Metabolic Consequences of (Regional) Total Pancreatectomy

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.

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

'Sweet.' 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.

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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.\textsuperscript{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.

**Diabetic management.** The patients were instructed in the use of a reflectance meter-assisted home glucose monitoring program\textsuperscript{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

<table>
<thead>
<tr>
<th>Table 1. Indications for Surgery</th>
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<tbody>
<tr>
<td>Histologic Diagnoses</td>
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<tr>
<td>Adenocarcinoma of the pancreas</td>
</tr>
<tr>
<td>Periampullary carcinoma</td>
</tr>
<tr>
<td>Islet cell carcinoma</td>
</tr>
<tr>
<td>Papilloectic adenocarcinoma</td>
</tr>
<tr>
<td>Pancreatitis</td>
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<tr>
<td>Lymphoma</td>
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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 were used to ascertain the degree of diabetic control. Vitamins A, E, 25-hydroxy, and 1,25-dihydroxy D and the trace elements copper and zinc were monitored every 6 months. Measurement of bone mineral content used direct photon absorptiometry technique at the distal third of the nondominant radius.

For the quantitative 72-hour fecal fat analyses, 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.

In selected patients the completeness of the pancreatic resection was verified by stimulated C-peptide levels. 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. In this assay cross-reactivity with glucagon-like 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.

**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 (hepatorenal failure, cirrhosis) 102 and 110 months after surgery, respectively. Two patients are alive and well at 113 and 117 months.

Of 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.

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.

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

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

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

* 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.

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**Table 3. Seventy-two-Hour Fecal Fat Excretion***

<table>
<thead>
<tr>
<th>Dietary Fat mmol/day (g/day)</th>
<th>Fecal Fat mmol/day (% Excreted)</th>
<th>Units Lipase/mmol (g) Fat Ingested</th>
</tr>
</thead>
<tbody>
<tr>
<td>527 ± 39</td>
<td>84 ± 11</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>(150 ± 11)</td>
<td>(24 ± 3)</td>
<td>179 ± 22</td>
</tr>
</tbody>
</table>

* 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.

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Pancreatogenic stimulated, well after when the stimulated expressed content in are and sex-matched determinations were vals this period; the tients.

The patients. of = (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 sub-normal 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 secretary 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, glucagon was virtually absent in 18 pancreatectomized patients: for the group as a whole, 3500-M, 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-

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**TABLE 4. Selected Nutritional Indices**

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

* 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.
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 fingertip 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.\textsuperscript{30}; and (4) maximal excursion of blood glucose, the largest unidirectional consecutive change in blood glucose observed during the day.\textsuperscript{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 ± 1.0 mmol/L (142 ± 20 mg/dL), with a mean blood glucose level of 10.9 ± 1.4 mmol/L (200 ± 25 mg/dL). The variables describing plasma glucose fluctuation within a 24-hour period were compatible with values seen in patients with brittle diabetes\textsuperscript{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.

Hb A\textsubscript{1c} 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\textsubscript{1c} 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\textsubscript{1c} 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\textsubscript{1c}) level of 10.7% ± 0.3%, and, more recently, the mean Hb A\textsubscript{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 malabsorption, and steatorrhea, results in excessive fecal fluid losses.\(^3\) Faster cycling of the bile salt pool reported after cholecystectomy may lower the diarrheal threshold as well.\(^3\) 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\(^6\) or after pyloric- and gastric-preserving pancreatic resection.\(^3\)

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.\(^3\) In addition the altered homeostatic balance of intestinal ion transport favors secretion.\(^3\) 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.\(^7\) In addition deficiencies of fat-soluble vitamins\(^3\) and trace elements\(^3\) 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\(^3\) 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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 sequela of insulin therapy reported in several large surgical series.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{51,52} Indeed basal glucagon replacement induced a further significant reduction in tissue insulin responsiveness.\textsuperscript{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, glucagon in totally pancreatectomized patients.\textsuperscript{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\textsuperscript{55} or delayed\textsuperscript{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,\textsuperscript{37} the absence of an increase in blood glucose during arginine infusion,\textsuperscript{58,59} and the abnormally elevated concentrations of the major glucogenic amino acids that decrease with physiologic glucagon replacement.\textsuperscript{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.\textsuperscript{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.\textsuperscript{52,63} 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 lipogenesis. The impact of the altered hormonal milieu of the postpancreatectomy state on hepatic lipogenesis is now being studied in our laboratory.
References


