Total or Near Total Pancreatectomy and Islet Autotransplantation for Treatment of Chronic Pancreatitis

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Total or near total pancreatectomy is the surest way to relieve the pain of chronic pancreatitis but is rarely applied because the metabolic consequences are so severe. For most patients drainage procedures are applicable, but pancreatectomy may be the only alternative for small duct disease or where procedures to improve duct drainage have failed. Preservation of endocrine function is a major problem in patients who require pancreatectomy. Experiments in pancreatectomized dogs have shown that intrasplenic or intraportal transplantation of unpurified pancreatic islet tissue dispersed by collagenase digestion can prevent diabetes. We have applied this technique to ten patients with chronic pancreatitis, small ducts, and intractable pain. The entire pancreas or >95% of the pancreas was excised, minced, dispersed by collagenase digestion and infused into the portal vein <2½ hours after removal. Mean (±SD) rise in portal pressure was 17 ± 8 cm of water. Liver function tests were altered minimally. All patients were relieved of pain. One patient died of a complication not related to the islet autotransplant; viable islets were identified in the liver at autopsy. Of the remaining nine patients, three have been insulin independent for 1, 9, and 38 months. One patient was insulin independent for 15 months and now takes 12 units of insulin daily. Three have nonketosis prone diabetes (tested by insulin withdrawal) and take 15–30 units of insulin per day. C-peptide studies in these patients show that functioning islets are present. Two patients are diabetic and require 35 and 60 units of insulin per day. In eight of nine patients tested serum insulin concentrations fell to undetectable levels during the interval between pancreatectomy and islet transplantation. Serum insulin levels during the first few hours after islet transplantation predicted success. In the insulin independent or in the patients with mild diabetes, insulin levels were persistently ≥6 μU/ml. In the other two patients, the increase in insulin concentration was not sustained. Islet tissue preparation from a diseased pancreas is difficult. The surgeon and the patient must still be willing to accept diabetes for relief of pain when performing this operation. In some patients, however, islet autotransplantation can prevent or partially ameliorate diabetes after pancreatectomy, and preservation of endocrine function is worthwhile.

TOTAL OR NEAR TOTAL pancreatectomy is the surest way to relieve the pain of chronic pancreatitis,[2,10] but the operation has severe metabolic consequences.[13] A variety of surgical procedures are available that will preserve pancreatic tissue, but pancreatectomy may be the only alternative for small duct disease or where procedures to improve duct drainage have failed.

More than 80% of patients with chronic pancreatitis who require operative treatment do not have overt diabetes at that time.[33] However, diabetes is a predictable event after major pancreatic resection,[9,13] and when more than 95% of a gland is removed, all patients become insulin dependent.[2,9]

We have attempted to prevent diabetes or to reduce the severity of the disease after pancreatectomy by performing an intraportal transplantation of autologous islet tissue prepared by dispersion of the excised pancreas.[29] The technique for pancreatic islet tissue preparation was similar to that used to prevent diabetes by autotransplantation after total pancreatectomy in normal dogs.[18,25] The initial outcome and the results of metabolic studies in our first case[29] and in two others[27,28] have previously been reported. In this article, our total experience to date with pancreatectomy and islet autotransplantation in ten patients with chronic pancreatitis is described.

Patient Population

Patients Undergoing Near Total Pancreatectomy Without Islet Autotransplantation and Outcome

Between 1966 and 1978, eight patients (seven males and one female) with chronic pancreatitis underwent total or near total (85–95%) pancreatectomy at the

Presented at the Annual Meeting of the American Surgical Association, Atlanta, Georgia, April 23–25, 1980.

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Supported by USPHS Grant AM 19269 and NIH Grant RR 400 from the Clinical Research Center Branch. Dr. Sutherland is a recipient of USPHS Research Career Development Award K04 AM00161.

0003-4932/80/1000/0526 $01.35

TABLE 1. *Biographic Information and Outcome in Ten Patients with Chronic Pancreatitis Treated with Total or Near Total Pancreatectomy and Intraportal Islet Autotransplantation*

Patient	Sex	Age (yrs)	Etiology of Pancreatitis	Years of Symptoms	Previous Operations	Date of Pancreatectomy and Islet Autotrans.	Histopath. Severity of Pancreatitis	Adjunctive Procedures or Complications	Insulin Dose	Ketosis Prone	C-Peptide Pres.	Length of Follow-up (mos.)	Comments
1. H.M.	F	39	Familial	20	Mult. gastric ops. 1967–1974	02-14-77	12	None	0	No	Yes	38	Normal GTT. Had islet hyperplasia
2. M.B.	M	35	Alcohol	5	Sphincteroplasty July 1979	11-22-77	13	Perf. colon. Died 12-3-77	—	—	—	—	Viable islets in liver at autopsy
3. V.M.	F	57	Idiopathic	4	Cholecystectomy 1960	02-23-78	2	None	12	No	Yes	26	On no insulin for first 15 months
4. B.M.	F	46	? Biliary	6	Cholecystectomy & CBDE Mar. 1979	07-16-79	18	Choledochoplasty with pancreatectomy. Duodenal ischemia; duodenectomy, choledochojejunostomy and gastrojejunostomy 8-13-79	23	No	Yes	9	Multiple giant cysts of pancreas
5. R.S.	M	29	Alcohol	3	Distal (70–80%) pancreatectomy Jan. 79	07-19-79	8	Duodenal structure from ischemia had gastrojejunostomy Nov 79	35	NT	NT	9	Has not returned for followup studies
6. C.R.	M	24	Alcohol	8	Exp. Lap. 1971 Hem. pancreatitis	07-23-79	20	None	60	NT	Low	9	Has not returned for followup studies
7. A.W.	M	32	Alcohol	4	Gastrectomy & B-II 1974	07-27-79	T/H* 19/9	Severe bleeding after t-tube pulled—8-17-79; required reoperation	30	NT	Low	9	Required little or no insulin until reoperation. C-peptide decreased after reoperation
8. K.N.	F	27	Idiopathic	4	Cholecystectomy 1975 Sphincteroplasty 1977	08-27-79	0/12	Partial duod. obst. Vag. & gastrojej. 10-18-79	0	No	Yes	8	Insulin dependent, but abnormal GTT
9. D.L.	M	41	Alcohol	5	Pancreatic abscess with rupture into colon, drained and ileostomy 1976	12-17-79	14	None	15	No	Yes	4	Had abscess in head of pancreas. Only pancreatic tail processed for islets
10. M.K.	M	35	Alcohol	4	Distal (30%) pancreatectomy & Roux-en-Y pancreaticojejunostomy Dec. 1978	03-24-80	14/0	None	0	No	Yes	1	Had only 90% pancreatectomy†

* T = Tail. H = Head.

† All other patients had >95% pancreatectomy. NT = Not Tested.

University of Minnesota Hospitals. They ranged in age from 25 to 68 years. The cause of diabetes was alcohol related in six patients, biliary tract disease related in one patient and idiopathic in one patient. Five patients had previous operations: 40% pancreatectomy in one patient; longitudinal Roux-en-Y pancreaticojejunostomy in one; cholecystectomy in two patients; and sphincteroplasty in one. The operations were unsuccessful. All eight patients were relieved of pain after pancreatectomy. All eight also became diabetic after the operation. No patient had been overtly diabetic before the operation. One patient died one year after pancreatectomy from hypoglycemia secondary to an insulin reaction. One patient died 11 years after pancreatectomy of a metastatic carcinoma with an unknown primary. The other six patients are alive 5–12 years after the operation, but all require exogenous insulin. The pancreases of four of these patients were graded for the severity of the histopathologic findings (see below for grading criteria); these pancreases received grades of 9, 14, 14 and 16. (Mean ± SD, 13. 3 ± 3.0)

Patients Undergoing Total or Near Total Pancreatectomy and Islet Autotransplantation

Between February 14, 1977, and March 24, 1980, ten patients with chronic pancreatitis were treated with total or near total pancreatectomy (>95% in all but one) and islet autotransplantation (Table 1). There were six males and four females. The age range was 24–57 years. Alcohol was implicated as the cause of the disease in six patients, although four probably did not drink alcohol at the time we treated them. In one patient the pancreatitis originally may have been induced by biliary tract disease; the other three patients had no obvious etiologic factors, although one had a history

