year is summarized in Figure 1. There has been a definite resurgence of interest in pancreas transplantation during the last three years.

As of October 31, 1980, 15 pancreatic grafts were functioning, four for more than one year, the longest for 2¼ years. The other grafts failed either from rejection, for technical reasons, or the patients died with functioning grafts. Although the long term success rate so far has been relatively low, the results are not necessarily discouraging. First, the need for exogenous insulin has been abolished in nearly all recipients of technically successful grafts, and carbohydrate metabolism has been normal or nearly normal until the grafts were rejected. In addition, the procedure is becoming safer. Of the 56 patients who received transplants before July 1, 1977, 29 (52%) either had a transplant related death or died within a few months of transplantation, and only 14 of the patients (25%) are still alive. In contrast, of the 64 patients who have received transplants since July 1, 1977, only 16 (25%) died with transplant or peroperative related problems and 42 (66%) of the patients are currently alive [301].

B. Patient, Selection, Immunosuppressive Treatment and Timing of Transplantation

Most recipients of pancreas transplants have had far advanced complications of diabetes – at a time when the risks of immunosuppression and transplantation are high. Ideally, pancreas transplantation should be performed early in the course of diabetes in order to prevent the secondary complications in the first place. Because of the uncertainty of success or failure, just the opposite has been the case.

The results of pancreas transplantation could undoubtedly be improved by earlier transplantation, but not all diabetic individuals will develop secondary complications. For those patients, who, at the moment, are free of compli-

Table 2. Summary of techniques used for clinical cases of pancreas transplantation

Type of transplant and technique	No. of cases	References[a]
Pancreaticoduodenal – 28 total		
Cutaneous duodenostomy	8	[310, 314]
Roux-en-Y duodenojejunostomy	20[b]	[296, 310–316]
Segmental – 100 total		
Deliberate cutaneous fistula	2	[321]
Duct ligation	7	[304, 317, 322–326]
Pancreatic ductoureterostomy	8	[297, 304, 327]
Intraperitoneal with open duct	15	[305, 314, 328–330]
Roux-en-Y pancreaticojejunostomy	21	[297, 299, 330–337]
Total duct occlusion with polymers or glues	47	[307, 308, 318, 338–354]

[a] Details on unpublished cases are available from the Registry [301]
[b] Includes the one whole pancreas case of Lillehei et al. [296] where the only portion of the duodenum transplanted was a button encompassing the ampulla of Vater

cations, the risks associated with immunosuppression may exceed the risks of secondary complications developing in the future. Even in the situation where there is abundant experience and the technical problems are largely solved, such as kidney transplantation, conventional immunosuppression (combination of azathioprine and prednisone with or without temporary administration of heterologous antilymphocyte globulin preparations) has a relatively high failure rate; the two year graft survival rate for renal allografts from cadaver donors is approximately 50% [302]. Early results suggest that a new immunosuppressive drug, cyclosporin A, may reduce the rejection rate of organ allografts [303], but this treatment still produces generalized immunosuppression. Until specific immunosuppression, i. e., tolerance induction, is possible in humans, pancreas transplantation will be restricted to patients who have already demonstrated their propensity to develop secondary complications or who are extremely labile in their exogenous insulin requirements.

An advantage of performing pancreatic transplants in diabetic patients who have had or who will require a kidney transplant is that the risks associated with immunosuppressive therapy are obligatory. A point of some controversy has been the timing of the procedures. In most patients, the two organs have been grafted simultaneoulsy. Synchronous transplantation was associated with a relatively high complication rate in the early experience of Lillehei et al. [296] at the University of Minnesota and Gliedman et al. [304] at Montefiore Hospital in New York. As a consequence, dysynchronous transplantation was used for subsequent patients at both institutions. Gliedman et al. [297] have performed a pancreas transplant first followed by a kidney transplant after recovery from the first operation. Just the opposite sequence was used for dysynchronous transplantation in the second series at Minnesota [305]. Diabetic patients are difficult to dialyze, uraemia is an immediate threat to life, and uraemia exacerbates the secondary complications of diabetes. Restoration of renal function is of prime importance in these patients [306], and for that reason the Minnesota group has chosen to transplant a kidney first and a pancreas second [305]. On the other hand, the transplant groups at Lyon [307] and Cambridge [308] have continued to perform synchronous transplants. In this situation both organs come from the same donar, and close monitoring of renal graft function may facilitate early diagnosis of pancreatic rejection [309].

Pancreas transplants in nonuraemic patients have been less frequent. The largest series is that of Groth et al. and includes six patients [299]. Of the 63 patients reported to the new Registry since July 1, 1977, 23 did not have end stage diabetic nephropathy, although proteinuria and other clinical manifestations of nephropathy were present in some of these patients [301]. More nonuraemic patients could be selected for pancreas transplantation if the results improve, but the number will probably not be large as long as generalized immunosuppressive therapy is required.

C. Techniques of Clinical Pancreas Transplantation

The single most important technical issue in pancreas transplantation is what provision should be made for handling of the exocrine secretions. A variety of methods have been used (Table 2).

1. Pancreaticoduodenal Transplantation. The technique of pancreaticoduodenal transplantation has been described in detail [310–313]. The pancreas, duodenum, an aortic patch encompassing the coeliac axis and superior mesenteric artery, and the portal vein are removed en bloc from the donor and vascular anastomoses are made to the iliac vessels of the recipient. In the pioneering series of Lillehei et al. [296, 310], the duodenum was brought out as a cutaneous duodenostomy in four patients; in eight patients the duodenum was anastomosed to a Roux-en-Y jejunal loop; in one instance the papilla of Vater was used for anastomosis [296]. Bewick [314] performed internal drainage to a Roux-en-Y jejunal loop in 3 and external drainage in 4 of 7 cases of pancreaticoduodenal transplantation. The 3 pancreaticoduodenal grafts of Connolly et al. [312], the 2 of Merkel et al. [311, 315], the 2 of Largiader [313], and the 1 of Alexander [316] were all drained into a jejunal loop.

Approximately half of the pancreaticoduodenal grafts were technically satisfactory and functioned until rejection or death. A variety of complications, including infections and vascular thrombosis, occurred in the others. Not all of

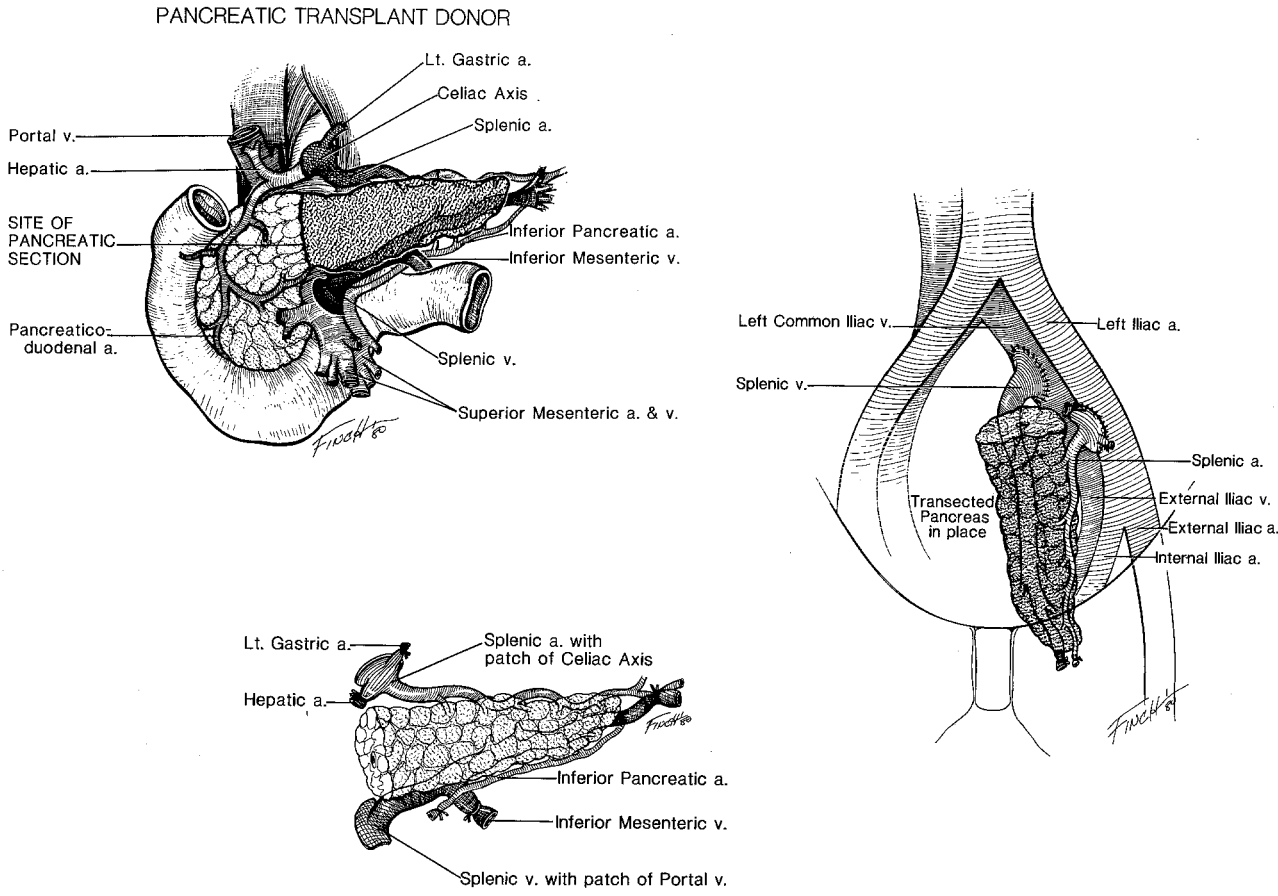

Fig. 2. Technique of segmental pancreas transplantation. Body and tail are transplanted with anastomoses of splenic vessels of donor pancreas to iliac vessels of recipient

the complications were related to the specific technique of transplantation, but in six cases, 3 of Lillehei et al. [296] and 1 each of Bewick [314], Connolly et al. [312] and Merkel et al. [315], duodenal necrosis or perforation occurred. Because of the complications and technical difficulties associated with pancreaticoduodenal transplantation, this approach has largely been abandoned in favour of segmental transplantation.

