Metabolic Consequences of (Regional) Total Pancreatectomy

CAROLYN M. DRESLER, M.D.,* JOSEPH G. FORTNER, M.D.,* KATHERINE McDERMOTT, R.N.,* and DAIVA R. BAJORUNAS, M.D.†

Little information has been reported on the metabolic characteristics of the totally pancreatectomized patient or the efficacy of medical management after radical pancreatic surgery. The prospective evaluation of 49 such patients, with 31% followed for 48 or more months, forms the basis of this report. The major immediate postoperative challenge is control of diarrhea and weight stabilization. Chronically patients have an increased daily caloric requirement (mean ± SE, 56 ± 1 kcal/kg), not wholly explained by moderate steatorrhea (fecal fat excretion, 16% ± 2% of unrestricted fat intake). Despite persistent malabsorption, deficiencies in fat-soluble vitamin, magnesium, and trace element serum levels can be prevented in most patients. Pancreatogenic diabetes is characterized by (1) absence of the major glucoregulatory hormones insulin and glucagon, (2) instability, and (3) frequent hypoglycemia, with the latter parameters improving with rigorous home glucose monitoring. No patient has developed clinically overt diabetic micro- or macrovascular disease. Performance status in long-term survivors has been reasonable. However adverse chronic sequelae of the operation occur and include an unusual frequency of liver disease, characterized by accelerated fatty infiltration, and osteopenia, with an 18% reduction in radial bone mineral content noted in pancreatectomized patients studied more than 5 years after surgery.

From the Departments of Surgery and Medicine,† Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, New York*

THE FIRST TOTAL PANCREATECTOMY in humans was performed in 1942.[1] The value of this procedure in treating a variety of tumors of the pancreas has been evaluated in many reports in the intervening 47 years.[2-12] Little information, however, has been reported on the metabolic characteristics of the totally pancreatectomized patient or the efficacy of medical management. The diabetic state is often characterized as 'brittle.' It is assumed that the diabetes is otherwise similar to the spontaneously occurring disorder in adults, requiring similar management. Pancreatic exocrine deficiency has been studied as it relates to steatorrhea but with limited information on other nutritional deficiencies. Particularly striking is the absence of information on the long-term consequences of the operation.

This report concerns the prospective evaluation of 49 patients who had a total pancreatectomy as part of a resection that included a regional lymph node dissection, sympathectomy, and segmental portal vein resection with reconstruction (regional total pancreatectomy). Acute and chronic indices of malabsorption are reported. The diabetic state is characterized and its management discussed. Adverse chronic sequelae of the operation include an unusual frequency of liver disease and osteopenia; noteworthy are the absence of clinically overt diabetic micro- and macrovascular disease and the reasonable performance status in long-term survivors.

Materials and Methods

Patient Characteristics

The study population consists of all patients who underwent a complete pancreatic resection at Memorial Sloan-Kettering Cancer Center by one surgeon (JG Fortner) during the period January 1978 to June 1988 (n = 45). Four additional patients who had the procedure earlier (1972, 1975, 1975, 1976) are included as well. The 28 men and 21 women were 54 ± 2 years in age (mean ± SE; range, 29 to 72 years) at time of surgery.

Two patients had a standard total pancreatic resection.

Supported in part by the General Motors Surgical Research Laboratory and General Clinical Research Center grant RR-00102 from the National Institutes of Health to the Rockefeller University.

Address reprint requests to Daiva R. Bajorunas, M.D., Division of Endocrinology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021.

Dr. Dresler's current address is Department of Surgery, Washington University School of Medicine, St. Louis, MO 63110.

Accepted for publication August 3, 1990.

The other 47 patients had a regional total pancreatectomy, which included a complete pancreatectomy, subtotal gastrectomy, duodenectomy, splenectomy, cholecystectomy with removal of the common bile duct, and regional lymph node dissection with accompanying resection of the celiac and superior mesenteric ganglia and removal of lymphatic and nerve tissues surrounding the superior mesenteric artery. A vagotomy was not done. The pancreatic portion of the portal vein was removed *en bloc* and reconstructed with an end-to-end anastomosis of the superior mesenteric vein to the portal vein. Details of the surgical procedure have been previously described.[13,14] Table 1 depicts the diagnoses prompting the surgical procedures.

Management Protocol

A team approach to patient management was used, with all patients followed by the same surgical and endocrine attending physicians (JG Fortner and DR Bajorunas) for the duration of the 11-year follow-up period. The team nurse clinician provided patient education on a daily basis during the initial hospitalization and was present at every outpatient visit.

Dietary guidelines. After operation all patients were managed for up to 3 days in the intensive care unit and after their transfer to the general surgical floor, total parenteral nutrition (TPN) was maintained until adequate oral feedings were clinically feasible. Thereafter the patients were placed on a high calorie (40 to 50 kcal/kg), three-meal, three-snack diet/day, limited in sucrose calories only if the patients were maintaining weight. Additional caloric intake was encouraged by the use of lactose-free, lower osmolarity oral formula supplements and the liberal use of medium-chain triglyceride (MCT) oil. No specific dietary fat restriction was placed and the overall caloric distribution approximated 35% to 40% fat, 45% to 50% carbohydrate, and 15% to 20% protein calorie intake. In patients whose diarrhea was protracted, an empiric lactose-free diet was instituted.

Patients were discharged from the hospital only when a trend toward weight stabilization was demonstrated and calorie counts showed an intake of at least 2000 kcal/day. Following discharge all patients were maintained on the same dietary guidelines that focused on calorie-dense foods, except that a simple sugar restriction (less than 5% sucrose calories) was introduced to aid glycemic control when dietary intake had stabilized. A registered dietitian evaluated the patients every 3 months for the first postoperative year and yearly thereafter.