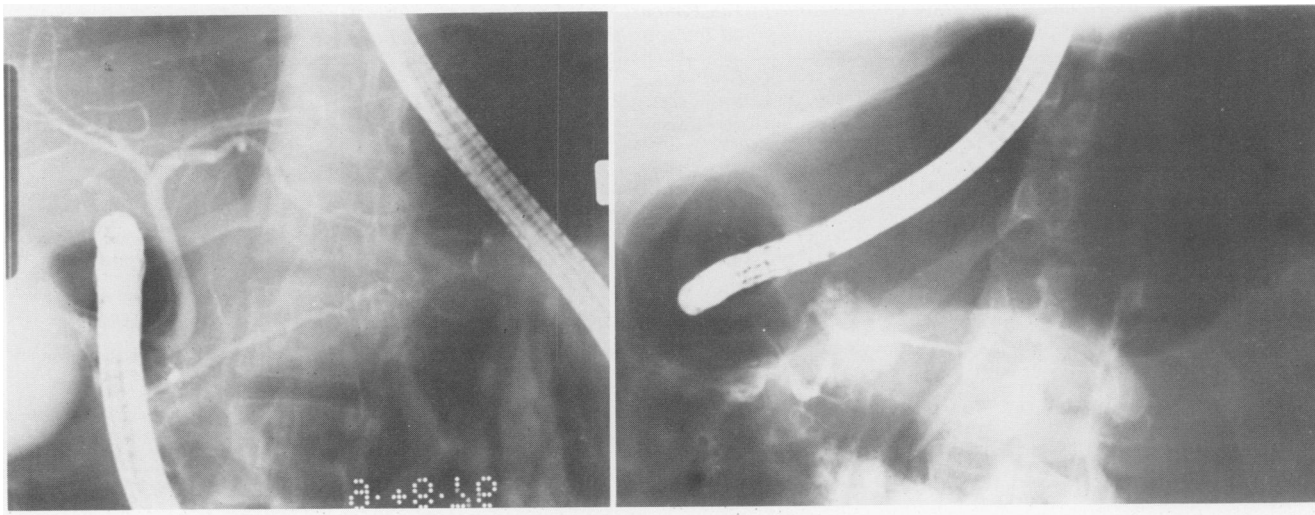

FIG. 1. Endoscopic retrograde pancreaticoductograms illustrating small duct disease in patients with chronic pancreatitis. (A, left) Patient No. 6 with small, diffusely irregular duct and no areas of dilation. (B, right) Patient No. 8 two years after sphincteroplasty with small duct and extravasation of dye into the head of the pancreas. No cyst was found at surgery.

suggestive of familial pancreatitis. All of the patients had been hospitalized repeatedly for their disease and required narcotics to treat the pain. All patients had had previous operations, seven directly related to the pancreas or biliary tract which did not relieve the pain. The pancreatic duct was either small, of normal caliber or only minimally dilated in all of the patients (Fig. 1). For these reasons, we felt that a major resection was the only procedure that would relieve their pain.

Operation

The operative technique was basically the same in all patients. The tail, body, head and the uncinate process of the pancreas were removed, along with the spleen (unless a splenectomy had previously been done). Two patients previously had had partial pancreatectomies, approximately 70% in one (#5), and approximately 30% in the other (#10). In most patients, the common bile duct was cannulated in an attempt to avoid injury during excision of the head of the pancreas. Except in one patient (#10), we made a special effort to remove virtually all of the pancreatic tissue along the duodenum. This operation, originally performed by Barret and Bowers,[2] has been well described[9] and if done meticulously removes >95% of the pancreas. In patient #10, the proximal head and uncinate process were relatively uninvolved with the disease, and a 2 × 2 cm portion of the uncinate process was left *in situ* along with a rim of tissue adjacent to the duodenum. In this patient it was estimated that an 85–90% pancreatectomy was done.

The blood supply to the pancreas was left intact as long as possible in order to minimize warm ischemia of the organ. The tail and body were mobilized, but the splenic artery and vein were not ligated until after the uncinate process and head of the pancreas had been dissected free and the vessels to these portions of the pancreas had been divided.

Preparation and Yield of Islet Tissue from the Excised Pancreas

Immediately after excision the pancreas was immersed in iced saline and the splenic artery was flushed with cold, heparinized Ringer's lactate solution. Biopsies from the tail and head of the pancreas were obtained for pathologic examination.

The pancreas was then transported in a sterile container to the laboratory and weighed. All procedures were carried out under sterile conditions within a laminar flow hood. The pancreatic duct was injected under pressure with cold Hanks' solution or Medium 199. In general, distention of the fibrotic glands was difficult. The pancreas was trimmed of necrotic tissue and fat and reweighed to calculate the weight of the tissue to be dispersed. The pancreas was then chopped, 4–5 g at a time, for one to two minutes in a mechanical tissue chopper.[21] Our objective was to produce tissue fragments which would pass through a 15 gauge needle, but this was not always possible. The chopped tissue was washed at least four times with cold Hanks' solution using a volume four to five times the volume of tissue. The tissue and supernate were separated by gravity.

The tissue was then digested at 37 C with collagenase (type IV, either obtained from Worthington Biochemicals, Freeport, New Jersey or Sigma Chemical Company, St. Louis, MO). We always used a collagenase

TABLE 2. *Results of Tissue Insulin and Amylase Measurements Before and After Dispersal of Pancreases Excised and Processed for Islet Autotransplantation to Patients with Chronic Pancreatitis*

Patient	Weight of Pancreas (gm)*	Total Tissue Insulin Content of Pancreas (μg)†	Total Tissue Amylase Content of Pancreas (mg)†	Collagenase Used for Digestion per gm of Tissue (units)‡	Collagenase Concentration During Digestion (g/dl)	Duration Collagenase Digestion (mins)	Insulin Content of Tissue After Collagenase Digestion (μg)§	Amylase Content of Tissue After Collagenase Digestion (mg)§	Islet Yield (%)‖	Residual Exocrine Tissue (%)‖
1	42	17,860	77	1440	0.30	20	9.877	20	55	26
2	60	13,895	29	2176	0.28	20	3,326	4	24	13
3	82	13,118	561	2000	0.46	20	7,247	281	55	50
4¶	48	>5,457	>53	940	0.12	25	977	<1	<18	<2
5#	41	3,781	239	1316	0.17	15	1,412	53	37	22
6	32	3,970	25	940	0.12	15	220	4	5.5	16
7	65	7,941	100	940	0.10	15	512	27	6.4	17
8**	72	6,434	251	940	0.13	12.5	5,331	52	83	21
9**	55	4,889	71	438	0.09	20	2,510††	19	<51††	27
10	45	3,051	112	940	0.09	20	1,404	4	46	3

* Weight of pancreas used for processing. Necrotic fat, inflammatory and other tissue attached to pancreas trimmed and discarded.

† Total tissue insulin and amylase content of pancreas was calculated from post chop tissue + post chop wash, or from post chop wash + post digest tissue + post digest wash values obtained on aliquots taken during and after processing.

‡ Microprotease, 0.5 mg/gm tissue, added for pancreas Nos. 4–8 & 10. DNase 2 mg added for Nos. 3 & 9.

§ Represents total insulin or amylase content of pancreatic islet tissue transplanted (insulin content is proportional to B-cell mass).

‖ Total insulin or amylase content of transplanted tissue expressed as per cent of total insulin or amylase content of pancreas before processing. Islet yield calculated from insulin content and exocrine residual from amylase content of processed tissue.

¶ Total tissue insulin and amylase content of pancreas No. 4 could not be calculated because the post chop wash sample was lost in a laboratory accident.

R.S. had had a 70% pancreatectomy and M.K. a 30% pancreatectomy at previous operations.

** Pancreas Nos. 8, 9 & 10 were minced less vigorously than Nos. 4–7. Tissue chopper was run at a slower speed and for a shorter time.

†† No. 9 was briefly rechopped after digestion, washing and suspension in solution for transplantation, so insulin content includes insulin released into solution during rechopping. Actual islet yield, therefore, is less than that calculated from insulin content.

lot that had previously been found to give satisfactory islet preparations for transplantation in dogs. The quantity and concentration of collagenase used and the duration of digestion for each pancreas is given in Table 2. The first three pancreases were digested in a beaker in a shaking water bath. The last seven were digested in a specially designed fluted glass flask with a magnetic stirrer at the bottom and an outer jacket through which water at 37 C was circulated. The latter method facilitated digestion and for that reason a lower concentration of collagenase was used.