2. Segmental Pancreas Transplantation. The first pancreas transplant performed was segmental [317], and all groups currently performing pancreas transplants use the segmental technique. With this approach the body and tail (approximately 50%) of the pancreas is removed and the splenic artery (or celiac axis) and splenic vein (or portal vein) are used for vascular anastomoses to the iliac vessels of the recipient (Figure 2). Either a retroperitoneal or intraperitoneal approach can be used to expose the vessels of the recipient; most transplants teams have used the former approach. The details of removal of segmental pancreas grafts from cadaver donors before [304, 305, 318] or after circulatory rest [319] have been well described. The segmental approach also allows the use of living related donors, since more than half of the pancreas can be removed from a normal individual without serious metabolic consequences, and the spleen will survive on the short gastric vessels [320].

Several methods have been used to drain or suppress the secretions of segmental pancreas grafts (Table 2):

a. A deliberate cutaneous fistula was created in two cases following pancreas transplantation to the neck [321]. There were numerous complications associated with this unusual approach and the grafts were removed at 6 and 120 days respectively.

b. *Duct ligation* has been used in seven cases [301, 304, 317, 322–326]. Three of the grafts failed for purely technical reasons [304, 322, 323]; the others were rejected and were removed between 12 and 59 days after transplantation, either with [317, 324, 326] or without [325] persistent technical problems. Duct ligation does not necessarily reduce the volume of pancreatic secretions, since cut lymphatics can act as accessary ducts. All seven of the grafts were placed in the retroperitoneal area. Fluid accumulation around the pancreas or pancreatic fistulas developed.

c. Pancreatic graft *ductoureterostomy* has been performed in eight patients. In one who was nonuraemic [327], the duct of the graft was anastomosed to the side of the recipient's ureter, and the ipsilateral kidney was not removed; the pancreas was rejected within a few days so the long term effect on the kidney could not be determined. In the series of Gliedman et al. [297, 304] the recipients' ipsilateral kidneys were removed and end-to-side ductouretero-

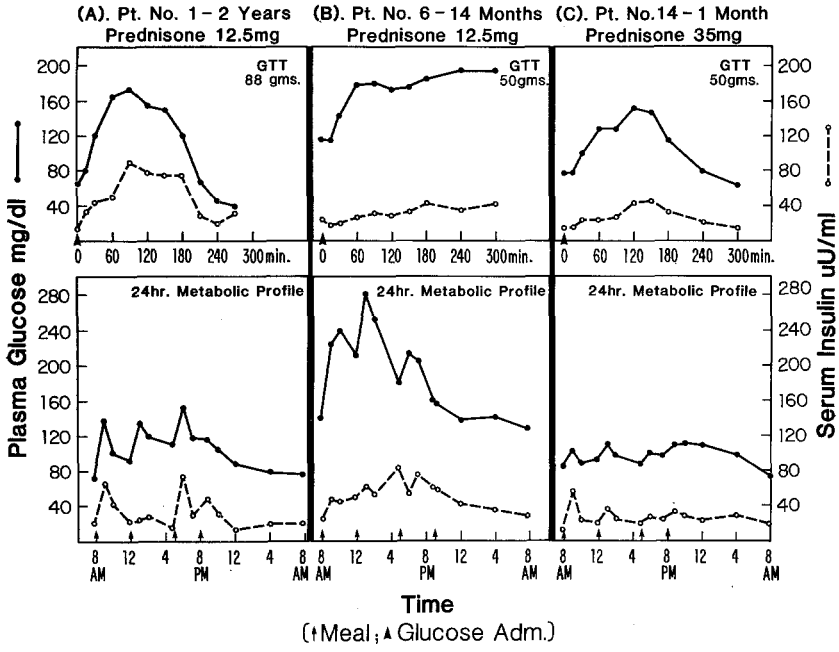

Fig. 3A–C. Results of metabolic studies after pancreas transplantation in three patients of second series at Minnesota selected to show individual variability in response to meals and glucose loading. The results are typical of those from other series

stomies were done; three of seven grafts failed because of vascular complications and three others were rejected within three months; the other graft functioned and the ureteral anastomosis remained patent until the recipient died at 49 months. Since anastomosis to the ureter may require sacrifice of the kidney, this technique is probably applicable only to uraemic patients.

d. Free intraperitoneal drainage with an *open duct* is possible because pancreatic proenzymes are not activated in the absence of enterokinase and the peritoneum can absorb pancreatic secretions [42, 44, 50, 52]. This approach has been used in 15 patients [52, 305, 314, 328, 329, 330]. In the Minnesota series, three patients developed ascites; one graft was removed at two weeks for this reason; in the other two patients the ascites disappeared after graft irradiation. Two Minnesota patients currently have open duct grafts functioning at 16 and 27 months; the other grafts were rejected (5 cases) or failed for technical reasons. An open duct graft of Dickerman et al. [300] was technically successful but was rejected at one month [330]. Intraperitoneal placement with an open duct is the simplest of all the pancreas transplant techniques and has been successful in several patients. In some patients, however, the graft secretion rate, may exceed the peritoneal absorption rate and the outcome is, therefore, unpredictable.

e. *Pancreaticojejunostomy* has been used in 21 cases of segmental pancreas transplantation [297, 299, 330–337]. None of the grafts transplanted by this technique are currently functioning [301]. Eight failed solely for technical reasons (2 anastomotic leaks, 2 abscesses, 4 vascular); nine grafts failed because of rejection, either with (5 cases) or without (4 cases) associated technical problems; four patients died with functioning grafts, three with and one without technical problems.

Some groups have created the Roux-en-Y jejunal loop in a separate operation before the actual transplant [331–333]. Theoretically, the complication rate should be reduced by the staged operation, but in practice the outcome has not been improved. Groth et al. [331] used this approach in 2 or their 8 cases of pancreaticojejunostomy; one developed an abscess and in the other the anastomosis disrupted before the graft was rejected. The three pancreaticojejunostomies in the New York series [333] were also staged; a leak lead to graft loss in one patient while the other two were rejected. Abscesses developed in the two recipients of pancreaticojejunostomies in another series [332]. Groth et al. [331] performed mucosal anastomoses of the duct to the jejunum in three of their cases; two had the problems described above and the other had a pancreatic leak until rejection occurred. This outcome is only slightly better than the results in their 5 cases where a nonmucosal anastomosis was made to a fresh Roux-en-Y loop; all failed. The eight cases in the other five series failed from rejection [330, 335, 337] with [335, 337] or without [330] a fistula [335] or abscess [337], or from jejunal loop necrosis [330], vascular thrombosis [336], or death from sepsis [334].

Pancreaticojejunostomy is the most physiological of all the techniques, but it results in inevitable enteric and microbial contamination, the pancreatic enzymes are activated, anastomotic breakdown occurs frequently, and the penalty for these complications in an immunosuppressed host is high. Until specific immunosuppression is possible, it appears best to use a technique that does not violate the bowel.

f. *Pancreatic duct occlusion* with synthetic polymers or other agents has been used for more pancreas transplants, 47, than any other technique [301]. The substances used include *neoprene* in 21 cases, 18 in Lyon [338–340] and three at Cincinnati [341, 342]; *polyisoprene* in 11 cases, all at Cambridge [343–345]; *prolamine,* an absorbable biological glue derived from corn protein [46 a], in ten cases

[346–352] and *cyanolacyralate* in five cases, all at Detroit [353].

Thirteen recipients of duct occluded grafts are currently (October 31, 1980) insulin independent, two for more than one year [301]. Of the 34 grafts that failed, 20 were rejected, 8 without and 12 with local wound problems; 4 patients died with functioning, technically satisfactory grafts; and 10 grafts failed for purely technical reasons (8 vascular and 2 infections).

Theoretically, total obliteration of the ductal system suppresses exocrine function more completely than simple duct ligation [318]. Leakage from the pancreatic surface, however, still occurs. Therefore, the Lyon group in ten of their cases [339, 340, 354], and the Cambridge [343–345], Minnesota [346, 347] and Zurich [351] groups have combined the technique of duct obliteration with total [347, 351, 354] or partial [344] intraperitoneal placement of the graft, or with omentoplasty [354], in order to provide a mechanism of resorption of pancreatic secretions. Only 4 of 26 recipients of ductal obliterated grafts placed by this technique had local wound problems and in only one instance did this complication lead to graft loss [301]. Six grafts failed because of vascular thrombosis, seven were rejected, one patient died with a functioning graft and 11 grafts are functioning.

Intraperitoneal exposure of duct obliterated segmental pancreas grafts appears to be a satisfactory method for handling the exocrine secretions. The main technical problem that remains is the tendency for primary vascular thrombosis to occur after transplantation of the pancreas, an organ with a relatively low blood flow rate (primary vascular thrombosis has occurred in 13% of all segmental grafts reported to the Registry [301]).

Another major question relates to the long term effect that the substances injected into the pancreas may have on endocrine function of the graft. The Lyon group has described extensive fibrosis in neoprene injected grafts [307], but cessation of function of technically successful grafts in their series occurred abruptly in a pattern consistent with acute rejection. Metabolic studies at 21 months in their one patient with a long-term functioning graft were nearly normal [338], and the Cambridge group has similar findings in a patient nearly one year after transplantation of a polyisoprene-injected graft [343].

In summary, the use of duct obliterated segmental grafts has been the most successful of the various techniques of pancreas transplantation. Intraperitoneal placement or omentoplasty permits residual secretions to be absorbed and is associated with the fewest graft losses for nonimmunological reasons. Finally, in the absence of local complications, the graft does not have to be removed if rejection occurs [52, 305, 347].

D. Pancreas Transplant Experience of Individual Institutions

Pancreas transplants have been performed at 23 institutions throughout the world (Table 3). Ten institutions have performed at least four transplants, but only five have experience with nine or more transplants. The individual experiences at these institutions illustrate the variations in and evolution of techniques and the approaches to patient selection and immunosuppressive treatment. Metabolic studies on selected cases provide examples of the results that can be achieved.

1. University of Minnesota. The first pancreas transplant in a human was performed at the University of Minnesota on December 17, 1966 [317]. The graft was segmental and failed within a few weeks from a combination of technical problems and rejection. Over the next six and a half years (Dec. 31, 1966 to January 11, 1973), Lillehei et al. [296, 310] performed an additional 13 pancreaticoduodenal transplants from cadaver donors in 10 uraemic and 3 preuraemic patients. Nine of these patients had synchronous kidney transplants. In the entire series of 14 transplants, three grafts failed solely for technical reasons (1 vascular, 1 ischaemic damage, 1 duodenal necrosis), two were rejected (1 with and 1 without technical complications) and nine patients died with functioning grafts, 4 with and 5 without technical complications [355]. Only one transplant functioned for more than one year, but this series showed that normal carbohydrate metabolism could be achieved in at least some patients by pancreas transplantation [296].