TABLE 1. *Indications for Surgery*

Histologic Diagnoses	No. of Patients
Adenocarcinoma of the pancreas	31
Periampullary carcinoma	7
Islet cell carcinoma	2
Papillocystic adenocarcinoma	1
Pancreatitis	7
Lymphoma	1

Diabetic management. The patients were instructed in the use of a reflectance meter-assisted home glucose monitoring program[15,16] before their discharge from the hospital. Comparable mean values to laboratory glucose determinations were achieved ($r = 0.85$, $p = 0.001$) when the patients were monitored as inpatients. Fingerstick glucose determinations were obtained before meals and at bedtime; in the immediate posthospital discharge period and periodically thereafter, patients were asked to check a 3 A.M. level. Compliance with this regimen on a long-term basis was readily achieved because both patients and their families thought that this technique provided them with increased security from hypoglycemia. At every subsequent hospital outpatient visit these glycemic records were reviewed with the patients and their families, and insulin dosage adjustments were instituted.

The patients were best managed on a regimen of 2:1 or 3:1 ratio of NPH/Lente:regular insulin administered subcutaneously in the morning, with an additional dose of regular insulin administered 30 minutes before dinner. Because of the frequency of nocturnal hypoglycemia, only the exceptional patient required a second (evening) injection of intermediate-acting insulin. All regular insulin was administered per a sliding scale regimen, depending on the result of the fingerstick glucose determination. A 'salvage' regular insulin sliding scale was prescribed to prevent excessive hyperglycemia before lunch and at bedtime. All patients were strongly encouraged to maintain a bedtime fingerstick glucose level of more than 11.2 mmol/L (200 mg/dL). Patients and family were well versed in the signs and symptoms of hypoglycemia, and glucagon (in 1 mg/mL vials) for parenteral administration by family members in the event of a serious hypoglycemic episode was routinely prescribed.

Management of pancreatic exocrine deficiency. The patients were instructed to take pancreatic enzyme replacement, consisting of variable amounts of lipase, amylase, and protease units depending on the commercial preparation used, as soon as oral intake was instituted. Doses were slowly increased to a usual maintenance dose of four to five capsules with meals and two to three capsules with snacks. The dosages of the enzymes were clinically adjusted on the basis of weight, serum magnesium levels, and stool characteristics. Antacids or H-2 blockers were not routinely prescribed. Enteric-coated microsphere formulations appeared to offer no specific advantage in this patient population. It was not unusual for tachyphylaxis

to develop to a specific enzyme preparation, requiring a product change. Patients were encouraged to take two multivitamins/day and were prescribed oral calcium (1 g) and pharmacologic vitamin D (4000 to 12,000 IU) supplementation daily.

Laboratory Analyses

Routine hematology, chemistry screening profiles, and magnesium levels were obtained at every visit (bimonthly for the first 6 months, then at 3- to 6-month intervals). Glycosylated hemoglobin levels[17] were used to ascertain the degree of diabetic control. Vitamins A,[18] E,[19] 25-hydroxy, and 1,25-dihydroxy D,[20,21] and the trace elements copper and zinc[22] were monitored every 6 months. Measurement of bone mineral content used direct photon absorptiometry technique at the distal third of the nondominant radius.[23]

For the quantitative 72-hour fecal fat analyses,[24] patients were admitted to the metabolic unit and maintained on a defined diet that mimicked their outpatient dietary regimen. The usual pancreatic enzyme replacement was maintained. Nonabsorbable stool markers ensured adequacy of the 72-hour stool collection. Such inpatient testing validating outpatient management was supported by the close reproducibility of results in the four patients in whom such testing was repeated after at least 18 months. Carbohydrate absorption testing used an oral 25-g dose of D-xylose, with serum levels and urinary excretion measured during the subsequent 5 hours.[25]

In selected patients the completeness of the pancreatic resection was verified by stimulated C-peptide levels.[26] Plasma immunoreactive glucagon (IRG) and IRG chromatographic profiles were assayed in the laboratory of Dr. Jonathan Jaspan, University of Chicago, using a double antibody radioimmunoassay technique with 30K antiserum.[13] In this assay cross-reactivity with glucagonlike immunoreactivity is minimal. Glucagon chromatographic profiles were obtained with a 1 × 50-cm BioGel P-30 column (Bio-Rad Laboratories, Richmond, CA), as previously described.[27,28]

Data Analysis

All data obtained through December 1988 was analyzed. Survival data are presented for all patients who had their procedure during the study period (n = 49). Metabolic parameters are presented for 35 of these patients. The data is expressed for every patient as the mean of all determinations obtained. The studies were begun no earlier than 6 months after the operation to avoid the influence of any postoperative surgical complications. Laboratory data are not included for terminally ill patients. However the final chemistry screening profile in four patients was obtained within 3 months of death from recurrent disease. All results are expressed as mean ± SE, unless otherwise stated.

Results

Surgical Outcome

The mean (±SE) postoperative follow-up for all patients has been 39 ± 6 months (median, 15 months; range, 1 to 174 months), with 31% of patients followed for 48 or more months. The seven patients who were operated on for benign disease (chronic pancreatitis) have had a mean survival time of 80 ± 24 months (median, 86 months; range, 1 to 174 months). There was one perioperative death due to intestinal ischemia. Three patients died 116 ± 29 months after surgery of cirrhosis of the liver (n = 2) and a cerebrovascular accident (n = 1). Three other patients are alive and well 12, 60, and 139 months after pancreatic resection.

The mean survival for the 7 patients with periampullary carcinoma was 70 ± 19 months (median, 102 months; range, 6 to 117 months). Three patients died of recurrent disease within 27 months of surgery, and two others died from non-neoplastic causes (hepatic/renal failure, cirrhosis) 102 and 110 months after surgery, respectively. Two patients are alive and well at 113 and 117 months.

The 31 patients with pancreatic adenocarcinoma have had a mean survival time of 17 ± 4 months (median, 13 months; range, 1 to 88 months). There were three perioperative deaths in this population. Eight other patients died of causes unrelated to their cancer diagnosis at 35 days (hypoglycemia), 5 weeks (suicide), 6 weeks (gastrointestinal bleeding), 2 months (cerebrovascular accident), 4 months (sepsis), 6 months (sepsis), 8 months (pulmonary embolus), and 16 months (undetermined cause) after surgery. Fourteen patients died of recurrent disease 14 ± 2 months (median survival, 14 months) after pancreatic resection. Six patients are alive without evidence of disease 6, 24, 25, 48, 83, and 88 months after their pancreatectomy. The survival experience in the larger number of patients with adenocarcinoma of the head of the pancreas undergoing a curative total or subtotal regional pancreatectomy is the subject of a recent review.[29]

The mean follow-up for the 35 patients surviving for more than 6 months after surgery is 53 ± 8 months (median, 26 months; range, 8 to 174 months). Of these 89% have been followed for more than 1 year and 37% have been followed for more than 5 years.

