ORIGINAL ARTICLE

Long-term Metabolic Results After Pancreatic Resection for Severe Chronic Pancreatitis

Thierry Berney, MD, MSc; Tatiana Rüdisühli, MD; José Oberholzer, MD; Aileen Caulfield, MD; Philippe Morel, MD

Hypothesis: Type and extent of pancreatic resection have little effect on long-term development of diabetes in patients with chronic pancreatitis (CP) considering the distinctive relentless progression of the disease.

Design: A case series of consecutive patients included over a 10-year period. Median duration of follow-up was 6.3 years. Follow-up of survivors was at least 5 years (median, 7.7 years).

Setting: A referral center in a university hospital.

Patients: All 68 patients (57 men and 11 women) who underwent pancreatic resection for CP during the study period were included. Median age of patients was 44 years. Complete follow-up was obtained for all patients.

Interventions: Resection procedures included 35 proximal pancreatoduodenectomies (51%), 31 distal pancreatectomies (46%), and 2 total pancreatoduodenectomies (3%). Four patients (6%) received autologous intraportal islet transplants.

Main Outcome Measures: Time from surgery to introduction of insulin therapy or death, perioperative morbidity and mortality, and pain control.

Results: Fifty-one patients (75%) had experienced acute episodes of CP 5 months to 13 years before resection. Perioperative mortality and morbidity were 1.5% and 21.0%, respectively. Satisfactory long-term pain control was achieved in 61 patients (90%). Actuarial survival was 54% at 10 years and was significantly worse for patients with alcoholic CP (48% vs 78%; $P=.04$). Diabetes-free survival was 26% at 10 years, with no difference according to type or extent of pancreatic resection.

Conclusions: Pancreatic resection for severe CP is safe and has good long-term results on pain control but is performed late in the course of disease. Earlier resection and islet of Langerhans autotransplantation should be considered for patients who are inexorably heading toward diabetes, regardless of type and extent of resection performed.

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From the Clinic of Digestive Surgery and Transplantation Unit (Drs Berney, Rüdisühli, Oberholzer, and Morel) and the Division of Diabetology (Dr Caulfield), Geneva University Hospital, Geneva, Switzerland. Dr Berney is now with the Diabetes Research Institute, University of Miami, Miami, Fla.

THE MANAGEMENT of chronic pancreatitis (CP) has seen few recent advances and continues to be a challenge. This disease is characterized by intractable pain, in most cases in a context of chronic alcohol intoxication. Pain is thus the major indication for surgery and is often associated with local complications of the disease.

Controversy still exists regarding the optimal timing for surgery in these patients, but by the time they are referred to the surgeon, patients are often in a state of opiate and alcohol addiction, denutrition, and sometimes diabetes or exocrine insufficiency.[1-3] There is also some debate concerning the best type of surgical procedure to use. Pancreatic resection is uncontestedly indicated for local complications of CP, such as symptomatic or expanding pseudocysts, venous thrombosis of the portosplenomesenteric axis, biliary or duodenal compression, or pseudoaneurysms, and for suspicion of neoplasia.[1] Resection is highly effective for pain control, but using the various procedures at hand leads to significant sequelae, such as splenectomy or pancreatic endocrine or exocrine failure,[4] although more conservative procedures such as pylorus- or duodenum-preserving pancreatoduodenectomy have recently been developed.[5,6] Derivative procedures to decompress pseudocysts or obstructive ducts, such as pancreaticojejunostomy or cystojejunostomy, might seem more conservative in terms of function. However, reintervention for pain relapse after derivative procedures

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PATIENTS AND METHODS

Computerized medical records of all patients admitted to Geneva University Hospital, Geneva, Switzerland, between January 1, 1984, and December 31, 1993, with a diagnosis of CP and having undergone pancreatic resection were retrospectively reviewed. Only patients whose histopathologic report showed CP in the absence of pancreatic malignancy were considered. Inclusion of patients was discontinued as of December 31, 1993, to have at least 5-year follow-up for survivors. No patient had undergone previous pancreatic resection.