After digestion, the tissue was diluted with cold Hanks' solution and washed four times. The first three washes were with Hanks' solution or Medium 199; the last wash was in GIB medium. The washes were performed by distributing the tissue among eight 50 ml sterile plastic centrifuge tubes. The tissue and supernate were separated by centrifugation at low speed for one minute. Sterility was maintained throughout the procedure by transferring the tissue to fresh tubes after each spin. After the final wash, the tissue was aspirated through a 15 or 18 gauge needle, diluted in 300 ml of GIB media, placed in sterile 50 ml syringes, and transported to the operating room for autotransplantation. It took approximately two hours to process the tissue and prepare it for transplantation.

Aliquots of the postchop tissue, postchop wash, postdigest tissue and postdigest wash were taken during processing. The samples were homogenized and assayed for insulin[12] and amylase.[17] The total tissue insulin and amylase content of each pancreas, the yield of islet tissue (proportional tissue to insulin content), and the degree of contamination of exocrine tissue (proportional to tissue amylase content) were calculated according to previously described methods.[30] The results of these measurements are summarized in Table 2. The islet yield expressed as a percentage of the original insulin content of the pancreas, ranged from 5.5 to 83%. A high yield, however, did not necessarily mean a large quantity of islets were transplanted, since some pancreases had a low insulin content before processing. The insulin content of the transplanted tissue ranged from 220 to 9,877 mg. A large insulin content is not necessarily indicative of a superior preparation, since the degree of tissue dispersal is also important for engraftment and a high insulin content might reflect an inadequate dispersal.[19] For human pancreases, we do not know the digestion conditions that will give the optimum dispersal with the least degree of islet destruction. Nevertheless, the most successful outcome from a metabolic standpoint was in the patient (#1) with the highest pancreatic tissue insulin content

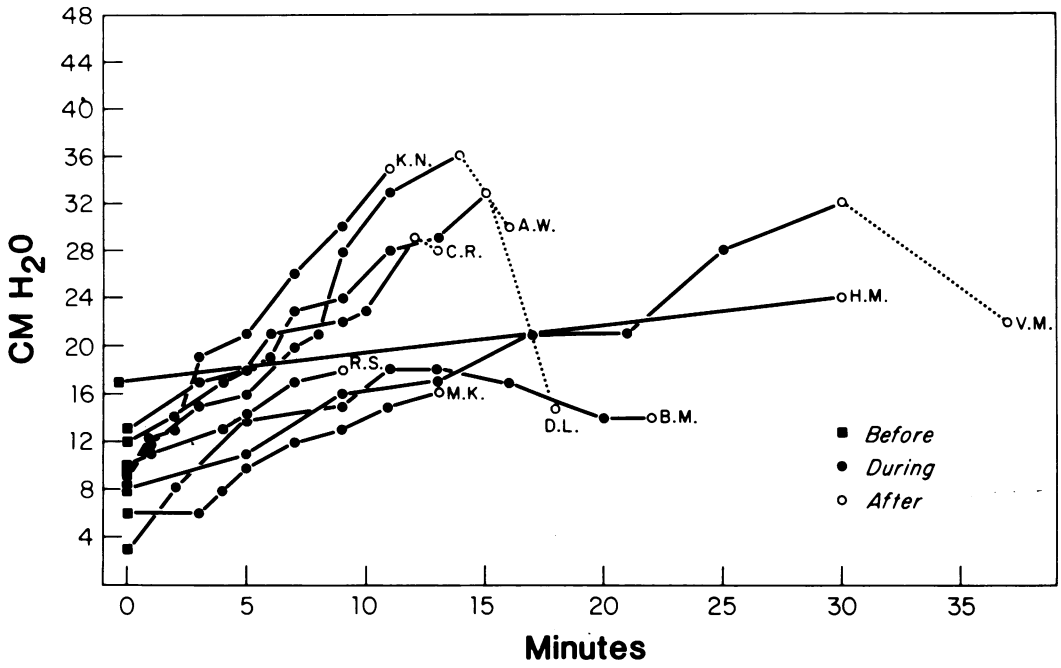

FIG. 2. Portal pressures before, during and after intraportal islet autotransplantation in patients undergoing pancreatectomy for chronic pancreatitis.

before and after processing, and the most unsatisfactory was in the patient (#6) with the lowest insulin content after processing.

Technique of Islet Transplantation and Intraoperative Studies

Each patient was given heparin 0.75 mg/kg body weight before intraportal islet autotransplantation. Protomine was not given at the end of the infusion. The tissue was infused into the portal vein via a catheter inserted into a mesenteric vein. The infusion times ranged from 11 to 30 minutes.

Portal Pressure

Portal pressure was measured before, during and after infusion and the results of these measurements are summarized in Figure 2. The portal pressure increased in each patient during infusion. The increase ranged from 7 to 28 cm of water (mean, 17 ± 8 SD), and the highest recorded pressure was 36 cm of water. In four patients the portal pressure was measured a few minutes after the completion of tissue infusion and in each case the portal pressure declined. The bowel retained its normal color and there were no apparent sequelae from the transient elevation of portal pressure.

Serum Insulin

Serum insulin levels were measured during the operation in each patient except one (#2). Samples were taken before, during and immediately preceding the completion of pancreatectomy; during the interval between pancreatectomy and islet infusion; and for at least two hours after islet transplantation. Insulin has a half life approximately 4.5 minutes, and it always disappears from the serum if the pancreatectomy is complete. The results of these measurements are summarized in Table 3. Insulin was virtually undetectable by 15 minutes after pancreatectomy in all of the patients except for patient 10 (the one patient where we intentionally left a remnant of the uncinate process). In all of the patients there was an abrupt appearance of a high concentration of insulin in the serum after islet transplantation. Insulin levels then declined, but remained at detectable levels in seven of the nine patients throughout the period of measurement. The serum insulin levels during the immediate posttransplant period roughly correlated with the ultimate metabolic status of the patient. The two in whom the increase in serum insulin was not sustained have minimal evidence of islet function, while in the others islet function is definitely present.

Histopathologic Studies of the Excised Pancreases

Each pancreas was graded histologically and given scores of 0 to 4+ (0 representing normal and 4+ representing the most severe change) relative to changes in: 1) ducts (obstruction, acute inflammation, chronic inflammation, fibrosis, dilation); 2) acini (overall loss in volume, overall fibrosis, acute necrosis, acute inflammation, chronic inflammation); 3) islets of Langerhans (inflammation, fibrosis and distortion, overall change

TABLE 3. *Plasma Insulin Concentrations (μU/ml) Before and After Pancreatectomy and After Islet Autotransplantation to the Portal Vein During Operation on Patients with Chronic Pancreatitis: Correlaton with Outcome*

Patient	Before Completion of Pancreatectomy		After Pancreatectomy*		After Islet Autotransplantation								Metabolic Status After Transplantation†
	< −30′	−30 to 0′	≤15′	>30′	≤5′	15′	30′	45′	60′	90′	120′	>120′	
1	8	8	6	<4	—	—	34	—	—	—	126	14	Excellent
3	15	13–8	6	<2	380	124	9	7	10	—	13	—	Good–Fair
4	23–55	30–10	4	<2	280	121	26	—	24	—	14	—	Fair
5	14–5	6	—	<2	64	6	<2	<2	<2	<2	—	<2	Poor
6	8–16	8–24	<2	<2	25	2	<2	<2	<2	<2	<2	<2	Poor
7	3	3	<2	<2	233	58	24	19	8	—	6	—	Fair
8	34–21	2	<2	<2	385	51	26	15	14	16	20	18	Good
9	9–107	160–19	4	2–3	270	58	30	24	21	20	17	—	Fair
10	4–26	14	5	3–16	269	55	32	31	27	18	21	18	Good

* Interval between pancreatectomy and islet autotransplantation ranged from 120 to 160 minutes.