Nutritional Status

The mean preillness weight of the study patients was 118% ± 3% of their ideal body weight (IBW). One half of

the patients were obese, as defined as a preillness weight more than 120% IBW. For all patients the mean weight loss before their pancreatic resection was 8 ± 2 kg.

Prior to 1978, before intensive postoperative nutritional support was instituted, the mean perioperative weight loss was 15.9 ± 3 kg. Following that time aggressive hyperalimentation was routinely administered, which resulted in a perioperative weight loss of 4.8 ± 0.8 kg. The mean duration of TPN was 19 ± 4 days/patient, because anorexia, early satiety, diminished gastric capacity, delayed gastric emptying, and persistent and troublesome diarrhea seriously limited early tolerance to oral feeding. In four patients adequate oral intake was not achieved during a prolonged period of inpatient observation, and they were supplemented by an intermittent (12 to 16 hours per 24 hours) pump infusion of a defined-formula diet, which provided hydrolyzed protein, low residue, and no lactose, and which was administered *via* nasogastric feeding tube on an outpatient basis until oral intake and weight stabilized.

All patients experienced severe and debilitating diarrhea during the immediate postoperative period, which responded variably to conventional antidiarrheal agents. In most patients watery diarrhea abated within 3 to 12 months, although formed bowel movements remained frequent (4 to 8 per day), urgent, and bulky. Approximately 10% of patients, however, have continued to have significant and troublesome chronic diarrhea. Other digestive disturbances in patients free of recurrent disease were distinctly unusual. No patient noted abdominal pain as a complication of the surgical procedure. Nausea, vomiting, and dumping were not experienced after the immediate postoperative period. All long-term survivors thought that their meal capacity exceeded their prepancreatectomy pattern.

TABLE 2. *Selected Serum Indices of Liver Function**

Indices	Patient Values	Normal Levels
Total Bilirubin		
μmol/L	15 ± 2	2–18
(mg/dL)	(0.9 ± 0.1)	(0.1–1.0)
Total Protein		
g/L	70 ± 2	63–81
(g/dL)	(7.0 ± 0.2)	(6.3–8.1)
Albumin		
g/L	39 ± 1	40–52
(g/dL)	(3.9 ± 0.1)	(4.0–5.2)
SGOT		
μkat/L	0.48 ± 0.27	0.01–0.2
(U/L)	(60 ± 34)	(0–25)
Alkaline Phosphatase		
μkat/L	5.6 ± 1.0	0.5–1.9
(U/L)	(338 ± 59)	(30–115)

* Data obtained at the time of every follow-up visit. All values (mean/patient) expressed as mean ± SE for the entire patient group. Common unit values are provided in parentheses.

SGOT, serum glutamic oxaloacetic transaminase.

TABLE 3. *Seventy-two-Hour Fecal Fat Excretion** †

Dietary Fat mmol/day (g/day)	Fecal Fat mmol/day (g/day)	% Fat Excreted	Units Lipase/mmol (g) Fat Ingested
527 ± 39 (150 ± 11)	84 ± 11 (24 ± 3)	16 ± 2	179 ± 22 (630 ± 77)

* Results expressed as mean ± SE, with common unit values in parentheses. Normal fecal fat excretion is <4% of a measured fat intake in a 3-day period, or <21 mmol/day (6 g/day).

† Fifteen patients, 20 studies.

For the patients as a whole, the outpatient weight at last follow-up was 99% ± 4% IBW. Of the patients who survived more than 18 months after their pancreatic resection, the mean weight change from their hospital discharge weight was +2.2 ± 2.2 kg. In seven weight-maintaining patients, adherence to the recommended high-calorie diet was assessed by a review of food diaries and recall histories, and 3-day food records were submitted for computer analysis to assess nutritional soundness as well as the actual composition of the diets ingested. Caloric intake ranged between 2500 and 5300 kcal/day (mean, 56 ± 1 kcal/kg; range, 36 to 74 kcal/kg), was identical to the distribution prescribed, and was not deficient in any essential nutrient.

Selected parameters of liver function for all patients are depicted in Table 2. Elevated levels of serum glutamic-oxaloacetic transaminase (SGOT/AST) and alkaline phosphatase were seen in virtually all the patients. Total protein levels were normal in all patients, but in one half of the patients serum albumin levels remained persistently decreased.

Malabsorption

Nine patients were studied for their ability to absorb carbohydrates by the standard D-xylose test. The mean urinary 5-hour excretion of D-xylose was 6.5 ± 0.7 g, with a range of 3.5 to 10.7 g. All but one patient demonstrated normal carbohydrate absorption.

Table 3 depicts the 72-hour fecal fat excretion data obtained in 15 totally pancreatectomized patients. As noted, on a diet unrestricted in fat calories, the mean 24-hour fecal fat excretion was 16% ± 2% of dietary fat intake. No correlation could be found between the amount of dietary fat ingested and the degree of steatorrhea noted (r = 0.13).

Mean serum fat-soluble vitamin, magnesium, and trace element levels were within the normal range (Table 4). However persistently low values could be demonstrated in individual patients: abnormal levels of vitamin A (n = 4 patients), vitamin E (n = 1), 25-hydroxyvitamin D (n = 4), 1,25-dihydroxyvitamin D (n = 3), magnesium

TABLE 4. *Selected Nutritional Indices**

Indices	Patient Values	Normal Levels
Vitamin A		
IU/L	1090 ± 170	650–2750
Vitamin E		
mg/L	8.8 ± 3.3	5–20
25-hydroxyvitamin D		
nmol/L	67 ± 30	25–137
(ng/mL)	(27 ± 12)	(10–55)
1,25-dihydroxyvitamin D		
ng/L	25 ± 2	20–76
Magnesium		
mmol/L	0.78 ± 0.02	0.70–1.10
(mEq/L)	(1.55 ± 0.03)	(1.4–2.2)
Copper		
μmol/L	19.8 ± 0.9	11.0–24.4
(mcg/dL)	(126 ± 6)	(70–155)
Zinc		
μmol/L	13.5 ± 1.4	7.7–22.9
(mcg/dL)	(88 ± 9)	(50–150)

* Data obtained every 6 months. All serum values (mean/patient) expressed as mean ± standard error for the entire patient group, with common unit values in parentheses.