Because of the relatively high complication rate with pancreaticoduodenal transplantation, between 1974 and 1978 an effort was made to apply islet transplantation to the treatment of diabetes [356–358]. These attempts were unsuccessful.

In 1978 a new series was begun at Minnesota, using the segmental technique [305]. Between then and October 1980, 16 diabetic patients received 17 pancreas transplants [301, 305, 328, 329, 346, 347]. One patient received a second graft two years after rejecting a primary graft [301, 347]. Fourteen of the patients had previously (6 months to 6 years) received renal allografts for treatment of end stage diabetic nephropathy; two patients were nonuraemic, but had early nephropathy or retinopathy. Twelve of the pancreas grafts were from cadaver donors while five were from related donors (1 mother and 4 HLA identical siblings) [320, 347]. Three of the related donors had previously given a kidney to the recipient [320].

All of the grafts were placed intraperitoneally. The duct was left open in the first 13 patients [52, 329]. The duct was occluded with prolamine in the last four patients, including the one retransplant [346, 347]. The recipients of the first 14 grafts were immunosuppressed with antilymphocyte globulin, azathioprine and prednisone [346]. The last two recipients of cadaver grafts were immunosuppressed with cyclosporin A and low dose prednisone [347].

Five patients currently have functioning grafts, two with open ducts at 17 (maternal donor) and 28 (cadaver donor) months; and three with prolamine occluded ducts at less than 2 months, two from cadaver donors (1 retransplant, both recipients on cyclosporin A) and one from a sibling donor [301, 347]. Six patients lost graft function between 2 and 9 months, presumably from rejection, but the grafts were not removed and they simply resumed exogenous insulin; there were no changes in function of the kidneys previously transplanted from different donors [301, 347]. Rejection occurred rapidly in 5 patients, with normal or nearly normal plasma glucose levels immediately preceding

Table 3. World experience with pancreas transplantation according to institution

Institution[a] (References[b])	ACS/NIH + New Registry Dec, 1966 to June, 1977 Txs (Pts)	New Registry July, 1977 to Oct, 1980 Tx (Pts)	Total no. Txs (Pts)	Current no. with functioning grafts
1. Univ. Minnesota, Mpls., USA [296, 305, 317, 347]	14[e]	17 (16)	31 (30)	5[f]
15. Herriot Hosp, Lyon, France [300, 307, 339, 340]	5	13 (12 new &1 old)	18 (17)	3[f]
8. Montefiore Hosp, New York, USA [297, 304, 333]	10[e]	1	11	0
19. Univ. Cambridge, England [308, 343, 344, 345[c]]	0	11 (10)	11 (10)	4[f]
13. Huddinge Hosp, Stockholm, Sweden [299, 361]	4 + 2(4)[d]	3 (2 new &1 old)	9 (6)	0
10. Guys Hosp, London England [314[c]]	6 (5) + 1[d]	1	8 (7)	0
12. Univ. Zurich, Switzerland [313, 332, 351[c]]	4	1	5	1
22. Mt. Carmel Hosp, Detroit, USA [353[c]]	0	5	5	0
5. Univ. Colorado, Denver, USA [315[c], 337[c]]	1	3 (2)	4 (3)	0
7. Univ. Cincinnati, USA [316[c], 341, 342[c]]	1	3 (2)	4 (3)	2
6. Univ. California, Irvine, USA [312]	3	0	3	0
16. Parkland Hosp, Dallas, USA [330]	0	3	3	0
3. Univ. Sao Paulo, Brazil [323, 336[c]]	2	0	2	0
4. Perrando Hosp, Resistemica, Argentina [321]	2	0	2	0
14. Univ. Gothenberg, Sweden [325, 326]	2 (1)	0	2 (1)	0
20. Univ. Munich, FRG [348, 349[c]]	0	2	2	0
21. Univ. Innsbruck, Austria [350[c]]	0	2	2	0
2. Univ. Rio de Janeiro, Brazil [322]	1	0	1	0
9. Northwestern Univ, Chicago, USA [311]	1	0	1	0
11. Rush Presb. Hosp, Chicago, USA [327]	1	0	1	0
17. Univ. Montpellier, France [334]	0	1	1	0
18. Univ. Iowa, Iowa City, USA [335]	0	1	1	0
23. Univ. Erlangen, FRG [351[c]]	0	1	1	0
Total no. transplants	57 + 3[d]	68	128	15
Patients	55 + 1[d]	64 (62 new)	118	

[a] No. before institution refers to chronological order of initial pancreas transplant
[b] References are not inclusive of all cases reported to the Registry
[c] Unpublished; Registry data only
[d] Two retransplants of Groth et al. (299) and 1 primary transplant of Bewick (314) performed in 1976 were missed by the ACS/NIH Registry and are included in the New Registry (301)
[e] 1 Minnesota patient and 1 New York patient receiving pancreas transplants before 1977 had functioning grafts and were insulin independent for >1 year before dying
[f] 2 Minnesota, 1 Lyon and 1 Cambridge patients currently are alive with functioning grafts for >1 year after transplantation. One Cambridge patient lost graft function after 1 year

sudden recurrence of hyperglycaemia [305, 347]. The other six grafts failed because of vascular thrombosis in two [328], removal for ascites in one [305], removal for infections (with subsequent death) in two [305, 346] and death in another [305].

The results of metabolic studies in the patients of the second series at Minnesota are typical of those in other series, and will be described in some detail as examples of the individual variability in response to pancreas transplantation. All of the Minnesota patients were ketosis prone and had serum C-peptide levels of <1 ng/ml and urinary C-peptide secretion rates of <1 nmol/24 h before transplantation [347]. After transplantation serum C-peptide levels ranged from 2 to 10 ng/ml and urinary C-peptide secretion rates ranged from 7 to 70 nmol/24 h; the excretion rate tended to be higher during the period of high dose steroid administration. Insulin antibodies disappeared in all patients by one month of transplantation. Fasting serum insulin levels ranged from as low as 4 μU/ml in some to as high as 70 μU/ml in other patients; peak postprandial levels ranged from 25 to 138 μU/ml. In some patients glucose tolerance tests have been normal; in others plasma glucose levels have been elevated and the return to baseline delayed (Figure 3). All of the patients with functioning grafts have released insulin promptly in response to meals but the excursions of plasma glucose have been variable (Figure 3).

These pertubations may relate to the systemic drainage of the pancreatic graft, since insulin is ordinarily secreted directly into the portal circulation. The corticosteroids the patients take for immunosuppression may also influence carbohydrate metabolism, but this explanation is not the sole one. In the examples given, one patient on a high dose of prednisone one month after transplantation had a normal glucose tolerance test curve and a normal metabolic profile (Figure 3C), while one on a low dose of prednisone more than one year after transplantation had distinctly elevated plasma glucose levels, even though the insulin

response was normal (Figure 3B). The abnormalities apparent in the patient of Figure 3B are not due to any inherent defect in the transplanted pancreas, since the donor (mother) has normal glucose tolerance with lower serum insulin levels than the recipient [347]. Immune damage of the allograft may be responsible for the abnormalities in some patients, but again it is not the sole explanation. In Figure 3B, the recipient has no evidence of rejection of a renal allograft from the same donor [347].

Systematic study of the variations in response to pancreas transplantation may give insights into abnormalities that could exist in diabetic patients independent of pancreatic endocrine dysfunction. The aberrations seen in some patients with functioning pancreatic grafts, however, appear to be minor when compared to the pretransplant state. Whether they are important in relationship to the ultimate objective of pancreas transplantation, prevention or arrest of the secondary complications of diabetes, remains to be established. Only a few patients have been followed for a long period so that only preliminary observations are possible. The patient used as an example in Figure 3A had had progression of mesangial and glomerular basement membrane thickening of a kidney transplanted six years prior to the pancreas transplant. Two years after the pancreas transplant, there appeared to be a decrease in mesangial but not glomerular basement membrane thickening. Immunofluorescent staining for albumin on renal extracellular membranes persisted, although the intensity was less (observations by S. M. Mauer). If rejection does not occur, long term observations should be possible in this and other patients.

Thus, the initial series at Minnesota had a high complication rate, but showed the potential of pancreas transplantation as a treatment for diabetes. The second series demonstrated that the peritoneal cavity is a suitable site for segmental grafts. Ascites occurred in some patients if the duct was left open, but occlusion of the duct and intraperitoneal placement has been satisfactory. Finally, the experience at Minnesota shows that the use of related donors is feasible.

2. Herriot Hospital, Lyon. The transplant group in Lyon was the first to suppress exocrine function of segmental grafts by injection of the duct with a synthetic polymer [318]. Between February 1976 and October 1980, 18 pancreatic grafts were placed in 17 patients [301, 307, 338–340]. Five patients were preuraemic while 12 were uraemic and on dialysis. Eight of the latter had kidney transplants, two subsequent to and six simultaneous with the pancreas transplant. In nine instances the grafts were placed retroperitoneally alone. Because of a relatively high incidence of fistulae or other wound problems, an omentoplasty was used to protect the other nine grafts, either with or without intraperitoneal placement [339, 340, 354].

Three patients currently have functioning grafts and are insulin independent at 1, 3 and 25 months after transplantation [301]. All three also have functioning renal allografts. Seven patients suddenly lost graft function between one and nine months, presumably from rejection, but sclerosis induced by the neoprene made histological evaluation difficult [300]. Six grafts failed for technical reasons; five were removed because of vascular thrombosis and one because of a peripancreatic abscess. Two patients died with functioning grafts, one at one month from cardiac failure and one at 11 months from meningitis. Four other patients died subsequent to loss of graft function from unrelated causes.

The Lyon group believes that simultaneous pancreas and kidney transplantation in uraemic diabetic patients makes the diagnosis of pancreatic rejection easier because an elevation of serum creatinine from renal allograft rejection may be manifested before hyperglycaemia from concurrent pancreatic graft rejection [309]. The Lyon group may have reversed, at least temporarily, pancreatic rejection in some patients by corticosteroid administration. Metabolic studies on patients with functioning grafts have been similar to those in the Minnesota series. Improvement in neuropathy has occurred in at least one patient [307].

The Lyon group demonstrated that segmental pancreas transplants can be performed in high risk patients by using a technique that minimizes the quantity of exocrine secretions. Their initiative has stimulated several groups to pursue pancreas transplantation over the last three years. The main question regarding their approach is the effect that the chronic inflammatory response induced by neoprene may have on long term endocrine function of the pancreas graft.

3. Montefiore Hospital, New York. Gliedman and associates performed the first large series of segmental grafts beginning in 1970 [297, 304, 333]. All eleven of their patients had nephropathy; the first eight were uraemic and received kidney transplants, three simultaneous and five one to twenty weeks after the pancreas graft; the last three were preuraemic and received a pancreas graft alone.