† Metabolic status indicative of long-term functional reserve of islets after autotransplantation: *Excellent*—Normoglycemic without need for exogenous insulin; *Good*—insulin independent, but abnormal glucose tolerance; *Fair*—exogenous insulin in small to moderate doses required to maintain normal blood sugar levels, but not ketosis prone; *Poor*—large doses of exogenous insulin required to maintain normal blood sugar levels.

of volume); and 4) presence or absence of abscess or pseudocyst. The scores for each patient are listed in Table 1. The changes were uniform throughout the pancreas in 7 patients and nonuniform in three patients (Nos. 7, 8 and 10). The mean score for the 10 pancreases was 12.6 ± 5.0, the same as in the patients that did not undergo islet autotransplantation. Representative histologic findings in the pancreases of those patients are illustrated in Figure 3. An attempt was made to correlate the histopathological scores with the metabolic outcome after transplantation in each patient, but this was difficult, perhaps because so many other variables are involved. A histopathologic study of the islets of Langerhans, using immunoperoxidase stains for insulin and other hormones, is underway, but this study has not been completed. It is interesting, however, that the one patient (#1) with the most successful outcome from the metabolic standpoint, and with the highest insulin content, had islet hyperplasia. The combination of hyperplastic islets (Fig. 4) and chronic pancreatitis may have fortuitously contributed to the good result with islet transplantation in this patient.

Outcome After Pancreatectomy and Islet Autotransplantation

Pain Relief

The principle objective in the treatment of these patients was to relieve the pain of chronic pancreatitis. This was achieved in each patient. Seven of the nine survivors were successfully withdrawn from narcotics after they recovered from the operation. The other two (#5 and 6) were addicted to narcotics; withdrawal has been difficult, and we are not certain of their drug status at this time.

Side Effects of Islet Transplantation

There were no serious complications from infusion of dispersed pancreatic islet tissue into the portal vein. Portal vein pressure increased (Fig. 2), but the acute systemic hemodynamic changes described by others[22,31] were not seen. Slight increases in bilirubin, SGOT and alkaline phosphatase occurred in some patients, but the values returned to normal and the alterations in liver function tests were minimal (Table 4).

Complications of Surgery

Five patients had postoperative complications. Patient #2 died ten days after surgery from a perforation of the transverse colon. At autopsy viable islets were identified in the liver. The histologic findings, including the results of immunoperoxidase stains, showing insulin containing beta and glucagon containing alpha cells in the liver of this patient, have previously been published.[28]

Patient #4 developed necrosis of a portion of the duodenum after pancreatectomy, and required duodenectomy, choledochojejunostomy and gastrojejunostomy at the second operation. This patient had multiple cysts of the pancreas that encompassed the blood supply to the duodenum.

Patient #5 developed a duodenal stricture, probably from ischemia, and had a gastrojejunostomy performed at another hospital two months after pancreatectomy and islet autotransplantation.

Patient #7 had a major bleed following removal of the T-tube from his common bile duct. At reoperation an arterial bleeder in the region of the common duct was ligated. A decrease in islet function occurred after this operation.

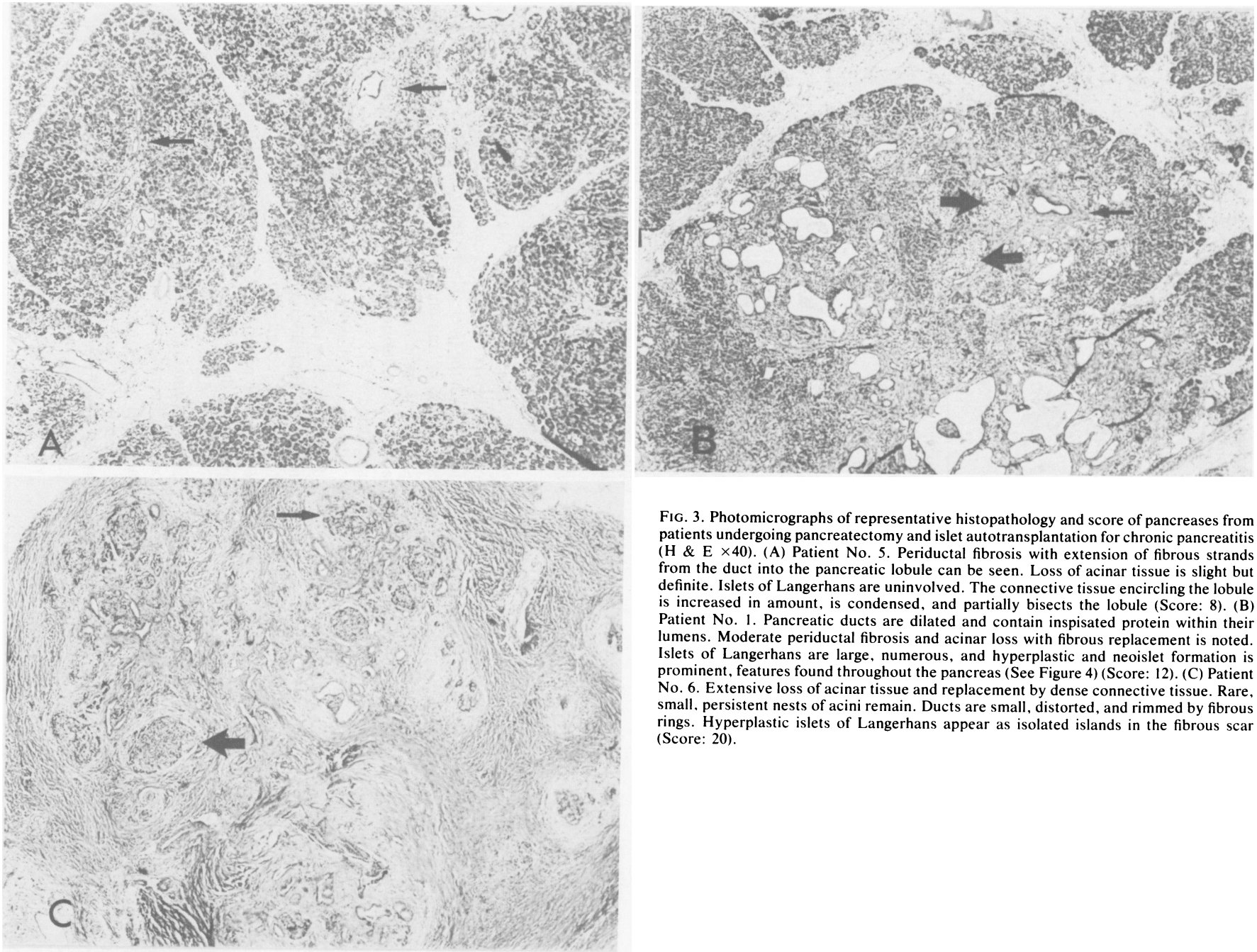

FIG. 3. Photomicrographs of representative histopathology and score of pancreases from patients undergoing pancreatectomy and islet autotransplantation for chronic pancreatitis (H & E ×40). (A) Patient No. 5. Periductal fibrosis with extension of fibrous strands from the duct into the pancreatic lobule can be seen. Loss of acinar tissue is slight but definite. Islets of Langerhans are uninvolved. The connective tissue encircling the lobule is increased in amount, is condensed, and partially bisects the lobule (Score: 8). (B) Patient No. 1. Pancreatic ducts are dilated and contain inspisated protein within their lumens. Moderate periductal fibrosis and acinar loss with fibrous replacement is noted. Islets of Langerhans are large, numerous, and hyperplastic and neoislet formation is prominent, features found throughout the pancreas (See Figure 4) (Score: 12). (C) Patient No. 6. Extensive loss of acinar tissue and replacement by dense connective tissue. Rare, small, persistent nests of acini remain. Ducts are small, distorted, and rimmed by fibrous rings. Hyperplastic islets of Langerhans appear as isolated islands in the fibrous scar (Score: 20).