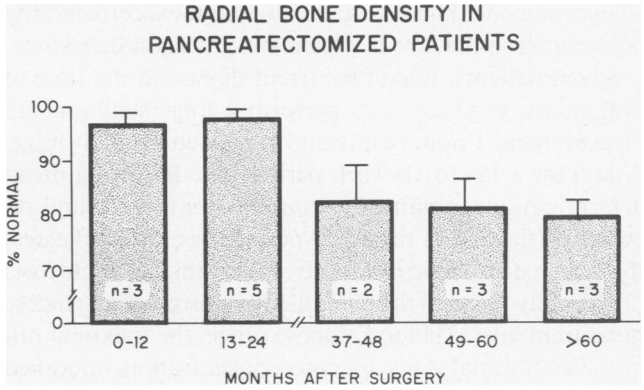

FIG. 1. Radial bone density in 10 pancreatectomized patients, expressed as a percentage of mean values obtained in age- and sex-matched normal subjects and plotted as a function of time (months) following pancreatic surgery. Total numbers of patients used to derive these mean values are indicated. Six patients had multiple values done, and they were meaned to give only a single value/patient for each respective time period depicted. Excluded were two patients with islet cell carcinomas and calcitonin production, and a patient with lymphoma who had evidence of osseous involvement.

(n = 4), and zinc (n = 1) were noted, despite multivitamin and pharmacologic vitamin D supplementation in all patients. The prothrombin time was normal in all patients except in whom severe hepatic insufficiency supervened, and no patient required supplemental vitamin K administration.

While the 24-hour urinary calcium excretion was normal in all patients, mean serum calcium levels were subnormal in nine patients. Furthermore the mean serum calcium level in the pancreatectomized patients, 2.32 ± 0.03 mmol/L (9.3 ± 0.1 mg/dL), was at the lower limits of normal for our laboratory, undoubtedly reflecting the prevailing lowered serum albumin level.

In 10 men and three women, bone densitometry values were obtained during the postpancreatectomy follow-up period; this measurement was repeated at variable intervals in eight patients. The mean radial bone mineral content determinations in pancreatectomized men and women, expressed as a percentage of that obtained in age- and sex-matched normal subjects and depicted according to when the measurement was obtained after the surgical resection, are shown in Figure 1. While the bone density obtained in patients within 2 years after surgery appeared well maintained, patients who were studied more than 5 years after pancreatectomy had a mean reduction in bone mineral content of 17.6% compared to controls.

Pancreatogenic Diabetes

Insulin secretory reserve. Eighteen patients have had stimulated C-peptide levels measured after pancreatic resection, and in every instance the levels were undetectable (less than 0.02 nmol/L). This finding confirmed the completeness of the surgical procedure.

Glucagon immunoreactivity and chromatographic profiles in pancreatectomized humans. Verified by chromatographic profiling in every instance, 3500-M_r glucagon was virtually absent in 18 pancreatectomized patients: for the group as a whole, 3500-M_r IRG comprised 1% to 2% of the total recovered IRG (Fig. 2). This pancreatic plasma IRG fraction was not stimulated by oral protein or intravenous arginine.

Glycemic lability. A pilot program of intensive home glucose monitoring was conducted to (1) assess the degree of diabetic instability existing in this population, (2) evaluate their insulin requirements, and (3) determine if near-

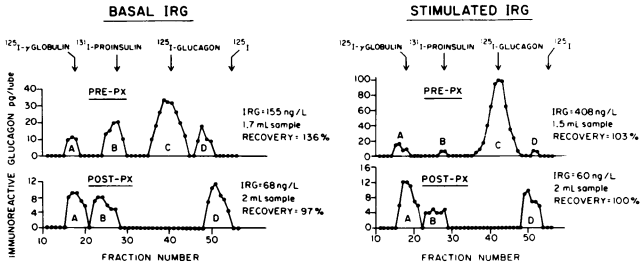

FIG. 2. Representative elution profiles of plasma IRG on 1 × 50 cm BioGel P-30 columns. Left panel shows the basal profile in a prepancreatectomy (top) or a postpancreatectomy (bottom) patient. Right panel shows the IRG response in a patient prepancreatectomy after intravenous arginine (top) *versus* that seen after pancreatectomy in response to oral protein (bottom). Arrows represent calibration points on column with labeled or unlabeled markers indicated.

euglycemia could be maintained without exacerbated hypoglycemia in the face of pancreatic glucagon deficiency.

Seven patients, free of recurrent disease at the time of evaluation, were asked to perform a fingerstick glucose measurement 1 hour before and after each meal (average, 8/day) for a 12- to 18-week period. The following mean determinations, obtained during the first month and repeated at the end of the study period, were used to assess the degree of diabetic instability: (1) fasting blood glucose; (2) the daily mean of the seven 1-hour postprandial glucose measurements; (3) blood glucose range, the maximal minus the minimal daily glucose concentration, modified from Reynolds et al.[30]; and (4) maximal excursion of blood glucose, the largest unidirectional consecutive change in blood glucose observed during the day.[31] For each of the four variables, the standard deviations for the 30 daily measurements in each of the initial and final periods were calculated to estimate day-to-day variation.