Preoperative data reviewed included cause of CP, medical and surgical history of CP, clinical variables (symptoms, diabetes, and exocrine insufficiency), and morphologic variables. Perioperative variables examined were indication for surgical resection, type of pancreatic resection performed, morbidity, and mortality. The cause of CP was classified as alcoholic or nonalcoholic. For accuracy purposes, the start of the disease was defined as the date of the first hospitalization for CP-related treatment. Acute episodes that occurred more than 3 months before the hospitalization during which surgery was performed were considered to be previous bouts of CP, whereas more recent attacks (<3 months) were arbitrarily considered to be part of the current episode.

Four types of resection were performed: (1) proximal pancreatoduodenectomy, with the Traverso-Longmire pylorus-preserving technique being preferred in the absence of a medical history of peptic ulcer disease, in which cases a Whipple procedure was performed; (2) minor distal pancreatectomy, with a resection left of the mesenteric vessels, and removing approximately 40% of the gland; (3) major distal pancreatectomy, with a resection extending beyond the mesenteric vessels, and removing approximately 80% to 95% of the gland; and (4) total pancreatoduodenectomy. In the last 2 years of the study, the technique of islet autotransplantation became available at our institution and was considered for the 2 latter groups. In these cases, vascularization of the pancreas was preserved until removal of the gland. Islet isolation was performed immediately by the automated collagenase digestion method described by Ricordi et al,[14] and the unpurified digest was infused into the liver via a right colonic vein under continuous monitoring of the portal pressure.

Perioperative morbidity and mortality were calculated 30 days after surgery or at the time of hospital discharge, whichever came last. Only patients with complications of grade II or higher according to the classification of Clavien et al[15] were considered for morbidity analysis. Briefly, complications requiring only minimal medical treatment and resulting in a hospital stay shorter than twice the median hospitalization of the series (grade I) were excluded. According to this classification, postoperative diabetes and steatorrhea were not considered complications, but sequelae.

Long-term follow-up was obtained by 2 different methods for each patient: (1) telephone interview with the patient or, in cases of death, his or her spouse and (2) written questionnaire sent to the family practitioner in charge of the patient. All interviews and questionnaire analysis were conducted by the same investigator (T.R.). In cases of rehospitalization, medical records were obtained and reviewed. Variables examined were date and cause of death, date and cause of rehospitalization or surgical reintervention, occurrence of diabetes and date of initiation of insulin treatment, occurrence and treatment of subjective exocrine insufficiency (diarrhea), pain control, and weight curve.

Seventy-two patients were identified. Complete follow-up was obtained for 68 patients (94%), with median follow-up of 6.3 years including deceased patients and 7.7 years for survivors alone. These 68 patients constitute the study group. There were 57 men and 11 women, with a median age of 44 years (range, 25-75 years) at the time of pancreatic resection.

Statistical analysis was performed using a statistical software package (Statistica; Statsoft, Tulsa, Okla). Actuarial survival and diabetes-free survival curves and confidence intervals were obtained with the Kaplan-Meier model. Differences between Kaplan-Meier curves were assessed with the log-rank test. Differences were considered statistically significant at $P<.05$.

is not rare because pain seldom seems to be due to cystic or pancreatic duct distension alone.[1,7,8] The minimally invasive approach combining endoscopic stenting with extracorporeal shock wave lithotripsy has not yet been shown to offer long-lasting relief of symptoms, and randomized trials against surgery are not available.[9]

Thus, it seems that the pursuit of pancreatic tissue conservation in severe cases of CP is a difficult goal to achieve and that most of these patients will eventually undergo pancreatectomy, with total removal of the gland in some cases. Pancreatectomized patients develop a type of diabetes that is particularly difficult to manage, because in addition to a complete suppression of insulin secretion they have total absence of glucagon counterregulation, which puts them at risk for severe and prolonged hypoglycemic events. However, the certainty of developing postpancreatectomy diabetes must be balanced with the high rate of diabetes (approximately 50% five years after onset) observed in the natural history of CP, even in the absence of surgery.[10]

From another standpoint, results of islet autotransplantation after extensive pancreatic resection are rapidly improving.[11-13] As this promising procedure is gaining recognition, it is becoming a clear option for the prevention, or at least the control, of the serious adverse effects of total or near-total pancreatectomy.