Their initial graft was duct ligated, a kidney was transplanted simultaneously, there were multiple complications, and the patient died from sepsis [304]. The next seven grafts had exocrine drainage into an establish pancreaticoureterostomy [297, 304]. The two grafts placed simultaneous with a kidney failed from vascular thrombosis. Of the five pancreatic grafts transplanted before a kidney transplant, one was removed at 1 month because of arterial bleeding; two were completely and one was partially rejected by three months, and one patient had a functioning pancreatic graft and was insulin independent until death 49 months after transplantation. The latter patient was only partially rehabilitated and had multiple complications from pre-existing vascular disease and from chronic immunosuppressive treatment. An autopsy in this patient showed no evidence of hyaline changes in the afferent and efferent glomerular arterioles of the kidney transplanted 44 months previously.

The last three grafts, placed in the nonuraemic patients, were anastomosed to a previously created Roux-en-Y jejunal loop. The first two were rejected within three months and the last was removed at one month because of an anastomotic leak. At this time five of their 11 patients are alive but none have functioning grafts.

In summary, of the 11 pancreas transplants by this pioneer group, 5 failed for technical reasons, 5 were rejected, and one functioned for 4 years, the longest duration in any series to date. Five of the 11 patients are still alive [301]. In the one patient with a long term functioning

graft, far advanced vascular complications of diabetes were not reversed. The most important aspect of this series, however, was the observation that light microscopic evidence of diabetic nephropathy did not occur in a kidney transplanted to the one patient with long term function of the pancreatic graft. This finding stands in contrast to the uniform development of microscopic lesions characteristic of diabetes within four years in kidneys transplanted to diabetic patients without a pancreas transplant [359].

4. University of Cambridge. Eleven segmental pancreas grafts were transplanted in ten patients by the Cambridge group between August 1974 and October of 1980 [303, 308, 343, 344, 345]. The ducts were occluded with polyisoprene [308, 344]. In some cases, a fistula was constructed between the graft's splenic artery and vein in an attempt to reduce the incidence of vascular thrombosis, a common cause of pancreatic graft failure [360]. The first eight grafts were transplanted simultaneously with another organ, seven kidneys and one liver. All patients received cyclosporin A for immunosuppression [303]. Rejection episodes were treated with corticosteroids.

As of October 31, 1980, four patients had functioning grafts and were insulin independent at <1 (retransplant, pancreas alone, on dialysis), 4 (pancreas alone), 8 (with kidney) and 14 (with kidney) months after transplantation. One patient died with a functioning graft at 3 days from pre-existing complications. Two grafts failed from vascular thrombosis. Two grafts were removed at approximately one month because of wound problems; one was associated with rejection and the patient subsequently died. Two patients had good pancreatic graft function for 5 and 12 months before hyperglycaemia recurred. The reasons for loss of pancreatic graft function are not known [301].

The most important and unique aspect of this series has been the use of a new immunosuppressive drug, cyclosporin A. This drug may be more effective than others in preventing rejection of organ allografts, and can reduce or eliminate the need for steroids in some patients [303]. It is not clear whether or not carbohydrate metabolism is more nearly normal in non-steroid than in steroid treated pancreatic graft recipients; the results of glucose tolerance and other tests in the Cambridge series [343] show minor abnormalities that are not dissimilar from those described by other groups in steroid treated patients. Nevertheless, if cyclosporin A consistently prevents rejection with a relatively low toxicity, this will represent a major advance in the application of pancreas transplantation for the treatment of diabetes.

5. Huddinge Hospital, Stockholm. The Stockholm series comprises nine segmental pancreas transplants in six patients, three of them undergoing retransplantation after the first graft failed [299, 324, 331, 361]. The patients were nonuraemic, but they had other complications of diabetes or were "hyperlabile". The first graft was duct ligated and was rejected at six weeks [324]. The other eight grafts had exocrine drainage established via a Roux-en-Y pancreaticojejunostomy [299, 331]. Of these, three grafts failed from vascular complications (with one death) and five grafts were rejected between one and seven weeks after transplantation (2 with major and 3 with minor local complications and 1 death). This group observed that postprandial hyperglycaemia associated with a low serum C-peptide level was an early sign of rejection [299, 361a]. Nevertheless, antirejection treatment was only temporarily effective in the few patients that they treated [361].

This series includes the largest group of patients to receive pancreas transplants before uraemia and the terminal stages of diabetes were reached. This group has taken the most physiological approach to establish exocrine drainage of the graft. They have also recognised the need for early transplantation, but their approach may be premature until more specific immunosuppression is available.

6. Pancreas Transplants by Other Groups. There are no long term functioning grafts in the smaller series of pancreas transplants. No one institution has encountered all the problems that have occurred with pancreas transplantation, and the results of each group are worth reviewing.

Bewick [314], in London, performed eight pancreas transplants (all but one pancreaticoduodenal) in seven desparately ill uraemic patients; synchronous with a kidney transplant in the recipients of primary grafts. Only one graft failed to function, but the patients all died within a few days or weeks from rejection or from vascular complications.

Largiader and associates [313, 332, 351] in Zurich have performed five combined pancreas-kidney transplants. The first four grafts, two pancreaticoduodenal [313] and two segmental [332], had exocrine drainage established via a Roux-en-Y jejunal loop. The patients were extremely ill before transplantation and died between two and sixteen weeks from a combination of rejection, sepsis and pre-existing complications. Steroid treatment temporarily reversed apparent rejection episodes in two patients. The most recent transplant (segmental), was placed intraperitoneally, the duct was injected with prolamine, and the graft continues to function at four months [351].

Toledo-Pereyra and associates [353] at Detroit have performed five segmental transplants (retroperitoneal, cyanoacrylate injected) in preuraemic patients. One graft had ischaemic damage and never functioned. The other four grafts were rejected within two months and were removed because of preceding local wound problems.

Four pancreas transplants in Denver were performed simultaneous with kidney transplants [315, 337]. The first, a pancreaticoduodenal graft developed duodenal necrosis [315]. Three segmental grafts were drained via pancreaticojejunostomies [337]. One patient died of a myocardial infarction. The other two grafts, placed sequentially in one patient, were both rejected, the last with an associated abscess.

Four pancreas transplants have been performed in three patients at Cincinnati, one pancreaticoduodenal [316] and three neoprene injected segmental grafts [341, 342]. The first patient received a synchronous pancreaticoduodenal-kidney graft and died at one month of multiple complications. An initial segmental graft in the next patient ceased to function at one month, even though a kidney from the same donor was not rejected [341]; this patient subsequently received a second segmental graft that has functioned for >2 months [342]. Synchronously placed

pancreas (segmental) and kidney grafts in a third patient are functioning at 2 months [342]. Information on cases from institution with ≤ 3 transplants can be obtained from the Registry [301].

In general the problems encountered in the smaller series (48 pancreas transplants in 44 patients at 18 institutions, 24 reported to the ACS/NIH and 24 to the New Registry) have been similar to those of the larger series (80 transplants in 74 patients at 5 institutions, 33 in the ACS/NIH and 47 in the New Registry). The success rate, however, has been lower in the smaller series suggesting that experience is a factor in the successful application of pancreas transplantation. The three segmental grafts in the smaller series that are currently functioning [342, 351] were transplanted according to the techniques developed by the more experienced groups [347].

D. Segmental Pancreas Autotransplantation

At least five cases of segmental pancreas autotransplantation with vascular anastomoses have been performed in attempts to preserve endocrine tissue after total or near total pancreatectomy for treatment of chronic pancreatitis [362, 363]. These patients provide an unique opportunity to assess the effect of transplantation in the situation where rejection cannot occur and corticosteroids or other immunopharmacological agents are not administered. On the other hand, interpretation or extrapolation of the results may be difficult if a pancreatic remnant large enough to maintain glucose homeostasis by itself is left in situ, or if the islets contained in the transplanted segment have been extensively damaged by the original disease. Nevertheless, insulin secretion from the venous effluent has been demonstrated from segmental autotransplants more than one year after transplantation, and diabetes has not occurred in these patients [362, 363].

E. Summary of Clinical Pancreas Transplantation

One hundred twenty-eight pancreas allotransplants were performed in 118 diabetic patients between December 17, 1966 and October 31, 1980. Fifteen patients currently have functioning grafts and are insulin independent, four for more than one year. Three other patients were insulin independent for at least one year. Of the 113 pancreas transplants that are not functioning, 30 failed for purely technical reasons, 53 were rejected (28 with, and 25 without technical problems) and 30 patients died with functioning grafts (16 with and 14 without technical complications).

When technical problems and rejection have not occurred, carbohydrate metabolism has been normal or nearly normal in most patients, but in some patients metabolic abnormalities have persisted for reasons that are not clear. Not enough patients with long term functioning grafts have been followed for a definitive statement to be made regarding the effect of pancreas transplantation on secondary complications, but anecdotal observations are consistent with the hypothesis that progression of early lesions may be prevented and that regression is possible.

Although the overall success rate has not been high, it is improving. Technical problems were responsible for most of the early graft losses, but they are becoming fewer. In addition, most of the early patients were moribund from secondary complications and a successful outcome was precluded. Since 1977, pancreas transplants in patients in relatively good condition have been accomplished with much less morbidity. The best approach at this time appears to be segmental transplantation, total ductal occlusion, and intraperitoneal placement to absorb residual secretions. The three series with the largest and most recent experience – Minnesota, Lyon, and Cambridge – have features to suggest that pancreas transplantation for treatment of diabetes could be as successful as kidney transplantation for treatment of end stage renal falure. Even this success rate, however, would not be sufficient for promotion of pancreas transplantation as a general treatment for diabetes. The only patients who can be selected for pancreas transplant at this time are those who already require immunosuppression or those whose complications of diabetes will predictably be greater than those of chronic immunosuppression.

VI. Human Islet Preparation and Clinical Transplantation

Islet transplantation was originially conceived as an alternative to pancreas transplantation because of the difficulties of the latter procedure. Some of the problems with pancreas transplantation are being solved, but islet transplantation remains an attractive alternative for a variety of reasons. First, it should be simpler and safer for the recipient. Second, one pancreas theoretically could provide islet tissue for more than one diabetic recipient. Third, the islet tissue might be manipulated in vitro prior to transplantation to reduce immunogenicity.

It may be possible to achieve these objectives under the highly artifical circumstances of animal experiments, but attempts at clinical application have been largely unsuccessful, if not premature. Procurement of a sufficient quantity of viable islet tissue from human pancreases is a major problem, and one that has received little attention except by those who are actually interested in clinical application of islet transplantation.