The initial mean fasting blood glucose level was 8.0 ± 1.1 mmol/L (142 ± 20 mg/dL), with a mean blood glucose level of 10.9 ± 1.4 mmol/L (200 ± 20 mg/dL). The variables describing plasma glucose fluctuation within a 24-hour period were compatible with values seen in patients with brittle diabetes[31]; the mean blood glucose range was 10.9 ± 1.4 mmol/L (194 ± 25 mg/dL), and the mean maximal excursion of blood glucose was 9.7 ± 1.2 mmol/L (173 ± 21 mg/dL). Fingerstick blood glucose determinations ≤2.8 mmol/L (50 mg/dL), often asymptomatic, occurred in the first month with a frequency of 0.9% to 8.6% in six patients; only the one patient with the highest glycemic indices was spared hypoglycemic episodes.

Figure 3 depicts the overall improvement in blood glucose control achieved with home glucose monitoring, as noted in serial glycosylated hemoglobin measurements.

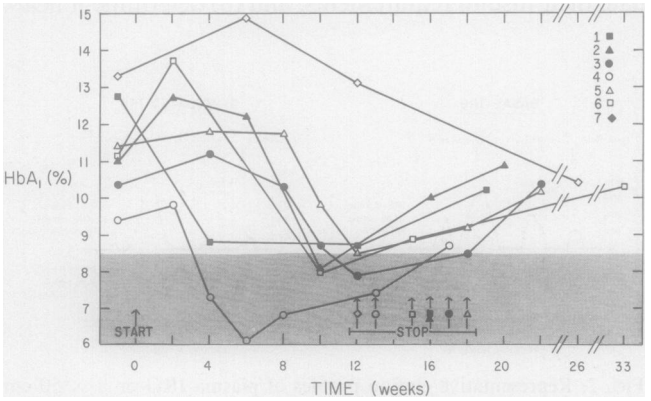

FIG. 3. Serial Hb A_1 (%) values plotted *versus* time (weeks). Solid arrows denote the times of starting and stopping the program of home glucose monitoring for all seven patients (depicted by symbols noted in the upper right hand corner). Stippled area represents our normal values for Hb A_1 (5.5%–8.5%).

Hb A_1 levels on entry into the study were elevated in all patients (mean 11.3% ± 0.1%), and following intensive diabetic management, reached a nadir in most patients by 10 to 12 weeks, with five patients normalizing their glycosylated hemoglobin level during this period of observation. However, despite the continuation of the program for another 4 weeks, Hb A_1 levels started to increase after 12 weeks. Nevertheless an overall improvement in glycemic control persisted, with a significantly improved ($p < 0.01$) mean Hb A_1 of 9.4% ± 0.7% (normal range, 5.5% to 8.5%) at the end of the study documenting very reasonable diabetic control.

In five patients significant improvement in parameters of diabetic control could be demonstrated after 3 months of intensive home glucose monitoring, and significantly decreased standard deviations for blood glucose and blood glucose range parameters suggested that these measurements became more stable in the final period with respect to day-to-day variation in every patient. Most importantly four patients experienced significantly less hypoglycemia.

Insulin requirements. The mean 24-hour insulin dose was 0.31 ± 0.03 U/kg body weight at time of discharge following pancreatectomy. In the long-term survivors, insulin requirements increased over the follow-up period of 74 to 174 months to 0.48 ± 0.04 U/kg body weight, probably as a result of their improved dietary intake. A mean total glycosylated hemoglobin (Hb A_1) level of 10.7% ± 0.3%, and, more recently, the mean Hb A_{1c} level of 8.5% ± 0.4% (normal ranges, 5.5% to 8.5% and 3.6% to 6.1%, respectively) confirmed that while normoglycemia was not achieved in these patients, reasonable diabetic control was indeed possible.

Long-term Sequelae

Patient performance status. Patients were able to resume reasonably active life styles within months of the surgery. Although every patient experienced a modification of their preillness regimen because of the necessity for frequent meals and blood glucose monitoring, most long-term survivors were able to return to their previous professional activities. No patient has remained home-bound or restricted in normal activity; vigorous physical exercise, however, is not recommended because of fear of hypoglycemia.

Diabetic sequelae. One patient died of documented hypoglycemia, which occurred shortly following hospital discharge after the pancreatic resection; in no other patients did symptomatic hypoglycemia occur that could not be treated at home. No patient required hospitalization for uncontrolled diabetes or diabetic ketoacidosis. No patient had evidence of diabetic retinopathy, as assessed by routine fundus examinations. Renal function

was well maintained in all patients but two: one in whom renal insufficiency developed as a terminal event, probably related to underlying cardiac and septic complications, and another with concurrent Sjogren's syndrome. No patient had laboratory evidence of proteinuria. Nerve conduction studies were not performed, but symptomatic neuropathy developed in only one patient. Electrolyte and magnesium deficiencies secondary to severe chronic diarrhea may have been contributory.

Hepatic dysfunction. Three patients died of cirrhosis of the liver. In one, antecedent (prepancreatectomy) alcohol intake may have contributed. The second patient had moderate centrolobular steatosis documented at biopsy 8 years after surgery, which progressed within 1 year to fulminant end-stage liver disease and death. At autopsy the liver had fully developed irregular cirrhosis with moderate fatty changes throughout the nodule. Because of clinically significant liver disease, the third patient had a liver biopsy 3 years after pancreatectomy and focal (minimal) steatosis was documented. The patient died of complications of hepatic insufficiency 3 years later. At autopsy fully developed irregular cirrhosis was noted, with moderate to severe steatosis throughout the nodule. Three other long-term survivors (7, 9, and 10 years after pancreatectomy) have biopsy and/or computed tomography (CT) scan evidence of fatty infiltration of the liver.

Other malignancies. Two patients with adenocarcinoma of the pancreas had a second malignancy (ovarian cancer found incidentally at time of pancreatectomy and breast cancer noted 6 months after pancreatic resection). Two other patients (one with chronic pancreatitis, the other with periampullary carcinoma) developed colon cancer 51 and 47 months, respectively, after pancreatectomy.

Discussion

Significant clinical morbidity can be expected to result from the physiologic sequelae of the surgical procedure, which includes gastric antral resection, cholecystectomy with resection of the common bile duct, pancreatectomy, and interruption in intestinal innervation and lymphatic drainage. The total pancreatectomy and intestinal denervation appear to cause the most severe physiologic abnormalities, resulting in acutely disordered intestinal function and a chronic diabetic state uniquely characterized by a lack of the major glucoregulatory hormones insulin and glucagon.