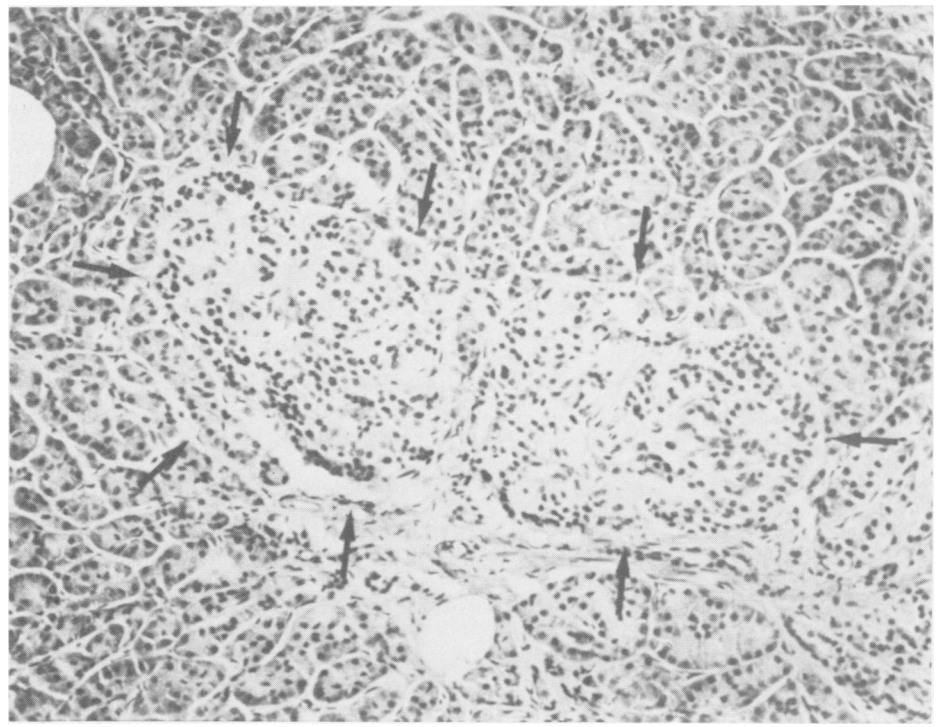

FIG. 4. Photomicrograph of pancreas from patient No. 1 with islet hyperplasia. Two adjacent islets of Langerhans are seen each of exceptionally large size. Note that the general architecture of the islets is normal and that they are free of inflammation (H & E ×160).

Patient 8 had a hematoma in the pancreatic bed after pancreatectomy and had functional obstruction of the duodenum six weeks after pancreatectomy. This was treated with a vagotomy and gastrojejunostomy.

Islet Function and Metabolic Status After Pancreatectomy and Islet Autotransplantation

The current metabolic status of the patients treated with pancreatectomy and islet autotransplantation are summarized in Table 5. Three patients (#1, 8, and 10) currently do not require insulin at >3 years, eight months and one month after islet autotransplantation.

One patient (#3) did not receive insulin for 15 months; she is now more than two years after transplantation and has been receiving 10–12 units of insulin daily for the past 11 months. Insulin withdrawal for 72 hours at two years did not result in ketosis.

Three patients (#4, 7, and 9) are receiving 23, 30 and 15 units at ten, nine, and four months. All have been tested by insulin withdrawal for 72 hours, and they did not become ketotic. One of these (#7) did not require insulin at three weeks after transplantation, but after reoperation for bleeding he became hyperglycemic and has required insulin since that time.

TABLE 4. *Results of Liver Function Tests (Mean ± SE) Before and After Pancreatectomy and Intraportal Islet Autotransplantation in Patients with Chronic Pancreatitis*

	Pre-operative Value	Highest Value After Operation	Days After Operation	Value at 1 Month
Bilirubin (mg/dl)	0.3 ± 0.1	1.3 ± 0.3	4.3 ± 0.8	0.4 ± 0.1
SGOT (I.U./L)	36 ± 14	112 ± 51	3.4 ± 0.7	28 ± 6
Alkaline Phosphatase (I.U./L)	238 ± 53	366 ± 64	5.9 ± 0.7	631 ± 37*

* Patient No. 4 had alkaline phosphatase of 1980 I.U./L at 1 month, related to biliary surgery.

TABLE 5. *Summary of Current Status of Ten Patients with Chronic Pancreatitis Treated with Total or Near Total Pancreatectomy and Intraportal Islet Autotransplantation*

Three patients, insulin independent
1 completely normal glucose tolerance—>3 years
2 with mild metabolic abnormalities—1 & 8 months

One patient, insulin independent for 15 months, now on 12 units/day; ketosis resistant on insulin withdrawal—>2 years

Three patients, require 15–30 units insulin/day, ketosis resistant on insulin withdrawal—4–9 months

Two patients, require 35 and 60 units, not yet tested by insulin withdrawal—both 9 months

One patient, died 10 days postoperatively, viable islets in the liver

Summary: All 9 survivors relieved of pain
Islet transplant results Excellent in 1, Good in 2, Fair in 4, and Poor in 2

TABLE 6. *Urinary C-Peptide Excretion (nMol/24 hrs)* Before and After Pancreatectomy and Islet Autotransplantation in Patients with Chronic Pancreatitis*

Patient	Preoperative	Posttransplant		
1	—	3 years 9.2 ± 2.0 (n = 3)		
3	26.6 ± 8.6 (n = 5)	3 mos 5.3 ± 1.1 (n = 5)	1 year 4.7 ± 0.8 (n = 4)	2 years 5.0 ± 2.6 (n = 5)
4	6.1 ± 1.5 (n = 4)	1 mo 6.9 ± 2.3 (n = 10)	4 mos 4.3 ± 2.1 (n = 4)	
6	24.5 ± 8.1 (n = 9)	1 mo 7.9 (n = 1)	2 mos 3.2 (n = 1)	
7	6.8 ± 4.1 (n = 3)	2 wks 4.3 ± 1.8 (n = 5)	2 mos 0.5 ± 0.2 (n = 4)	6 mos 0.6 ± 0.3 (n = 7)
8	39.4 ± 17.4 (n = 4)		4 mos 13.8 ± 2.2 (n = 5)	
9	9.3 ± 8.5 (n = 4)	1 wk 9.1 ± 0.8 (n = 2)	6 wks 7.5 ± 3.0 (n = 8)	4 mos 6.6 (n = 1)
10	6.1 ± 3.2 (n = 3)		1 wk 9.4 ± 3.9 (n = 2)	

* Mean ± SD. Normal: 19.1 ± 10.4 (n = 10). Range: 8.4–35.3.

The other two patients (#5 and 6) are receiving 60 and 35 units of insulin at nine months. They have not been tested by insulin withdrawal.

The patients who require insulin and who are ketosis resistant have some islet function, as determined by urinary C-peptide[16] measurements (Table 6). In these patients (#3, 4, 7 and 9) urinary C-peptide secretion rates are well above those seen in patients with juvenile onset diabetes. Urinary C-peptide measurements are higher, however, in the patients who do not require insulin (#1, 8 and 10).

The results of other metabolic studies in individual patients are summarized in their case histories.

Case Reports

Patient 1. A detailed case history[29] and the results of metabolic studies up to two years after pancreatectomy and islet autotransplantation in this 39-year-old woman have previously been published.[28] Glucose tolerance tests at three weeks, eight months and three years, have been normal (Fig. 5). She had hyperinsulinemia before pancreatectomy (up to 224 μU/ml during glucose tolerance testing) and islet hyperplasia was found after excision of the pancreas (Fig. 4). This fortuitous circumstance may account for the good outcome in her case.

Patient 2. This 35-year-old alcoholic male died ten days after pancreatectomy and islet autotransplantation from a perforated colon. Islets were found in the liver, as previously described.[28]

Patient 3. Some of the details on this 57-year-old nonalcoholic patient during her first 15 months after pancreatectomy and islet autotransplantation have previously been published.[28] Plasma glucose levels during the first four months ranged from 92 to 169 mg/dl (mean: 113 ± 21 mg/dl). Between five and 14 months glucose levels ranged from 120 to 274 (mean: 184 ± 33 mg/dl). Glucose tolerance tests over this period showed some deterioration in carbohydrate metabolism.[28] At 15 months she was started on exogenous insulin so that plasma glucose levels could be maintained within a normal range,[28] and she currently takes 12 units per day. However,