A. Preparation and Isolation of Human Islet Tissue

Most reports on preparation and isolation of human islet tissue have focussed on in vitro metabolic studies. Human fetal pancreatic or adult islet adenoma fragments have been held in tissue cultures for days or weeks and the ability to release insulin in response to appropriate stimuli has been demonstrated [260, 364–368]. In vivo evidence of functional viability of cultured human islet tissue has not been obtained, but growth and differentiation of fresh human fetal pancreatic fragments has been demonstrated histologically following subcutaneous transplantation to nondiabetic nude mice [256]. Human fetal pancreas fragments have also been successfully cryopreserved, as judged by the ability of the tissue to incorporate amino acids into protein following thawing and in vitro incubation [278]. Very little is known about the expression of histocompatibility antigens on human fetal tissue, but there is no reason to believe that it is not immunogenic [369].

Infant human pancreas also has an extremely low exocrine enzyme content and a relatively large islet mass, and infant cadavers are potential sources of islet tissue for transplantation. In one study, the average weight of pancreases from infants less than one year old was only 4%, while the total islet mass was 25% that of an adult pancreas [370]. When the infant pancreases were dispersed by collagenase digestion, according to the technique found optimal to prepare neonatal rat pancreatic islet tissue for transplantation, more than 70% of the islet tissue was destroyed or lost. The final average tissue insulin content of one dispersed infant pancreas was only 6.5% of that contained in an entire intact adult pancreas. Minimal or no effect on carbohydrate metabolism was discerned after transplantation of dispersed infant pancreas to diabetic recipients [356].

Although fetal and neonatal human pancreases are relatively rich in islet tissue, unless the capacity to proliferate after transplantation is retained [118, 172, 260], more than one pancreas will probably be required to provide sufficient beta cell mass to ameliorate diabetes. Furthermore, the number of infant cadavers that will be suitable as donors is likely to be limited; the same may apply to fetal donors, for ethical if not for practical reasons.

Adult cadavers are probably the best potential source of islet tissue for transplantation. Islets can be isolated from adult human pancreases by using the collagenase digestion technique [98, 99, 128, 257, 276, 370–376]. Isolated human islets can synthetize insulin and glucagon [98, 375, 377] and can release insulin in response to in vitro challenge with glucose or other secretagogues [99, 276, 375, 376]. Isolated humans islets have been maintained in tissue culture for several weeks and in vitro evidence of viability has been obtained [257, 372, 375]. Unfortunately, the size, architecture, and compact, fibrous nature of the human pancreas has made the islets separation procedure more difficult than it is in animals and the yields have been low.

For transplantation purposes, it is impossible to use hand dissection for isolation of islets after collagenase digestion. The Minnesota group has attempted to isolate human islets on a large scale using the Ficoll gradient purification technique [98, 99, 370]. Islet yields, as determined by total tissue insulin content before and after processing, were extremely variable, but the average yield was less than 5%. Islet purity was also variable, as judged by the tissue insulin/amylase ratios. At least some of the isolated islets were viable according to the in vitro tests, but there was no significant effect following transplantation to diabetic humans [356, 357]. Although rejection probably contributed in part to failure, it appears that density gradient separation techniques will not consistently provide a sufficient quantity of purified islets for human transplantation and that other approaches must be used for islet preparation [100].

The most practical approach for preparation of human islet tissue is not to attempt purification. Animals experiments have shown that purification is unnecessary for successful transplantation [83, 84]. Although there may be an immunological advantage to purification in the allograft situation [235], methods other than reducing graft immunogenicity for prevention of rejection will probably have to be used for human transplantation in the absence of a technique that can purify islets on a large scale. Human pancreases have been dispersed by mincing and collagenase digestion for both allotransplantation [358, 378, 379] and autotransplantation [357, 358, 380–385] according to techniques used for successful islet transplantation in dogs [107, 109, 178]. Crude and probably unreliable methods based on gross morphology have been used by most groups to estimate islet yields. The Minnesota group measured tissue insulin content as an approximation of B cell mass [358, 382]. The final islet yield in dispersed tissue prepared from normal cadaver donor pancreases [358] ranged from 20 to 60% (mean 39 ± 15%). The same techniques applied to pancreases removed from patients with chronic pancreatitis [382] resulted in yields of 5 to 83% (mean 38 ± 25%). Although the islet recovery rate was much higher when the steps necessary for purification were eliminated, it is not know whether the conditions employed gave the optimal balance between the degree of dispersion necessary for engraftment and the islet yield or B cell mass necessary for successful transplantation.

The optimal conditions for digestion of human pancreatic tissue cannot necessary be extrapolated from the animal experiments because of the more fibrous nature of the human pancreas. The experimental techniques used to determine the appropriate condition for dispersion and transplantation of unpurified pancreatic islet tissue in animals are also difficult to apply to human pancreases. An unlimited number of animals can be used to determine the optimal conditions. The number of human trials required to determine the optimal conditions may be as large as for animal trials, and the probability of initial success in a clinical series is small. In addition, if transplanted allogeneic islets do not immediately ameliorate the diabetic state, it may be impossible to distinguish between failure for technical reasons and failure for immunological reasons. These difficulties in the interpretation of results must be kept in mind when evaluating the clinical trials conducted to date.

B. Islet Transplant Registry

Before the current surge of interest in experimental islet transplantation began, a few attempts had been made to transplant free grafts of allogeneic pancreatic tissue to diabetic patients. The tissue was derived from fetal [386] or still born infant pancreases [14], adult cadavers [387] or islet adenomas [388, 389], transplantation was usually to an IM or SC site, no patients were ameliorated of diabetes, and evidence of even transient function was unconvincing. The historical aspects of human islet transplantation have been previously summarized [77, 390].

The ACS/NIH Registry recorded no information on islet transplantation. According to published cases and cases submitted to the new Human Pancreas and Islet Transplant Registry over the past decade, there have been 74 islet allotransplant procedures in 68 diabetic patients [298, 301, 329]. Almost all these attempts have failed. Four patients became insulin independent for sustained periods after islet transplantation [379, 391–393], but insufficient details have been reported on the cases for critical analysis. A variety of sources, techniques and sites have

been used for tissue preparation and transplantation. Histocompatibility data has often been lacking, some patients have not even been immunosuppressed, and an overall interpretation of the results is extremely difficult. The statement made by Largiader [394] in 1977 still seems to apply: islet transplantation is a safe but ineffective procedure. No patients have died as a result of an islet transplant, although at least 7 patients (10%) have subsequently died from complications of their disease [301]. Information that is available, limited in many instances, on islet transplant cases from various institutions is summarized in the following section.

C. Islet Transplant Experience at Individual Institutions

1. University of Minnesota. Eighteen islet allotransplants were performed in 13 patients between 1974 and 1978 at the University of Minnesota [356–358]. All of the patients had previously received renal allografts and were already on immunosuppression. There were two series. One patient received transplants in both series.

In the first series (10 transplants in 7 patients) the islets were either *purified* from adult cadaver pancreases using the collagenase digestion-Ficoll separation technique (4 instances) or the islets were prepared by collagenase dispersion of infant human pancreases (6 instances) [356, 357]. The islet tissue was implanted IM in one instance, IP in five instances and infused into the portal vein in four instances. No patients could be completely withdrawn from exogenous insulin therapy, although insulin doses were reduced temporarily in seven cases with no change in metabolic control of diabetes. In this trial only small quantities of islet tissue were transplanted and immunosuppression was minimally augmented.

In the second series (8 transplants in 7 patients) *unpurified* dispersed pancreatic islet tissue prepared from cadaver donors was infused into the portal vein of each recipient, either immediately or after a period of cold storage [358]. Islet yield after pancreatic dispersal ranged from 20 to 60%. Portal pressure transiently increased after islet transplantation but liver function did not deteriorate in any patient. No patients were permanently ameliorated of diabetes. Two recipients were withdrawn from exogenous insulin therapy for short periods, one between the second and fourth days and one between the thirteen and seventeenth days after transplantation. During these intervals plasma glucose levels were nearly normal, but hyperglycaemia then recurred. Two other patients had temporary increases in urinary C-peptide excretion rates, but neither could be withdrawn from exogenous insulin therapy.

In both series, islet allotransplantation was a safe but metabolically inefficient procedure. Technical problems and rejection probably contributed to the failure to ameliorate diabetes. The yield of islets was improved in the second series by using unpurifed tissue, but dispersion, viability or both may have been inadequate. The diabetogenic effect of the corticosteroids administered to the recipients could have masked marginal graft function in some patients. In two cases it appeared that rejection was the main cause of failure.

2. University of Zurich. Largaider and associates [378, 391, 395] have transplanted unpurified islet tissue, prepared by collagenase dispersion of cadaver pancreases, to seven uraemic diabetic patients. The islet transplants were performed simultaneously with kidney transplants from the same donors and the recipients were immunosuppressed. In the first four patients the tissue was infused into the portal vein. There was no evidence of islet function in these cases; there were also no complications. Two patients rejected the kidneys after five months.

In the other three cases the tissue was implanted into the recipient's spleens. In two patients there was no or only transient evidence of islet function. The other patient, an insulin dependent diabetic for 22 years, was withdrawn from exogenous insulin therapy at nine months [391] and remained insulin independent until shortly before she died suddenly 20 months after transplantation [395]. This sequence of events is remarkable because the patient was treated for three rejection episodes of the kidney prior to insulin withdrawal and the patient resumed haemodialysis 15 months after the transplant. Presumably at least some of the islets, derived from a two and a half year donor, survived the rejection episodes; because of the young age of the donor the islets may have had the capacity for growth. No direct evidence to support this hypothesis was obtained during the life of the recipient [394] or at her autopsy [Largaider, F. M., communicated to the Registry (301)].

3. Huddinge Hospital, Stockholm. Groth et al. [396] transplanted minced fetal pancreas to nine patients with long standing diabetes. No recipients could be withdrawn from exogenous insulin therapy. In six patients (four preuraemic, nonimmunosuppressed; two post-kidney transplant, immunosuppressed), only a single donor was used and the tissue was placed IM. In the other three patients (post-kidney transplant, immunosuppressed), multiple donors were used; the tissue was injected into the spleen of one patient and into the portal vein in two patients. The details of one of the latter cases have been reported [397]. There was no improvement in the diabetic state of this patient, but urinary C-peptide excretion, virtually nil before transplant, increased to 5% of normal values and then, at four months, disappeared concomitant with the detection of islet cell surface antibodies in the patient's serum [396]. The significance of the latter observation is uncertain. No information on histocompatibility or even on the blood group of the donors was obtained, so insurmountable immunological barriers may have existed in some of the attempts.