The early postoperative state is marked by diarrhea, which hampers timely convalescence and hospital discharge. Multiple aspects of the surgical procedure can result in impaired gastrointestinal motility, absorption, and secretion. Pancreatic exocrine deficiency *per se*, with maldigestion, malabsorption, and steatorrhea, results in excessive fecal fluid losses.[32] Faster cycling of the bile salt pool reported after cholecystectomy may lower the diarrheal threshold as well.[33] We could not note a difference in the postoperative course of the two patients who did not have regional total pancreatectomy. However the diarrhea experienced by patients in the current series does seem to be of greater magnitude than that reported after standard total pancreatic resection[6,9] or after pyloric- and gastric-preserving pancreatic resection.[34]

Unique to the regional total pancreatectomy are the lymphatic interruption and surgical sympathectomy. Lacking information on mucosal morphology in this population, the exact role of altered lymphatic drainage is unclear. Intestinal denervation, however, can result in diarrhea by at least two distinct mechanisms. Resection of the celiac and superior mesenteric ganglia affects small intestinal motility *via* loss of the tonic inhibitory effects of sympathetic nerves on gastrointestinal function.[35] In addition the altered homeostatic balance of intestinal ion transport favors secretion.[36] Remarkably the diarrhea abates spontaneously in most patients after a variable period of time. However, in the acute postoperative state, bile acid sequestrants, somatostatin analogues, and alpha-2-adrenergic agonists may be found beneficial in future controlled studies.

Previous investigators have found weight loss in 30% to 40% of patients and weight maintenance to be a significant chronic problem after total pancreatectomy.[7,8] In addition deficiencies of fat-soluble vitamins[37] and trace elements[38] are common in patients with chronic exocrine pancreatic insufficiency despite adequate pancreatic supplements. The current experience differs from that expected in this patient population. After the early postoperative period, patients free of recurrent disease gained or maintained weight in every instance despite the presence of modest steatorrhea. Furthermore nutritional deficiencies were prevented in all but a small number of patients. This was accomplished by conventional enzyme replacement therapy (at least 20,000 U lipase/major meal), routine calcium and vitamin supplementation, and scrupulous adherence to a regimen of multiple calorie-dense meals per day without dietary fat restriction. A high caloric requirement was a consistent finding in all patients, not fully explained by the degree of steatorrhea present. Basal metabolic rate determinations have not been performed and may be of interest in such patients. Because of the persistence of severe hypoalbuminemia, one patient underwent a detailed investigation for a protein-losing enteropathy, with negative results.

Given the antral resection and malabsorption, it is expected that the pancreatectomized patient will be at risk for the development of osteopenia,[39,40] and these data, while clearly preliminary, support this. Despite measures

that prevented calcium and vitamin D deficiencies in most patients, radial bone mineral content was decreased with time after surgery. The longitudinal use of the more sensitive technologies currently available, such as vertebral/femoral neck dual photon or dual-energy x-ray absorptiometry or CT scanning,[41,42] is recommended, so that more aggressive, bone-preserving strategies could be instituted promptly when indicated.

The diabetes of the totally pancreatectomized patient has unique clinical and metabolic features. Diabetic instability is a constant finding. There is an erratic pattern of glycemic fluctuations, an impressive postprandial hyperglycemia, and delayed, often nocturnal decreases in blood glucose levels. The 'brittle' nature of blood glucose profiles is similar to that seen in young patients with insulin-dependent diabetes mellitus (IDDM) and is not improved by glucagon replacement.[43] Thus it would appear that endogenous insulin reserve is a primary determinant of diabetic stability in patients with pancreatogenic diabetes, as has been suggested in other diabetic populations.[30,44,45]

An important characteristic of the labile diabetic milieu in this population is the ease with which hypoglycemia can be induced. Review of the surgical literature confirms the increased susceptibility of these patients to severe hypoglycemia, with brain dysfunction, coma, and death as a sequelae of insulin therapy reported in several large surgical series.[6-8,46] The incidence of hypoglycemia, often asymptomatic, was unacceptably high in this series until the institution of rigorous home glucose monitoring and administration of multiple, small daily doses of insulin as required. It was not possible to achieve persistent normalization of glycemic control in any patient in this study. However, given the morbidity of uncontrolled glycemic excursions, vigorous efforts at blood glucose stabilization in a population of pancreatectomized patients are essential.

This labile and 'brittle' pattern of glycemic control has led to the widespread clinical impression that patients with pancreatogenic diabetes are unusually insulin sensitive. Previous uncontrolled studies have suggested that totally pancreatectomized patients need less insulin than patients with IDDM.[47,48] This has been confirmed by a study using Biostator glucose-controlled insulin infusion system (Life Science Instruments, Ulm, Germany) and identical inpatient dietary regimens: following total pancreatectomy, a significant and substantial ($\approx$35%) decrease in insulin requirements was noted compared to patients with subtotal pancreatectomy or IDDM.[49]

The locus of enhanced insulin responsiveness does not appear to be peripheral tissues. While enhanced peripheral glucose uptake in response to insulin was reported in patients with pancreatogenic diabetes,[50] more recent studies in well-characterized completely pancreatectomized patients have demonstrated significant insulin resistance in this population, comparable to that seen in patients with IDDM.[51,52] Indeed basal glucagon replacement induced a further significant reduction in tissue insulin responsiveness.[53]

The primacy of glucagon in the maintenance of postabsorptive glucose concentrations is well established. Where the completeness of the surgical procedure was established, studies using column chromatography have detected absent or markedly reduced 3500-M_r glucagon in totally pancreatectomized patients.[28,54] Impaired counter-regulatory hormone responsiveness has been demonstrated in these patients; two separate laboratories have found no increase of glucagon and a reduced[55] or delayed[56] epinephrine response to insulin-induced hypoglycemia. Certain metabolic features in this diabetic state are consistent with a chronic lack of biologically active pancreatic glucagon as well: the delayed increase of blood glucose and ketone bodies after cessation of insulin therapy,[57] the absence of an increase in blood glucose during arginine infusion,[58,59] and the abnormally elevated concentrations of the major glucogenic amino acids that decrease with physiologic glucagon replacement.[43,49,60,61] Furthermore pancreatectomized patients have an exaggerated hyperglycemic response to glucagon administration compared to that seen in comparably insulin-deficient patients with IDDM, suggesting that chronic glucagon deficiency enhances sensitivity to exogenous glucagon.[43] It would appear, therefore, that impaired regulation of hepatic glucose production subsequent to surgically induced pancreatic alpha cell insufficiency is a probable cause for the frequent hypoglycemia seen in these patients. Whether glucagon replacement therapy in this population would reduce the incidence of this morbid complication remains an intriguing therapeutic option worthy of further study.