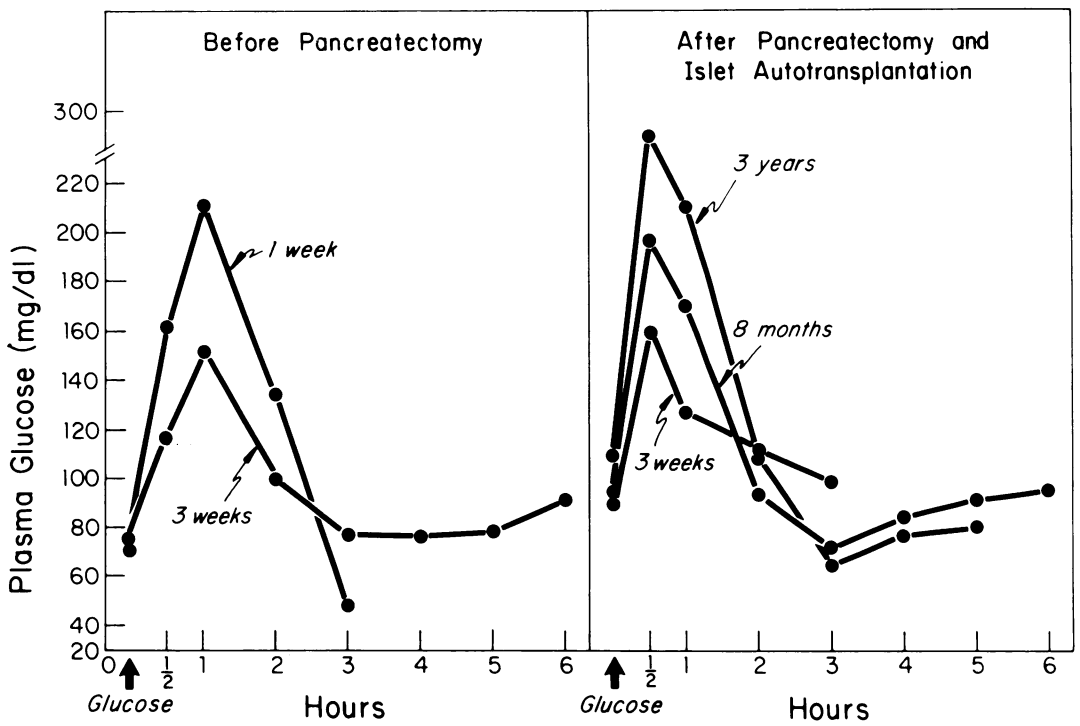

FIG. 5. Results of glucose tolerance tests before and three years after pancreatectomy and islet autotransplantation in Patient No. 1.

there has been no further deterioration of islet function and the glucose tolerance test at two years (performed during a period of insulin withdrawal) was essentially the same as one performed at one year (Fig. 6). Urinary C-peptide excretion has also remained constant. Interestingly, in the tests performed at two years C-peptide excretion increased when insulin was temporarily withdrawn (2.89, 4.22 and 2.52 mm/24 hrs on insulin and 7.17 and 8.24 mm/24 hrs off of insulin).

Patient 4. This 46-year-old woman had chronic pancreatitis associated with cholelithiasis and choledocholithiasis. Multiple small and large cysts of the pancreas were found at the time of the cholecystectomy and common bile duct exploration in March, 1979. That operation did not relieve her pain. A T-tube was left in her common duct and a cholangiogram showed a stricture of the bile duct where it passed through the pancreas (Fig. 7A). Computerized axial tomography of the abdomen demonstrated multiple cystic lesions in the pancreas (Fig. 7B). She had mild glucose intolerance before her operation (plasma glucose of 157 mg/dl at three hours after ingestion of 50 g of glucose). At the time of pancreatectomy and islet autotransplantation, an attempt was made to perform a plastic repair of the bile duct stricture over a long armed T-tube. She developed partial necrosis of the duodenum and one month later a duodenectomy, choledochojejunostomy, and gastrojejunostomy were performed. She was discharged home on 27 units of insulin daily, but since that time it has been reduced to 23 units. Serum C-peptide levels[24] have ranged from 1.7 to 3.2 ng/ml (in patients with juvenile diabetes, serum C-peptide levels are less than 1.0 ng/ml). Urinary C-peptide excretion rates at one and four months were the same or slightly less than preoperative values and well above the excretion rates of patients with juvenile diabetes (Table 6). Serum and urinary beta-hydroxybuturate levels did not rise during insulin withdrawal at four months.

Patient 5. This 29-year-old man had recurring attacks of pancreatitis over a three-year period and underwent a 70% pancreatectomy in January of 1978. He continued to have pain after this operation. He had mild glucose intolerance (plasma glucose 170 mg/dl two hours after ingestion of 50 gm of glucose). He did not have a sustained increase in plasma insulin after pancreatectomy and islet autotransplant and has required insulin since the operation. He was discharged one month after the operation. We have not seen him since he returned home to California, and we have not been able to perform metabolic studies. He had a gastrojejunostomy performed because of a duodenal stricture after he returned home. When last seen by us he required 35 units of insulin per day.

Patient 6. This 24-year-old man had chronic pancreatitis since age 16 secondary to alcohol. He had been hospitalized over 40 times because of abdominal pain. He had mild glucose intolerance (plasma glucose 162 at one hour and 149 at two hours after ingestion of 50 g glucose). After pancreatectomy he had some initial evidence of islet function according to urinary C-peptide data (Table 6) and received only 18 units of insulin daily. However, within three months he had an increase in insulin requirements and currently takes 60 units daily. The insulin content of the tissue transplanted to this patient was the lowest in the entire series. He has not returned for metabolic studies.

Patient 7. This 32-year-old man had chronic pancreatitis, originally on an alcoholic basis, but had stopped drinking with no relief of pain. He had mild glucose intolerance (plasma glucose 206 mg/dl two hours after ingestion of 50 g of glucose). The insulin content of the transplanted tissue was also small (Table 2). Nevertheless, he had a good initial response as indicated by his need for little or no insulin (0–6 units/day) and by his urinary C-peptide excretion during the first three weeks after operation (Table 6). At three weeks he bled after removal of the T-tube. After re-exploration and ligation of an arterial bleeder, he required insulin. Subsequent urinary

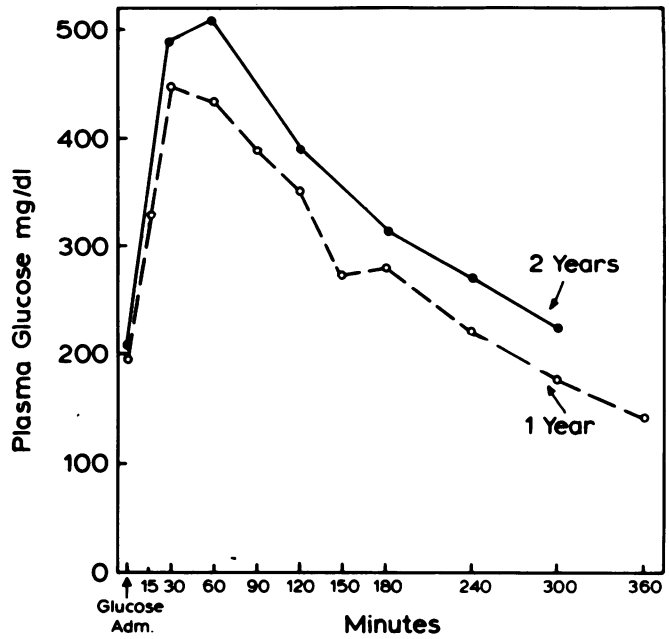

FIG. 6. Results of oral glucose tolerance tests after pancreatectomy and islet autotransplantation in Patient No. 3. At one year she was not receiving insulin. She was temporarily withdrawn from insulin for the glucose tolerance test at two years. There was no apparent deterioration in islet function during that interval.

C-peptide measurements showed a marked decrease in C-peptide excretion. However, his C-peptide excretion rate is still higher than that of patients with juvenile diabetes. During a 48-hour period of insulin withdrawal in January 1980, he did not become ketotic and urinary excretion beta-hydroxybuturate was only 0.3 mMol/L over the last 24 hours. Currently he takes 30 units of insulin daily.

Patient 8. This 27-year-old woman developed pancreatitis after a cholecystectomy in 1975. Although she did not have a dilated duct, in 1977 a sphincteroplasty was performed at another hospital with no relief of her pain. She had normal glucose tolerance (plasma glucose 103 mg/dl two hours after ingestion of 50 g glucose). After pancreatectomy and islet autotransplantation, she required insulin only during the early posttransplant period and while she was on hyperalimentation. She had abnormal glucose tolerance test results five months after the operation (Fig. 8). However, urinary C-peptide secretion was relatively high (Table 6). She does not require exogenous insulin.

Patient 9. This 41-year-old man had chronic pancreatitis secondary to alcohol and has been hospitalized repeatedly during the past five years. A pancreatic abscess ruptured into the colon (1976) and an ileostomy was done at the time of drainage. This was repaired in 1977, but he continued to have pancreatitis and at the time of admission to the University of Minnesota he could not tolerate oral feedings. An I.V. glucose tolerance test was abnormal and showed a peak glucose value of 385 mg/dl at 15 minutes; and the potassium value was −1.3%. At the time of pancreatectomy and islet autotransplant, an abscess in the head of the pancreas was discovered. This portion of the pancreas was not used for islet tissue preparation. He has received insulin since pancreatectomy, but the dose has gradually been reduced to 15 units daily. Insulin withdrawal for 72 hours at one month resulted in no increase in serum or urinary beta-hydroxybuturate. Urinary C-peptide excretion is only slightly less than before pancreatectomy and islet autotransplant (Table 6).