Long-term data regarding the development of diabetes after pancreatic resection for CP are scant. In this study, we put surgical resection in perspective with the history of CP by looking at medical history since onset of disease and long-term survival, with particular emphasis on diabetes development. Data were analyzed according to the cause of the disease and the type and extent of pancreatic resection.

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Table 1. Indications for Surgical Resection in 68 Patients With Chronic Pancreatitis*

Indication	Patients, No. (%)
Pain	61 (90)
Pseudocysts	55 (81)
Complicated pseudocysts†	15 (22)
Venous compression or thrombosis‡	38 (56)
With segmental portal hypertension	20 (29)
Main bile duct compression	13 (19)
Gastroduodenal compression	11 (16)
Pancreatic fistula	5 (7)
Pseudoaneurysms§	5 (7)
Arterial stenosis or thrombosis‖	3 (4)

**Most patients had several complications.*
†*Complicated pseudocysts included infected, ruptured, or bleeding pseudocysts.*
‡*Thrombosis or compression of 1 or more veins of the splenomesentericoportal axis.*
§*Pseudoaneurysms of the pancreaticoduodenal arcades or the splenic artery.*
‖*Stenosis of the celiac artery; thrombosis of the splenic artery.*

Table 2. Types of Pancreatic Resection and Associated Surgical Procedures Performed in 68 Patients With Chronic Pancreatitis

Pancreatic Resection	Patients, No. (%)	Associated Procedure	Patients, No. (%)
Proximal pancreatoduodenectomy	35 (51)		
Pylorus preserving	26 (38)		
Classic Whipple	9 (13)		
Left splenopancreatectomy	31 (46)	Pancreaticojejunostomy	6 (9)
Limited resection	13 (19)	Cystojejunostomy	6 (9)
Extended resection	18 (26)	Hepaticojejunostomy	1 (1)
		Intraportal islet autotransplantation	3 (4)
Total pancreatectomy	2 (3)	Intraportal islet autotransplantation	1 (1)
Pylorus preserving	1 (1)		
Whipple procedure	1 (1)		

RESULTS

MEDICAL HISTORY

Exaggerated alcohol intake was the main cause of CP and was observed in 56 patients (82%). Other causes included familial hyperlipidemia (n=1), trauma (n=1), and pancreas divisum (n=1). Nine cases (13%) were idiopathic.

Previous recorded symptomatic episodes had occurred in 51 patients (75%), whereas CP was diagnosed in the remainder (25%) at the time of hospitalization for pancreatic resection. Patients with a history of CP had experienced 1 to 9 episodes (median, 2 episodes) 5 months to 13 years (median, 1.8 years) before resection. Of these patients, 16 had undergone 22 surgical procedures 5 months to 12 years previously (median, 1.2 years), including 16 percutaneous procedures (pseudocyst drainage and peritoneal lavage) and 6 laparotomies (pancreaticojejunostomy, n=1; gastrojejunostomy, n=1; cholecystectomy, n=2; and explorative laparotomy, n=2). In addition, 26 surgical procedures were performed in 22 patients in the 3 months before pancreatic resection, including 21 percutaneous procedures (pseudocyst drainage and peritoneal lavage), 1 endoscopic cystogastrostomy, and 4 laparotomies (cystojejunostomy, n=1; surgical sphincterotomy, n=2; and ethanol splanchnicectomy, n=1).