4. University of Genoa. Valente et al. [393] have reported an experience with IP (two cases) and IM (ten cases) transplantation of four day cultured (four instances) or uncultured (eight instances) dispersed fetal pancreatic fragments (2–5 donors per recipient), in twelve nonimmunosuppressed patients with insulin dependent diabetes of 6–28 years duration. One recipient of noncultured tissue implanted IM had an increase in serum insulin and C-peptide levels and was withdrawn from exogenous insulin at five months. The other patients remained insulin depend-

ent. Again, no information on HLA or ABO types of the donors were reported.

In another series Valente et al. [379] transplanted small quantities of collagenase dispersed, cultured adult pancreatic tissue enclosed within 1 to 5 diffusion chambers, IP in one and SC in 12 patients with long standing diabetes. Eleven of the patients continue to require insulin; some of the chambers were removed after several months and were found to be encased in fibrous tissue. Two patients were withdrawn from insulin three months after transplantation. One patient had to resume exogenous insulin within a few months. The other patient has received no insulin for over one year. The patients had previously received exogenous insulin for many years, but no mention was made as to whether they were formally tested with insulin withdrawal prior to transplantation, nor were C-peptide results reported. Transplants in diffusion chambers have largely been unsuccessfull in animal experiments. It seems unlikely that the small number of islets contained within the chambers were responsible for the insulin independence exhibited by the one patient in this series. Further details are needed for critical analysis.

5. Islet Transplantation by Other Groups. Only sporadic attempts at clinical islet transplantation have been made by other groups in recent years. A few details on four cases have been published. Urca et al. [398] implanted a pancreatic insulinoma from an ABO compatible donor intramuscularly in an immunosuppressed 17-year-old patient with brittle diabetes of two years duration; pancreatic tissue was demonstrated on biopsies at 3 but not at 10 months, there was no evidence of function and the patient remained insulin dependent. Narasimhan et al. [399] transplanted cultured pancreatic islet cells from a single fetus to multiple sites in a renal allograft recipient, but the patient remained insulin dependent. Fragments from two fetal pancreases were implanted subcutaneously in a diabetic renal allograft recipient of blood group AB by Usadel et al. [256]; there was no increase in C-peptide levels and the patient remained insulin dependent. Chaston et al. [392, 400] transplanted cryopreserved-cultured fragments derived from multiple fetal pancreases to an IM site in a 29-year-old insulin treated patient who had been diabetic for only one year. Several weeks after transplantation this nonimmunosuppressed patient was withdrawn from insulin. A single serum insulin determination of 15 μU/ml before transplantation suggested that the patient had substantial endogenous B cell reserve. Critical studies to indicate whether the graft is responsible or whether there has been partial remission of the short term diabetes in this patient have not been reported.

Six other cases of islet transplants are recorded in the Registry [301]. All patients continued to require exogenous insulin treatment after transplantation [301].

D. Islet Autotransplantation

Fifty-three cases of intraportal islet autotransplantation after total (12 patients) or near total (41 patients) pancreatectomy for treatment of chronic pancreatitis have been reported to the Human Pancreas and Islet Transplant Registry [298, 329]. Five additional patients had islet tissue implanted at other sites. Twenty-five recipients of intraportal islets were reported to be insulin independent after the operation, but only one of these had had a total pancreaticoduodenectomy. Thus, it is likely that the small pancreatic remnant left in situ was at least partially responsible for maintaining glucose homeostasis in some of the other patients. Direct evidence of function of intraportal transplanted islets has been obtained by Cameron et al. [381] in one patient; serum insulin concentrations were higher in hepatic veins than in the portal vein during intravenous glucose tolerance tests. The exact incidence of insulin dependent diabetes after near total pancreatectomy is difficult to ascertain but it is much higher than 50% in most series [382, 401] and it seems likely that at least some of the islet autotransplants have been successful.

Several groups have published the results of their experience. Ten patients received intraportal islet autotransplants after total (one case) or near total (9 cases) pancreatectomy at the University of Minnesota [357, 358, 382]. One patient died; three are insulin independent, but only one is metabolically normal; the others require insulin, although C-peptide measurements show that some of the patients have B cell function [382]. Transient elevations of portal pressure occurred in some patients during tissue infusion; otherwise there were no complications of the transplant itself.

Nine of ten partially pancreatectomized recipients of intraportal islet autotransplants reported by Valente et al. [383] are insulin independent. Hepatic and portal vein insulin levels were equivalent in five patients who had samples drawn 15 days after transplantation.

Dobroschke et al. [380, 402] has reported on intraportal islet autotransplantation after near total pancreatectomy in one patient and after total duodenopancreatectomy in three patients. All four patients became insulin dependent diabetics after the operation, but metabolic studies, including C-peptide measurements, indicated that some of the transplanted islets functioned in at least one totally pancreatectomized patient.

Traverso et al. [384] have performed intraportal islet autotransplants after total pancreaticoduodenectomy in four patients with calcific pancreatitis. Their patients experienced systemic hypotension and portal hypertension during graft infusion. All of the patients became insulin dependent diabetics, although evidence for intrahepatic insulin production was obtained in one patient.

Cameron et al. [381, 403] have performed distal pancreatectomy and islet autotransplantation in eight patients. Six patients became normoglycaemic within 90 days of the operation; three of these redeveloped hyperglycaemia and insulin dependency between 3 and 8 months after surgery, while the others have remained normoglycaemic for at least 9 to 22 months. Portal hypertension occurred in all of their patients; it persisted and was a serious problem in one patient [184, 403]. This group found preoperative glucose tolerance test K values predictive of whether the patient would be insulin dependent or independent after the operation.

Lorenz et al. [385] reported on four patients who underwent intraportal islet autotransplantation after total

pancreaticoduodenectomy. Their series includes the only patient who was completely insulin independent after total pancreatectomy; metabolic studies in this patient before and after the operation showed nearly the same glucose tolerance.

The overall results of islet autotransplantation after pancreatectomy are difficult to evaluate. Some of the patients had impaired B cell function prior to the procedure. In addition, animal experiments have demonstrated that the preparation of islet tissue from diseased pancreases is more difficult than with normal pancreases [107], and it is likely that the situation is no different with human pancreases.

E. Summary of Clinical Islet Transplantation

Clinical islet allotransplantation has been a safe, but largely unsuccessful enterprise. It has been difficult to apply techniques that might overcome the islet yield and allograft rejection problems encountered in animal experiments. Over the past decade only 4 of 74 attempts at islet transplantation have been followed by long term withdrawal of exogenous insulin therapy, and there are problems with intrepretation of the outcome in each of these cases, as discussed in the preceding section.

In the islet allograft situation, the failures may have been for technical or for immunological reasons. In the autograft situation, rejection could not occur and the failures were clearly technical. The success rate with islet autografts gives some indication as to what might be achieved with islet allotransplantation if rejection could be prevented in the latter situation. The islet autotransplant experience is not entirely predictative, however, for two reasons: 1) the uncertainty over the contribution of the pancreatic remnant to carbohydrate metabolism when less than the total pancreatectomy is done; 2) the increased difficulty with liberating islets from diseased, fibrotic pancreases. For both islet allo- and autotransplantation, the success rate will probably remain low until more effective techniques are developed for preparation of islets from adult pancreases. For the allograft situation, additional advances will be needed in immunosuppression or in techniques to alter islet graft immunogenicity in order to overcome the rejection phenomenon.

VII. Prospects

Current evidence favours the concept that the secondary complications of diabetes will be prevented or their progression halted if homeostatic control of carbohydrate metabolism can be provided, control that is ideally provided by functioning islet tissue. In experimental animals both pancreas and islet transplantation have achieved this objective.

Clinical application of pancreas and islet transplantation is difficult, but if the rejection problem can be solved the prospects appear excellent. Pancreas transplantation has been able to correct the major metabolic abnormalities in most diabetic recipients when technical problems and rejection have been avoided. In the most recent series, segmental transplantation with duct occlusion has been done with relative safety.

Islet transplantation is an even safer procedure, but at this time it is clearly less efficient than pancreas transplantation. A major problem is islet yield. Ultimately, however, it should be possible to transplant several diabetic recipients with islet tissue prepared from one donor. This potential does not exist with pancreas transplantation.

Although widespread application of pancreas or islet transplantation will not be possible until specific immunosuppression, i. e., tolerance is available, pancreas transplantation could be used at this time to treat selected diabetic patients the same way as kidney transplantation is used to treat patients with end stage failure. Patients who receive kidney transplants can return to haemodialysis if rejection occurs. Diabetic patients receiving pancreas transplants could likewise return to insulin therapy if rejection occurs. This approach should be considered for diabetic renal allograft recipients or for nonuraemic patients with advancing retinopathy and neuropathy.

Ultimately, a serious question will be the availability of suitable donors for the number of patients who could potentially benefit from islet or pancreas transplantation. For some patients, related donors can be used – as has already been applied at Minnesota – but cadaver donors will probably be the major source of tissue for most recipients. A reliable method will be needed to identify, early in the course of their disease, patients whose diabetes cannot be adequately controlled by exogenous insulin and who will develop progressive complications. A sufficient number of donor pancreases should be available for treatment of this selected group of diabetic patients. When abrogation of a specific immune response in humans is possible, the full potential of clinical pancreas and islet transplantation will be realized.