Patient 10. This 36-year-old man had pancreatitis for four years,

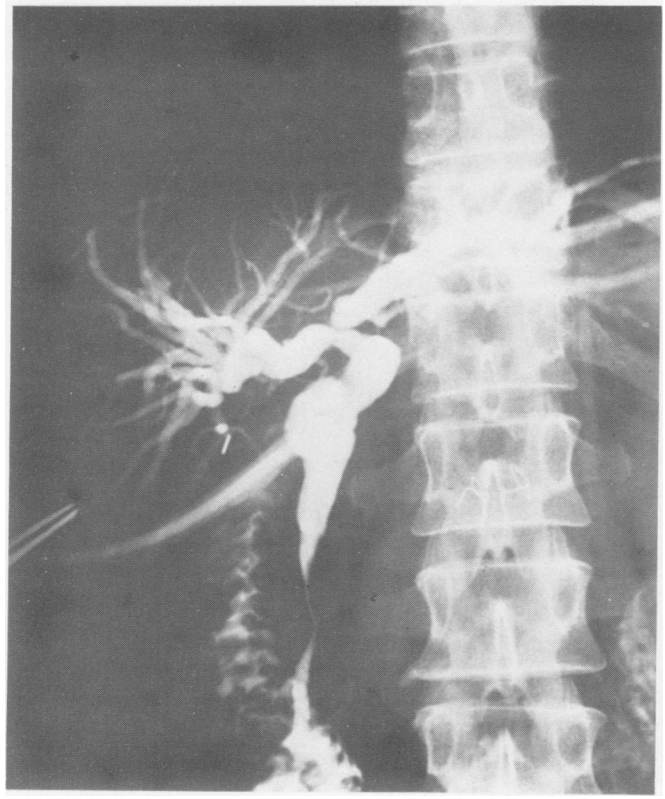

FIG. 7A. Patient No. 4. T-tube cholangiogram after her cholecystectomy and common bile exploration. Note stricture of intrapancreatic portion of the bile duct. Small pancreatic duct is barely visualized.

probably related to alcohol. In December of 1978 a retrograde pancreaticoductogram showed an obstruction of the midpancreatic duct, and he underwent a distal (30%) pancreatectomy and Roux-en-Y pancreaticojejunostomy. His pain was not relieved, and he required several hospitalizations for treatment of pancreatitis. He had a nearly normal glucose tolerance test, with a peak glucose value of 166 mg/dl and a two-hour value of 129 mg/dl. On March 24, 1980 a pancreatectomy was performed with preservation of a small portion of the uncinate process. Urinary C-peptide excretion at one week after the operation was unchanged from the preoperative rate (Table 6). He is insulin independent one month after operation.

Discussion

Surgery for chronic pancreatitis must be individualized to fit the pathology of the patient and the pancreas.[8,14,33] The primary objective of surgery for chronic pancreatitis is to relieve pain. Procedures that do this and still preserve pancreatic function are the first choice. The indications for total or near total pancreatectomy are involvement of the entire pancreas, a small duct or a failure of other procedures, and the willingness to accept diabetes for relief of pain.

A 95% pancreatectomy for treatment of chronic pancreatitis was first described by Barret and Bowers.[2] The operation has been used by many surgeons since that time,[3,14,34,35] although the largest experience has been at the University of Michigan.[5,9–11] The incidence of diabetes after this operation is virtually 100%, although this figure cannot be precisely derived from the literature since all reports do not separate the patients undergoing 80 to 95% pancreatectomy from those undergoing >95% pancreatectomy.

Since diabetes is inevitable, the only advantage of a 95% pancreatectomy over a total pancreaticoduodenectomy are elimination of the needs for intestinal and biliary anastomosis, and preservation of the duodenum. Preservation of the duodenum significantly reduces fecal fat loss after pancreatectomy,[13] and is worthwhile.

The concept that diabetes induced by pancreatectomy is not as severe a disease as idiopathic juvenile onset diabetes is probably not correct.[36] Patients with diabetes after pancreatectomy rapidly become hyperglycemic and develop ketosis if insulin is withdrawn.[1] In addition, they will develop the secondary complications of diabetes if they live long enough.[7] The most serious complications of diabetes in individuals pancreatectomized because of chronic pancreatitis, however, are in those with an alcoholic origin. They are usually noncomplying patients or they manage their diabetes poorly, and hypoglycemia from insulin reactions are as much a threat as ketoacidosis.[13]

Patients who require total or near total pancreatectomy could greatly benefit if diabetes could be prevented by selective preservation of endocrine tissue. One alternative is to transplant the tail of the pancreas as an immediately vascularized graft with anastomosis of the splenic vessels.[15,32] Although exocrine tissue remain intact with this operation, it is completely denervated, and in the few cases reported it has apparently caused no problem in its heterotopic position. The other alternative is to transplant dispersed pancreatic islet tissue as a free graft.[29]

Islet transplantation is highly successful in various animal models,[21] and one of our major interests has been the development of this technique for the treatment of human diabetes. Our efforts to reverse diabetes by allotransplantation as either purified human islets[24] or by intraportal transplantation of unpurified dispersed pancreatic islet tissue have been unsuccessful.[28] We were unsure if the failure to ameliorate diabetes was due to technical failures or secondary to allograft rejection. We hoped that islet autotransplantation after pancreatectomy would clarify this situation, since in these cases immunological rejection would not occur (unless as an autoimmune response against unmasked antigens).

Unfortunately, autotransplantation of dispersed pancreatic tissue prepared from patients with chronic pancreatitis may not allow us to answer the question. Mehigan et al.[23] have shown that autotransplantation of

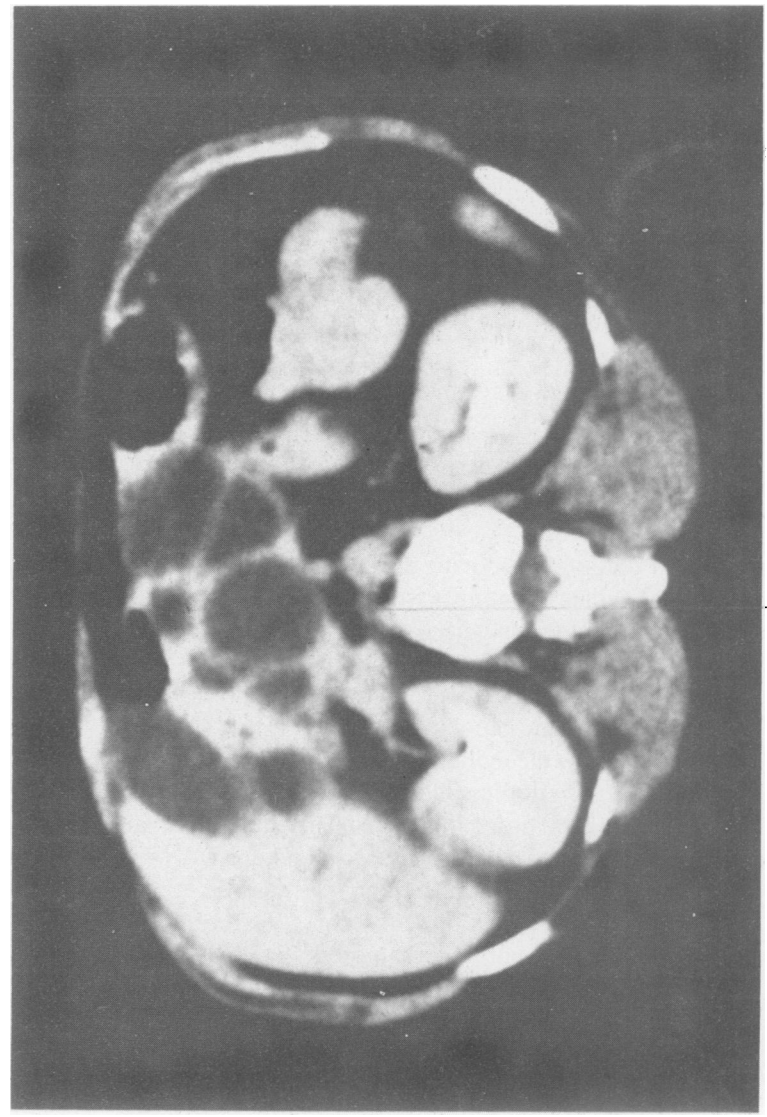

FIG. 7B. Computerized axial tomogram of Patient No. 4 showing multiple cysts throughout the pancreas.

dispersed pancreatic islet tissue, prepared by collagenase digestion from the pancreases of dogs with chronic pancreatitis induced by prior duct ligation, will obviate diabetes in only a small percentage of totally pancreatectomized recipients; while in normal dogs, diabetes is almost always obviated by autotransplantation prepared by collagenase dispersal after total pancreatectomy. Various alterations in collagenase digestion conditions did not improve the results in the experiments of Mehigan et al.[23]

Since there are no indications for pancreatectomy and islet autotransplantation in patients with a normal pancreas (except, perhaps, for trauma), with the current status of immunosuppressive therapy we will probably not be able to work out the optimal conditions for preparation of human islets by assessing *in vivo* function independent of rejection.