Table 3. Significant Complications After Pancreatic Resection for Chronic Pancreatitis

Complications	Patients, No.
Intra-abdominal	
Abdominal collection	6
Biliary leak	3
Intra-abdominal hemorrhage	1
Splenic vein occlusion	1
Other	
Pulmonary embolism	2
Lung atelectasis	1

SURGICAL INTERVENTION: INDICATION AND TYPE

The most frequent signs and symptoms at the time of pancreatic resection were abdominal pain (n=61, 90%) and weight loss (n=37, 54%). Other complaints included vomiting (n=13, 19%), ascites (n=11, 16%), fever (n=7, 10%), jaundice (n=6, 9%), and diarrhea (n=4, 6%). Indications for pancreatic resection are summarized in **Table 1**.

Types of pancreatic resections and associated surgical procedures are shown in **Table 2**.

MORBIDITY AND MORTALITY

Fourteen patients had significant postoperative complications (morbidity, 21%) (**Table 3**), with 1 death due to massive intra-abdominal hemorrage (mortality, 1.5%). Percutaneous or open surgical procedures were performed in 11 of these patients in the perioperative period. The median postoperative hospital stay was 17 days (range, 6-60 days).

LONG-TERM RESULTS

During follow-up, 29 patients (43%) were rehospitalized for recurrence of CP-related symptoms or for late morbidity of the surgical procedure. These hospitalizations led to 16 new surgical or invasive procedures in 9 patients (13%).

At the time of the interview, or just before death, 42 patients (62%) had perfect pain control (no abdominal pain without analgesia). Nineteen patients (28%) had persisting chronic abdominal pain requiring mild and intermittent analgesic treatment and 6 (9%) had recurring bouts of acute abdominal pain requiring occasional opiate-based analgesia. The 6 patients with significant pain had all undergone proximal pancreatoduodenectomy; only 1 of them developed insulin-requiring diabetes.

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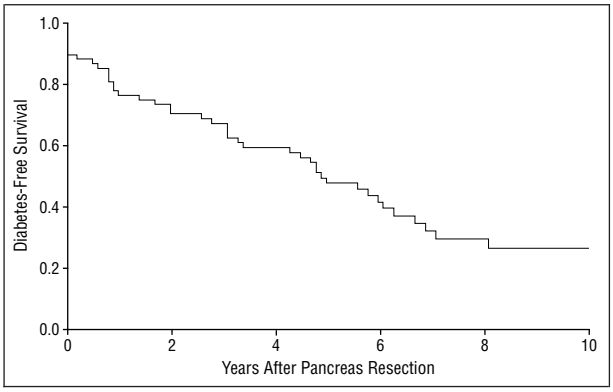

Figure 1. *Kaplan-Meier analysis of insulin-independent diabetes-free survival after pancreatic resection for chronic pancreatitis (n=64). Four patients who underwent islet of Langerhans autotransplantation were excluded from analysis. Diabetes-free survival is calculated as of date of resection. Date of death and definitive introduction of insulin therapy were considered for analysis.*

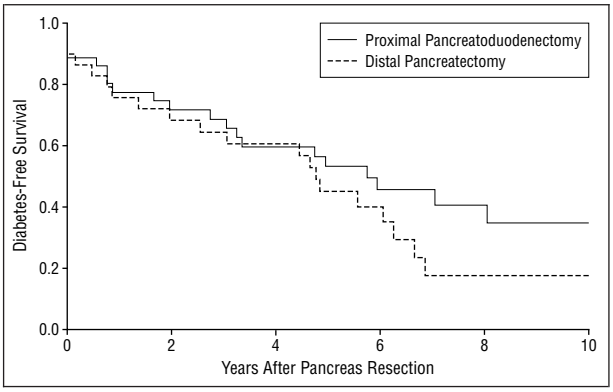

Figure 2. *Kaplan-Meier analysis of insulin-independent diabetes-free survival is similar after proximal pancreatoduodenectomy (n=35) or distal pancreatectomy (n=29) (P>.5). Two patients with total pancreatectomy are included in the latter group because it involves resection of the endocrine-rich tail of the pancreas. Patients who underwent islet of Langerhans autotransplantation were excluded from analysis. Diabetes-free survival is calculated as of date of resection. Date of death and definitive introduction of insulin therapy were considered for analysis.*

Exocrine dysfunction was present to some extent in 43 patients (64%), 34 (51%) of whom were receiving pancreatic enzyme substitution treatment and 9 (13%) of whom complained of chronic diarrhea without enzymatic treatment. Simultaneous endocrine and exocrine insufficiency was present in 31 patients (46%). Body weight since the intervention had been stable for 40 patients (60%) or increasing for 7 patients (10%), whereas 20 patients (30%) had lost weight.