An uncommon but worrisome finding in prolonged follow-up of totally pancreatectomized patients has been the development of accelerated lipid accumulation in the liver, with end-stage liver disease as a cause of death noted in three such patients in this study. This complication has been described as well in experimental pancreatectomized animals.[62,63] While poorly controlled diabetes, weight loss, and malabsorption can be contributing factors, the severity of hepatic steatosis noted in patients who have been in reasonable diabetic control suggests additional pathogenic mechanisms. Preliminary information suggests that the storage triglycerides are not dietary in origin but result from altered hepatic metabolism. The impact of the altered hormonal milieu of the postpancreatectomy state on hepatic lipogenesis is now being studied in our laboratory.

References

1. Priestley JT, Comfort MW, Randcliff J. Total pancreatectomy for hyperinsulinism due to an islet cell adenoma. Ann Surg 1944; 199:211–221.
2. Collins JJ, Craighead JE, Brooks JR. The rationale for total pancreatectomy for carcinoma of the pancreatic head. N Engl J Med 1966; 274:599–602.
3. Ross DE. Cancer of the pancreas. A plea for total pancreatectomy. Am J Surg 1954; 87:20–83.
4. Levin B, ReMine WH, Hermann RE, et al. Panel: cancer of the pancreas. Am J Surg 1978; 135:185–191.
5. ReMine WH, Priestley JT, Judd ES, et al. Total pancreatectomy. Ann Surg 1970; 172:595–603.
6. Ihse I, Lilja P, Arnesjo B, Bengmark S. Total pancreatectomy for cancer. Ann Surg 1977; 186:675–680.
7. Pliam MB, ReMine WH. Further evaluation of total pancreatectomy. Arch Surg 1975; 110:506–512.
8. Braasch JW, Vito L, Nugent FW. Total pancreatectomy for end-stage chronic pancreatitis. Ann Surg 1978; 188:317–322.
9. Brooks JR, Brooks DC, Levine JD. Total pancreatectomy for ductal cell carcinoma of the pancreas: an update. Ann Surg 1989; 209: 405–410.
10. Trede M. The surgical treatment of pancreatic carcinoma. Surgery 1985; 97:28–35.
11. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg 1988; 207:39–47.
12. Moossa AR. Tumors of the Pancreas. Baltimore: Williams & Wilkins, 1980, pp 457–460.
13. Fortner JG, Kim DK, Cubilla A, et al. Regional pancreatectomy: en bloc pancreatic, portal vein and lymph node resection. Ann Surg 1977; 186:42–50.
14. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla and other related sites. Ann Surg 1984; 199:418–425.
15. Sonksen PH, Judd SL, Lowy C. Home monitoring of blood-glucose. Lancet 1978; i:729–732.
16. Peterson CM, Jones RL, Dupuis A, et al. Feasibility of improved blood glucose control in patients with insulin-dependent diabetes mellitus. Diabetes Care 1979; 2:329–335.
17. Abraham EC, Huff TA, Cope ND, et al. Determination of the glycosylated hemoglobins (Hb A_1) with a new microcolumn procedure. Diabetes 1978; 27:931–937.
18. De Leenheer AP, Bevere VO, De Ruyter MG, et al. Simultaneous detection of retinol and alpha tocopherol in human serum by high performance liquid chromatography. J Chromatogr 1979; 162:408–413.
19. Catignani GL, Bieri JG. Simultaneous determination of retinol and α-tocopherol in serum or plasma by liquid chromatography. Clin Chem 1983; 29:708–712.
20. Dabek JT, Harkonen M, Wahlroos O, Adlercreutz H. Assay for plasma 25-hydroxy vitamin D_2 and 25-hydroxy vitamin D_3 by "high-performance" liquid chromatography. Clin Chem 1981; 27:1346–1351.
21. Bishop JE, Norman AW, Coburn JW, Henry HL. Determinations of concentrations of 25-hydroxy-, 24,25-dihydroxy- and 1,25-dihydroxy vitamin D in a 2.0 ml plasma sample. J Mineral Electrolyte Metab 1980; 3:181–186.
22. Lowry SF, Smith JC, Brennan MF. Zinc and copper replacement during total parenteral nutrition. Am J Clin Nutr 1981; 34:1853–1860.
23. Cameron JR, Sorenson J. Measurement of bone mineral in vivo: an improved method. Science 1963; 142:230–232.
24. Van de Kamer JH, Ten Bokkel Huinink H, Weijers HA. A rapid method for the determination of fat in feces. J Biol Chem 1949; 177:347–352.
25. Finlay JM, Hogarth J, Wightman KJR. A clinical evaluation of the D-xylose tolerance test. Ann Intern Med 1964; 61:411–418.
26. Kuzuya H, Blix PM, Horwitz DL, et al. Determination of free and total insulin and C-peptide in insulin treated diabetics. Diabetes 1979; 26:22–27.
27. Kuku SF, Zeidler A, Emmanouel DS, et al. Heterogeneity of plasma glucagon: patterns in patients with chronic renal failure and diabetes. J Clin Endocrinol Metab 1976; 42:173–176.
28. Bajorunas DR, Fortner JG, Jaspan JB. Glucagon immunoreactivity and chromatographic profiles in pancreatectomized humans: paradoxical response to oral glucose. Diabetes 1986; 35:886–893.
29. Fortner JG. Radical abdominal cancer surgery: current state and future course. Jap J Surg 1989; 19:503–509.
30. Reynolds C, Molnar GD, Horwitz DL, et al. Abnormalities of endogenous glucagon and insulin in unstable diabetes. Diabetes 1977; 26:36–45.
31. Tamborlane WV, Sherwin RS, Genel M, Felig P. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. N Engl J Med 1979; 300:573–578.
32. Fine KD, Krejs GJ, Fordtran JS. Diarrhea. *In* Sleisenger MH, Fordtran JS, eds. Gastrointestinal Disease, Vol. 1. Philadelphia: WB Saunders, 1989, pp 290–316.
33. Vernick LJ, Kuller LH. Cholecystectomy and right-sided colon cancer: an epidemiological study. Lancet 1981; ii:381–384.
34. Braasch JW, Deziel DJ, Rossi RL, et al. Pyloric and gastric preserving pancreatic resection. Experience with 87 patients. Ann Surg 1986; 204:411–418.
35. Chang EB. Experimental diabetic diarrhea in rats. Intestinal mucosal denervation hypersensitivity and therapy with clonidine. Gastroenterol 1986; 91:564–569.
36. Chang EB, Bergenstal RM, Field M. Diarrhea in streptozocin-treated rats. Loss of adrenergic regulation of intestinal fluid and electrolyte transport. J Clin Invest 1985; 75:1666–1670.
37. Dutta SK, Bustin MP, Russell RM, Costa BS. Deficiency of fat-soluble vitamins in treated patients with pancreatic insufficiency. Ann Intern Med 1982; 97:549–552.
38. Boosalis MG, Evans GW, McClain CJ. Impaired handling of orally administered zinc in pancreatic insufficiency. Am J Clin Nutr 1983; 37:268–271.
39. Meredith SC, Rosenberg IH. Gastrointestinal-hepatic disorders and osteomalacia. Clin Endocrinol Metab 1980; 9:131–150.
40. Seeman E, Melton LJ III, O'Fallon WM, Riggs BL. Risk factors for spinal osteoporosis in men. Am J Med 1983; 75:977–983.
41. Hall FM, Davis MA, Baran DT. Bone mineral screening for osteoporosis. N Engl J Med 1987; 316:212–214.
42. Sartoris DJ, Resnick D. New radiographic technique may renew credibility of bone densitometry. Mayo Clin Proc 1988; 63:1147–1150.
43. Bajorunas DR, Fortner JG, Jaspan J, Sherwin RS. Total pancreatectomy increases the metabolic response to glucagon in humans. J Clin Endocrinol Metab 1986; 63:439–446.
44. Shima K, Tanaka R, Morishita S, et al. Studies on the etiology of brittle diabetes. Relationship between diabetic instability and insulinogenic reserve. Diabetes 1977; 26:717–725.
45. The DCCT Research Group. Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual β-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). J Clin Endocrinol Metab 1987; 65:30–36.
46. Frey CF, Child CG, Fry W. Pancreatectomy for chronic pancreatitis. Ann Surg 1976; 184:403–414.
47. Barnes AJ, Bloom SR, Crowley MF, Tuttlebee JW. Is glucagon important in stable insulin-dependent diabetics? Lancet 1975; ii: 734–737.
48. Kiviluoto T, Schroder T, Karonen SL, et al. Glycemic control and serum lipoproteins after total pancreatectomy. Ann Clin Res 1985; 17:110–115.
49. Del Prato S, Tiengo A, Baccaglini U, et al. Effect of insulin replacement on intermediary metabolism in diabetes secondary to pancreatectomy. Diabetologia 1983; 25:252–259.
50. Nosadini R, Del Prato S, Tiengo A, et al. Insulin sensitivity, binding, and kinetics in pancreatogenic and type I diabetes. Diabetes 1982; 31:346–355.
51. Bajorunas DR, Dresler CM, Horowitz GC, et al. Insulin resistance is present in the chronic glucagon-deficient state. Diabetes 1985; 34:45(Abstr).