References

1–294. Sutherland DER (1981) Pancreas and islet transplantation. I. Experimental studies. Diabetologia 20: 161–185
295. Gerrish EW (1977) Final Newsletter, American College of Surgeons/National Institutes of Health Organ Transplant Registry
296. Lillehei RC, Ruiz JO, Acquino C, Goetz FC (1976) Transplantation of the pancreas. Acta Endocrinol (Kbh) 83 [Suppl 205]: 303–321
297. Gliedman ML, Tellis VA, Soberman R, Rifkin H, Veith FJ (1978) Long term effects of pancreatic transplantation in patients with advanced juvenile onset diabetes mellitus. Diabetes Care 1: 1–9
298. Sutherland DER (1980) International human pancreas and islet transplant registry. Transplant Proc 12 [Suppl 2]: 229–236
299. Groth CG, Lundgren G, Gunnarson R, Arner P, Berg B, Ostman J (1980) Segmental pancreatic transplantation with duct-ligation or draining to a jejunal roux-en-Y loop in nonuremic diabetic patients. Diabetes 29 [Suppl 1]: 3–9
300. Traeger J, Dubernard JM, Touraine JL, Neyra P, Malik MC, Pelissard C, Ruitton A (1979) Pancreatic transplantation in man: A new method of pancreas preparation and results on diabetes correction. Transplant Proc 11: 331–335
301. Sutherland DER (1980) Human Pancreas and Islet Transplant Registry (298) Tabulation, October 31
302. Opelz G, Mickey MR, Terasaki PI (1977) Calculations on long term graft and patient survival in human kidney transplantation. Transplant Proc 9: 27–30
303. Calne RY, Rolles K, Thiru S, McMaster P, Craddock GN, Aziz S, White DJG, Evans DB, Dunn DC (1979) Cyclosporin A initially as the only immunosuppressive drug in 34 recipients of cadaveric organs. Lancet II: 1033–1036

304. Gliedman ML, Gold M, Whittaker J, Rifkin H, Soberman R, Freed S, Tellis V, Veith FJ (1973) Clinical segmental pancreatic transplantation with ureter-pancreatic duct anastomosis for exocrine drainage. Surgery 74: 171–180
305. Sutherland DER, Goetz FC, Najarian JS (1979) Intraperitoneal transplantation of immediately vascularized segmental grafts without duct ligation: A clinical trial. Transplantation 28: 485–491
306. Najarian JS, Sutherland DER, Kjellstrand CM, Ramsay RC, Goetz FC (1979) A ten year experience in kidney transplantation in juvenile onset insulin dependent diabetes. Ann Surg 190: 487–500
307. Traeger J, Dubernard JM, Touraine JL, Malik MD, Ruitton C (1980) Clinical experience with 15 neoprene-injected pancreatic allografts. Transplant Proc 12 [Suppl 2]: 44–50
308. McMaster P, Calne RY, Gibby OM, Evans DB (1980) Pancreatic transplantation in man. Transplant Proc 12 [Suppl 2]: 58–61
309. Dubernard JM, Traeger J, Touraine JL, Malik MC (1980) Rejection of human pancreatic allografts. Transplant Proc 12 [Suppl 2]: 103–106
310. Lillehei RC, Simmons RL, Najarian JS, Weil R, III, Uchida H, Ruiz JO, Kjellstrand CM, Goetz FC (1970) Pancreaticoduodenal allotransplantation. Experimental and clinical experience. Ann Surg 172: 405–436
311. Merkel FK, Poticha SM, Nudelman EJ, Colwell JA, Bergan JJ (1971) Pancreas transplantation in man. I. The donor and recipient operation. Arch Surg 103: 205–210
312. Connolly JE, Martin RC, Steinberg J, Gwinup O, Gazzanige AB, Bartletta RH (1973) Clinical experience with pancreaticoduodenal transplantation. Arch Surg 106: 489–493
313. Largiader F, Uhlschmid G, Binswanger U, Zaruba K (1975) Pancreas rejection in combined pancreaticoduodenal and renal allotransplantation in man. Transplantation 19: 185–187
314. Bewick M: Unpublished cases of pancreas transplantation (7 pancreaticoduodenal and 1 segmental) at Guy's Hospital, London. Reported to the ACS/NIH (295) and New Pancreas Transplant Registries [301]
315. Merkel FK, Starzl T: Unpublished case of pancreaticoduodenal transplantation at the University of Colorado reported to the ACS/NIH Organ Transplant Registry [295]
316. Alexander W: Unpublished case of pancreaticoduodenal transplantation at the University of Cincinnati. Reported to the ACS/NIH Organ Transplant Registry [295]
317. Kelly WD, Lillehei RC, Merkel FK, Idezaki Y, Goetz FC (1967) Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 61: 827–837
318. Dubernard JM, Traeger J, Neyra P, Touraine JL, Troudiant D, Blanc-Brunat N (1978) A new method of preparation of segmental pancreatic grafts for transplantation: Trials in dogs and in man. Surgery 84: 633–639
319. Bjorken C, Lundgren G, Ringden O, Groth CG (1976) A technique for rapid harvesting of cadaveric renal and pancreatic grafts after circulating arrest. Br J Surg 63: 517–519
320. Sutherland DER, Goetz FC, Najarian JS (1980) Living related donor segmental pancreatectomy for transplantation. Transplant Proc 12 [Suppl 2]: 19–25
321. Bortagaray MC, Zelasco JF, Bava A, et al (1970) Homotransplante parcial del pancreas en el diabetico. Prensa Med Argent 57: 220–224
322. Teixeira E, Monteiro G, DeCenzo M, Teixeira A, Bergan JJ (1970) Transplantation of the isolated pancreas. Bull Soc Int Chir 29: 337–339
323. Vaconcelos E: Unpublished case of segmental pancreas transplantation at the Univ. of Sao Paulo. Reported to the ACS/NIH Registry [295]
324. Groth CG, Lundgren G, Arner P, Cellste H, Hardstedt C, Lewander R, Ostman J (1976) Rejection of isolated pancreatic allografts in patients with diabetes. Surg Gynecol Obstet 143: 933–940
325. Brynger H, Blohme G, Claes G, Gustafson A, Gelin LE (1975) Transplantation of a duct-ligated pancreatic allograft to a diabetic patient. Scand J Urol Nephrol [Suppl] 24: 59–62
326. Brynger H, Gelin LE (1980) Clinical experience in transplantation of the duct ligated pancreas segment. Transplant Proc 12 [Suppl 2]: 91–92
327. Merkel FK, Ryan WG, Armbrusler K, Seim S, Ing TS (1973) Pancreatic transplantation for diabetes mellitus. IMJ 144: 477–479
328. Sutherland DER, Goetz FC, Najarian JS (1980) Report of twelve cases of segmental pancreas transplantation at the University of Minnesota. Transplant Proc 12 [Suppl 2]: 33–39
329. Sutherland DER, Goetz FC, Najarian JS (1981) Review of world's experience with pancreas and islet transplantation and results of intraperitoneal segmental pancreas transplantation from related and cadaver donors at Minnesota. Transplant Proc 13: 291–297
330. Dickerman RM, Raskin P, Fry W, Elick BA (1980) Clinical case reports: Pancreatic transplantation. Transplant Proc 12 [Suppl 2]: 86–90
331. Groth CG, Lundgren G. Gunnarson R, Hardstedt C, Ostman J (1980) Segmental pancreatic transplantation with special reference to the use of ileal exocrine diversion and to the hemodynamics of the graft. Transplant Proc 12 [Suppl 2]: 62–67
332. Largiader F (1980) Clinical cases of pancreatic organ allotransplantation. Transplant Proc 12 [Suppl 2]: 81–82
333. Tellis VA, Veith F, Gliedman ML (1980) Ten year experience with human pancreas transplantation. Transplant Proc 12 [Suppl 2]: 78–80
334. Marchal G, Mirouze J, Selam JL, Pham JC, Giordan J (1980) Report of a clinical case of segmental pancreatic transplantation with the aid of the artificial pancreas. Transplant Proc 12 [Suppl 2]: 95–97
335. Corry RJ, West JC (1980) Pancreatic graft duct drainage through a long polyethylene catheter in Roux-en-Y limb. Transplant Proc 12 [Suppl 2]: 93–94
336. Raia AA: Unpublished case of segmental pancreas transplantation at the University of Sao Paulo. Reported to the ACS/NIH Registry [295]
337. Weil R, Starzl T: Unpublished cases of 3 segmental pancreas transplants in 2 patients at the University of Colorado. Reported to the new Pancreas transplant Registry [301]
338. Traeger J, Dubernard, JM, Ruitton C, Malik MC, Touraine JL (1981) Function of 15 pancreatic allografts in man. Transplant Proc 13: 299–304
339. Traeger J, Dubernard, JM, Malik MC, Touraine JL, Ruitton C (in press) Clinical Eperience with 17 Neoprene Injected Pancreatic Allografts in Man. Proc. 1980 EASD Satellite Symposium Islet-Pancreas Transplantation and Artificial Pancreas. Horm Metab Res
340. Traeger J, Dubernard JM: Unpublished case of segmental pancreas transplantation at Herriot Hospital, Lyon. Reported to the New Pancreas Transplant Registry [301]
341. Munda R, Alexander JW, First RM, Knowles HC, Weiss MA (1980) Synchronous transplantation of a kidney and duct obliterated segmental pancreas: Report of a case. Transplant Proc 12 [Suppl 2]: 98–102
342. Alexander JW, Munda R: Unpublished cases of two segmental pancreas transplants (one retransplant) as the University of Cincinnati. Cincinnati. Reported to the New Pancreas Transplant Registry [301]
343. McMaster P, Gibby OM, Calne RY, Loke M, Luzio SP, Rolles, K, Evans, DB, White DJG (1981) Human pancreatic transplantation: Preliminary studies of carbohydrate control. Transplant Proc 13: 371–373
344. McMaster P, Gibby OM, Evans DB, Calne RY (in press) Human pancreatic transplantation with polyisoprene and cyclosporin A – immunosuppression. Proc. 1980 EASD Satellite Symposium Islet-Pancreas Transplantation and Artificial Pancreas. Horm Metab Res
345. Calne RY: Unpublished case of segmental pancreas transplantation at University of Cambridge. Reported to the New Pancreas Transplant Registry [301]
346. Sutherland DER, Goetz FC, Najarian JS (in press) Pancreas and islet transplantation in man. Proc. 1980 EASD Satellite Symposium Islet-Pancreas Transplantation and Artificial Pancreas. Horm Metab Res
347. Sutherland DER, Goetz FC, Rynasiewicz JJ, Baumgartner D, Elick BA, Najarian JS (in press) Segmental pancreas transplantation from living related and cadaver donors: A clinical experience. Surgery 90
348. Land W, Liebe W, Kuhlmann H, Eberhard E (1980) Simultaneous kidney and pancreas transplantation using prolamine for duct obstruction. Transplant Proc 12 [Suppl 2]: 76–77
349. Land W: Unpublished case of segmental pancreas transplantation at the University of Munich. Reported to the new Pancreas Transplant Registry [301]
350. Margrieter R: Unpublished cases of two segmental pancreas transplants at University of Innsbruck. Reported to the New Pancreas Transplant Registry [301]
351. Largiader F: Unpublished case of segmental pancreas transplantation at the University of Zurich. Reported to the New Pancreas Transplant Registry [301]
352. Gebhardt C, Meister R: Unpublished case of segmental pancreas transplantation at University of Erlangen. Reported to the New Pancreas Transplant Registry [301]
353. Toledo-Pereya L: Unpublished cases of 5 segmental pancreas transplants at Mt. Carmel Hospital, Detroit. Reported to the New Pancreas Transplant Registry [301]
354. Dubernard MJ, Traeger J, Devonec M, Touraine JL (1980) Pancreatic transplantation in man: Surgical technique and complications. Transplant Proc 12 [Suppl 2]: 40–43
355. Sutherland DER, Goetz FC, Carpenter AM, Najarian JS, Lillehei RC (1979) Pancreaticoduodenal grafts: Clinical and pathological observations in uremic versus nonuremic recipients. In: Touraine JL, et al