In the experiments of Mehigan et al.,[23] the fact that they did succeed in ameliorating diabetes in a few dogs after excision of a diseased pancreas and islet autotransplantation, shows the potential for autotransplantation in patients with chronic pancreatitis who require pancreatectomy. However, the success rate will probably be low, until more effective techniques for liberation of the islets from fibrotic pancreases are developed.

Nevertheless, the procedure of islet autotransplantation is worthwhile in patients undergoing total and near total pancreatectomy, if the facilities for pancreatic islet tissue preparation are available. We encountered no serious complications from the islet transplant procedure itself. In three of our ten patients the need for exogenous insulin has been obviated. One patient died of complications independent of the islet transplant and in this patient islets were found in the liver. In the other six patients, four have a mild, nonketosis prone diabetes; serum C-peptide levels and urinary C-peptide

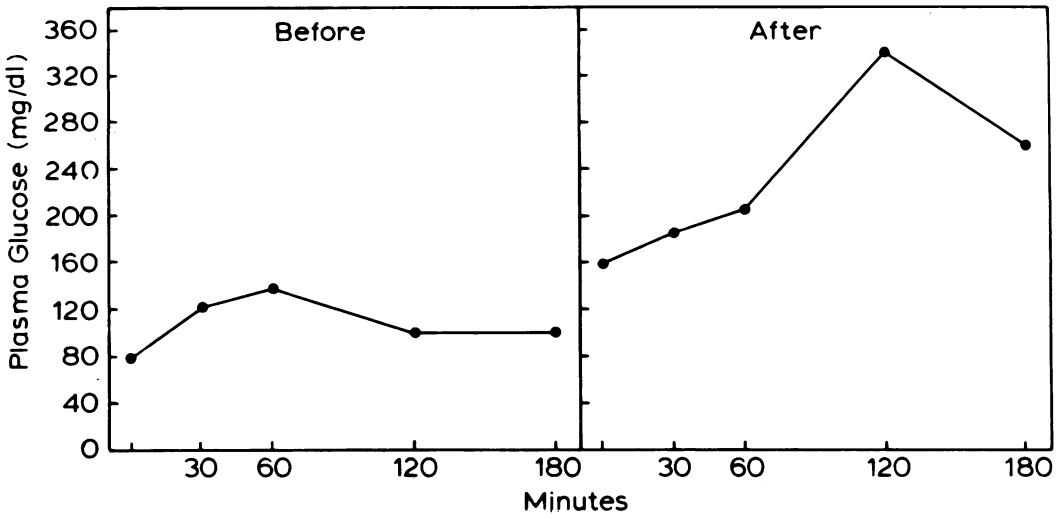

FIG. 8. Results of oral glucose tolerance test in Patient No. 8 before and five months after pancreatectomy and intraportal islet autotransplantation. The results after transplantation are not normal, however, she does not require insulin.

excretion definitely indicate the presence of functioning islets. Studies of patients with spontaneous diabetes have shown that those with C-peptide levels indicating some endogenous beta cell function are more stable, easier to manage, and less prone to complications than those with undetectable C-peptide.[26]

In our patients, the evidence that it is the transplanted islets that are functioning and not the islets in whatever residual pancreatic tissue that remains is circumstantial; although one of our patients had a duodenectomy (#4) and almost certainly has no remnant. Cameron et al.,[4] however, at Johns Hopkins University, have reported on one of their cases of pancreatectomy and islet autotransplantation. They have direct evidence of function of the transplanted islets. Selective measurement of insulin and glucagon levels in the portal and hepatic veins following intravenous glucose stimulation definitely showed hormone secretion from the liver at four months after operation. The pancreatic remnant probably made some contributions to glucose homeostasis, since insulin levels were still higher in the portal than in the hepatic veins. It may be that islet autotransplantation will obviate the need for exogenous insulin in the situation where either the transplanted islets or pancreatic remnant by themselves would not be adequate.

In the particular case of Cameron et al.,[4] the patient suddenly became diabetic at six months and required exogenous insulin. They have seen the same phenomenon of sudden loss of islet function in three other patients, but they also have three patients who are more than one year since pancreatectomy and islet autotransplantation who do not require insulin (Cameron et al., personal communication). We have also seen late deterioration of islet function after islet autotransplantation, although its occurrence has not been as dramatic as that observed by Cameron et al.[4] In one of our patients (#3), a moderate elevation of plasma glucose occurred at four months and glucose tolerance test results gradually deteriorated. In the other case (#7), insulin was required after reoperation for bleeding at three weeks. The reasons for deterioration in these cases is not clear, but it may be that an inadequate islet mass was grafted and islet function became exhausted, or fibrosis and scarring, already induced in the islets by the chronic pancreatitis, continued after islet autotransplantation.

Mehigan et al.[22] have also reported the occurrence of severe portal hypertension and disseminated intravascular coagulation (DIC) in one patient undergoing intraportal islet autotransplantation. Experiments in dogs show that this phenomenon was probably due to the presence of tissue thromboplastin in the pancreatic islet tissue homogenate and that this complication could be prevented by addition of heparin and aprotinin (Trasylol®) to the tissue preparation. We have routinely heparinized our patients prior to islet autotransplantation. Although elevations of portal pressure have occurred during pancreatic islet tissue infusion in our patients, we have not seen DIC in our islet autotransplant recipients. We also have not observed this phenomenon in 18 attempts of human islet allotransplantation,[28,29] although marked, but transient, portal hypertension occurred in one case.[28]

Islet autotransplants after total pancreatectomy have also been performed in four patients at the University of California in Los Angeles (Traverso and Longmire, personal communication). They were unsuccessful in obviating diabetes. In addition to portal hypertension, they observed transient systemic hypotension in three patients during tissue infusion.[31] Again, we have not observed this phenomenon in any of our autograft or allograft recipients. The reasons for these differences are not clear.

In summary, we have had experience with intraportal

islet autotransplantation after total or near total pancreatectomy in ten patients with chronic pancreatitis. Our initial case was the most successful.[29] The complete obviation of diabetes in this patient led us to hope that the procedure would allow us to broaden the indications for extensive pancreatectomy to relieve pain, and to avoid reoperation because of the relatively high failure rate with other procedures. However, with our larger experience it is apparent that we cannot predict that diabetes will be prevented. Preparation of islets from diseased pancreases is difficult. The indications for total or near total pancreatectomy remain the same. The surgeon and the patient must be willing to accept diabetes for relief of pain. Islet autotransplantation should still be done; it may obviate the need for exogenous insulin or lessen the severity of diabetes, but it is a bonus and not a guarantee.

Acknowledgments

Drs. James Cohen and Charles Morrow contributed to the retrospective analysis on the patients undergoing pancreatectomy without islet autotransplantation. Drs. Daniel Dunn and Caliann Lum made significant contributions to the care of the patients undergoing islet autotransplants. The Clinical Research Center staff performed the metabolic studies on these patients. Beryl Greenberg and Reynold Francis performed the insulin and C-peptide assays on blood and urine samples from the patients. Phyllis Gorecki, Julie Hustad, Jane Field, Anne Lowe, Darlene McMannus, Elizabeth Frenzel, June Eckhardt and Marie Wiklund helped with the preparation of human islet tissue and performed the analyses of tissue insulin and amylase content. Mary Brozic and Jerry Vincent prepared the illustrations. Michelle Gahlon, Janet Sanders and Kathryn Thompson prepared the tables and manuscript.

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