52. Jarvinen HY, Kiviluoto T, Taskinen MR. Insulin resistance is a prominent feature of patients with pancreatogenic diabetes. Metabolism 1986; 35:718–727.
53. Bajorunas DR, Dresler CM, Horowitz GD, et al. Basal glucagon replacement in chronic glucagon deficiency increases insulin resistance. Diabetes 1986; 35:556–562.
54. Muller WA, Berger M, Suter P, et al. Glucagon immunoreactivities and amino acid profile in plasma of duodeno-pancreatectomized patients. J Clin Invest 1979; 63:820–827.
55. Polonsky KS, Herold KC, Gilden JL, et al. Glucose counterregulation in patients after pancreatectomy: comparison with other clinical forms of diabetes. Diabetes 1984; 33:1112–1119.
56. Horie H, Matsuyama T, Namba M, et al. Responses of catecholamines and other counterregulatory hormones to insulin-induced hypoglycemia in totally pancreatectomized patients. J Clin Endocrinol Metab 1984; 59:1193–1196.
57. Barnes AJ, Bloom SR, Alberti GMM, et al. Ketoacidosis in pancreatectomized man. N Engl J Med 1977; 296:1250–1253.
58. Muller WA, Brennan MF, Tan MH, Aoki TT. Studies of glucagon secretion in pancreatectomized patients. Diabetes 1974; 23:512–516.
59. Gerich JE, Karam JH, Lorenzi M. Diabetes without glucagon. Lancet 1976; i:855.
60. Muller WA, Cuppers HJ, Zimmermann-Telschow H, et al. Amino acids and lipoproteins in plasma of duodenopancreatectomized patients: effects of glucagon in physiological amounts. Eur J Clin Invest 1983; 13:141–149.
61. Boden G, Master RW, Rezvani I, et al. Glucagon deficiency and hyperaminoacidemia after total pancreatectomy. J Clin Invest 1980; 65:706–716.
62. Bennett LL. What causes fatty liver after pancreatectomy—an unresolved and forgotten controversy. Perspect Biol Med 1983; 26: 595–612.
63. Chernick SS, Scow RO. Early effects of 'total' pancreatectomy on fat metabolism in the rat. Am J Physiol 1959; 196:125–131.