(eds) Transplantation and clinical immunology, Vol X. Excerpta Medica, Amsterdam Oxford, p 190–195
356. Najarian JS, Sutherland DER, Matas AJ, Steffes MW, Simmons RL, Goetz FC (1977) Human islet transplantation: A preliminary report. Transplant Proc 9: 233–236
357. Sutherland DER, Matas AJ, Najarian JS (1978) Pancreatic islet cell transplantation. Surg Clin North Am 58: 365–382
358. Sutherland DER, Matas AJ, Goetz FC, Najarian JS (1980) Transplantation of dispersed pancreatic islet tissue in humans: autograft and allografts. Diabetes 29 [Suppl 1]: 10–18
359. Mauer SM, Barbosa J, Vernier RL, Kjellstrand CM, Buselmeier TJ, Simmons RL, Najarian JS (1976) Development od diabetic vascular lesions in normal kidneys transplanted into patients with diabetes mellitus. N Engl J Med 295: 916–920
360. Calne RY, McMaster P, Rolles K, Duffy TJ (1980) Technical observations in segmental pancreas allografting: Observations on pancreatic blood flow. Transplant Proc 12 [Suppl 2]: 51–58
361. Groth CG, Lundgren G, Ostman J, Gunnarsson R (1980) Experience with nine segmental pancreatic transplantations in pre-uremic diabetic patients in Stockholm. Transplant Proc 12 [Suppl 2]: 68–71
361a. Ostman J, Arner P, Groth CG, Heding LG, Lundgren G (1980) Plasma C-peptide and serum insulin antibodies in diabetic patients receiving pancreas transplants. Diabetologia 19: 25–30
362. Hogle HH, Reemtsma K (1978) Pancreatic autotransplantation following resection. Surgery 83: 359–360
363. Tosatti E, Valente U, Campisi C, Barabino C, Pozzati A (1980) Segmental pancreas autotransplantation in man following total or near total pancreatectomy for serious recurrent chronic pancreatitis. Transplant Proc 12 [Suppl 2]: 15–17
364. Chick WL, Lauris V, Soeldner JS, Tan MH, Grinberg M (1973) Monolayer culture of human pancreatic beta cell adenoma. Metabolism 22: 1217–1224
365. Leach FN, Aschworth MA, Barson AJ, Milner RDG (1973) Insulin release from human foetal pancreas in tissue culture. J Endocrinol 59: 65–79
366. Goldman H, Colle E (1976) Human pancreatic islets in culture. Effects of supplementing the medium with homologous and heterologous serum. Science 192: 1014–1016
367. Maitland JE, Parry DG, Turtle JR (1980) Perifusion and culture of human fetal pancreas. Diabetes 29 [Suppl 1]: 57–63
368. Agren A, Andersson A, Bjorken C, Groth CG, Hellerstrom C, Lindmark G, Lundqvist G, Petersson B, Swenne I (1980) Human fetal pancreas culture and function in vitro. Diabetes 29 [Suppl 1]: 64–69
369. Siegler HF, Metzgar RS (1970) Embryonic development of human transplantation antigens. Transplantation 9: 478–486
370. Sutherland DER, Matas AJ, Steffes MW, Najarian JS (1976) Infant human pancreas: A potential source of islet tissue for transplantation. Diabetes 25: 1123–1128
371. Ashcroft SJG, Bassett JM, Randle PJ (1971) Isolation of human pancreatic islets capable or releasing insulin and metabolising glucose in vitro. Lancet I: 888–889
372. Andersson A, Borg H, Groth CG, Gunnarsson R, Hellerstrom C, Lundgren G, Weckman J, Ostman J (1976) Survival of isolated human islets of Langerhans maintained in tissue culture. J Clin Invest 57: 1295–1301
373. Ferguson J. Allsopp RH, Taylor RMR, Johnston IDA (1977) Isolation of viable human pancreatic islets. World J Surg 1: 69–77
374. Reemstma K, Weber CJ, Pi-Sunyer FX, Lerner RL, Hardy MA (1980) Alternatives in pancreatic islet transplantation: tissue culture studies. Diabetes 29 [Suppl 1]: 45–51
375. Jahr H, Lorenz D, Besch W, Zuhlke H, Schmidt S, Lippert H, Bibergeil H (1980) (Pro)Insulin biosynthesis and secretion of islets prepared from human pancreas biopsies. Horm Metab Res 12: 83–84
376. Grant AM, Christie MR, Ashcroft SJH (1980) Insulin release from human pancreatic islets in vitro. Diabetologia 19: 114–117
377. Noe BD, Bauer GE, Steffes MW, Sutherland DER, Najarian JS (1975) Glucagon biosynthesis in human pancreatic islets: Preliminary evidence for a biosynthetic intermediate. Horm Metab Res 7: 314–322
378. Kolb E, Largiader F (1980) Clinical islet transplantation. Transplant Proc 12 [Suppl 2]: 205–207
379. Valente U, Ferro M, Campisi C, Parodi F, Tosatti E (1980) Allogeneic pancreatic islet transplantation by means of artificial membrane chambers in 13 diabetic recipients. Transplant Proc 12 [Suppl 2]: 223–228
380. Dobroschke J, Schwemmle K, Lanhott G, Laube H, Bretzel RG, Federlin K (1978) Autotransplantation von Langerhans'schen Inseln nach totaler Duodenopankreatokromie bei einer Pankreatitis. Dtsch Med Wochenschr 103: 1905–1910
381. Cameron JL, Mehigan DG, Harington DP, Suidema GD (1980) Metabolic studies following intrahepatic autotransplantation of pancreatic islet grafts. Surgery 87: 397–400
382. Najarian JS, Sutherland DER, Rynasiewicz JJ, Baumgartner D, Matas AJ, Goetz FC (1980) Total or near total pancreatectomy and islet autotransplantation for treatment of chronic pancreatitis. Ann Surg 192: 526–542
383. Valente U, Ferro M, Campisi C, Cataldi L, Traverso C, Fontana I, DeRosa E, Cama A, Tosatti E (1980) Report of clinical cases of islet autotransplantation. Transplant Proc 12 [Suppl 2]: 202–204
384. Traverso LW, Alou-Zamzam AN, Longmire WP (1981) Human pancreatic cell autotransplantation following total pancreatectomy. Ann Surg 193: 191–195
385. Lorenz D, Wolff H, Lippert H (1981) The transplantation of islets of Langerhans in patients which chronique pancreatitis. In: Bretzol R, Federlin K, Scholz H (eds) Proceeding of 1980 Geissen workshop on islet isolation, culture and cytopreservation. Thieme, Stuttgart
386. Stone HB, Owings JC, Gey GO (1938) Further reports on grafting of endocrine glands. Miss Doc J 15: 6–9
387. Pybus PC, Durh MS (1924) Suprarenal and pancreatic grafting. Lancet II: 550–551
388. Murry MR, Bradley CF (1935) Two island cell adenomas of the human pancreas cultured in vitro. Am J Cancer 25: 98
389. Kooreman PJ, Gaillard PJ (1950) Transplantatie van homoioplastisch incretorisch klierweefsel. Ned Tijdschr Geneeskd 14: 1012
390. Brooks JR (1972) Endocrine tissue transplantation. Charles C Thomas, Springfield Ill, p 83–85
391. Largiader F, Kolb E, Binswanger U (1980) A long term functioning human pancreatic islet allotransplant. Transplantation 39: 76–77
392. Chaston Ph, Berjon JJ, Gomez H, et al (1980) Implantation de pancréas foetau chez un diabétique insulino-dépendent. Nouv Presse Med 9: 353–354
393. Valente U, Ferro M, Barocci S, Campisi C, Parodi F, Cataldi L, Arcuri V, Tosatti E (1980) Report of clinical cases of human fetal pancreas transplantation. Transplant Proc 12 [Suppl 2]: 213–217
394. Largiader F (1977) Farewell to pancreatic organ transplantation? Eur Surg Res 9: 399–402
395. Kolb E, Largiader F (1981) Transplantation of pancreatic microfragments in patients with juvenile diabetes. In: Bretzol R, Federlin K, Scholz H (eds) Proceedings of 1980 Geissen workshop on islet isolation, culture and cytopreservation. Thieme, Stuttgart
396. Groth CG, Andersson A, Bjorken C, Gunnarsson R, Hellerstrom C, Lundgren G, Petersson B, Swenne I, Ostman J (1980) Attempts at transplantation of fetal pancreas to diabetic patients. Transplant Proc [Suppl 2]: 208–212
397. Groth CG, Andersson A, Bjorken C, et al (1980) Transplantation of fetal pancreatic microfragments in the portal vein to a diabetic subject. Diabetes 29 [Suppl 1]: 80–83
398. Urca I, Kott I, Lev-Ran A (1970) Transplantation of a pancreatic insulinoma into an insulin-resistant patient with juvenile diabetes. Diabetes 19: 182–185
399. Narasimhan MJ, Anderson JA (1977) Immune co-culture of B-cells and immune coded transplantation. Proc. IX Congress International Diabetes Fed. Excerpta Med Int Congr Series 413: 521–528
400. Chaston Ph, Berjon JJ, Gomez H, Meunier JM (1980) Treatment of an insulin-dependent diabetic by homograft of fetal pancreas removed before the tenth week of pregnancy: One-year follow-up. Transplant Proc 12 [Suppl 2]: 218–222
401. Griffen WO (1978) Metabolic complications of pancreatectomy. In: Buchwald H, Varco RC (eds) Metabolic surgery. New York, Grune and Stratton, p 111
402. Dobroschke J, Langhoff G, Kunze JJ, Laube H, Schwemmle K (1981) Intraportal transplantation of human islets of Langerhans. In: Bretzol R, Federlin K, Scholz H (eds) Proceedings of 1980 Geissen workshop on islet isolation, culture and cytopreservation. Thieme, Stuttgart
403. Cameron JL, Mehigan DG, Broe P, Zuidema GD (in press) Distal pancreatectomy and islet autotransplantation for chronic pancreatitis. Ann Surg

Received: November 21, 1980

Dr. David E. R. Sutherland
Box 253 Mayo Memorial Building
University of Minnesota Hospitals
420 Delaware Street S. E.
Minneapolis, MN 55455
USA