The patient who died in the perioperative period was not considered for long-term results analysis.

DIABETES

Before pancreatic resection, 6 patients had diabetes, 3 of whom required insulin therapy. The remaining 3 patients were treated with oral antidiabetic drugs or diet. Patients had onset of diabetes 6 months to 14 years before pancreatic resection.

Immediate postoperative diabetes was observed in 22 patients (32%), including 6 who were already diabetic before the intervention. However, 10 of these patients (15%) had normal blood glucose levels without medication use at the time of discharge. The other patients were discharged with insulin therapy (n=7, 10%) or oral antidiabetic drug treatment (n=5, 7%).

At the time of follow-up interview (or death, for deceased patients), 45 patients (67%) were taking antidiabetic medications, including 32 (48%) taking insulin. Insulin-independent diabetes-free survival was 76% at 1 year, 48% at 5 years, and 26% at 10 years, with a median of 4.9 years (95% confidence interval, 3.3-6.3 years) (**Figure 1**). There was no difference in diabetes-free survival when patients were analyzed according to type of pancreatic resection (**Figure 2**), extent of pancreatic resection (**Figure 3**), or cause of CP (data not shown).

SURVIVAL

Twenty-seven patients (40%) died during follow-up, a median of 4.8 years (range, 0.2-11.6 years) after pancreatic resection. The most frequent causes of death were

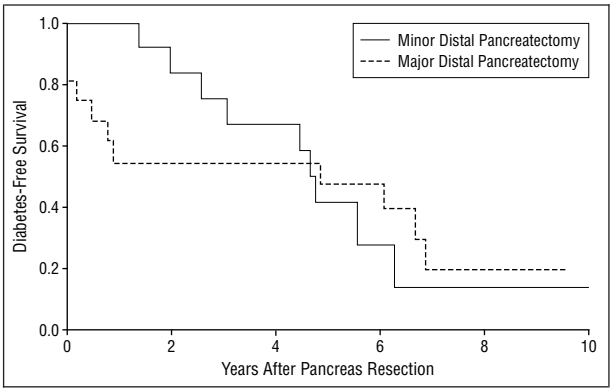

Figure 3. *Kaplan-Meier analysis of insulin-independent diabetes-free survival is similar after minor (n=13) or major (n=16) distal pancreatectomy (P>.5). Two patients with total pancreatectomy are included in the latter group. Patients who underwent islet of Langerhans autotransplantation were excluded from analysis. Diabetes-free survival is calculated as of date of resection. Date of death and definitive introduction of insulin therapy were considered for analysis.*

cardiovascular disease (n=6), extrapancreatic malignancy (n=6), infection (n=5), and liver failure (n=3), in a context of long-term tobacco or alcohol abuse in every case. Overall actuarial survival was 97% at 1 year, 78% at 5 years, and 54% at 10 years, with a median survival of 10.5 years (95% confidence interval, 7.4-13.5 years). Actuarial survival was significantly worse for patients with alcoholic CP (48% vs 78% at 10 years; $P=.04$) (**Figure 4**), but type and extent of pancreatic resection had no effect on survival (data not shown).

COMMENT

Severe CP is a self-sustained disease that seems to follow a relentless course regardless of the type of medicosurgical therapies applied. In addition, most patients with CP have chronic alcoholism and several concurrent pathological conditions that affect their prognosis. Indeed, the only factor affecting long-term outcome of severe CP is alcoholic etiology, which is associated with

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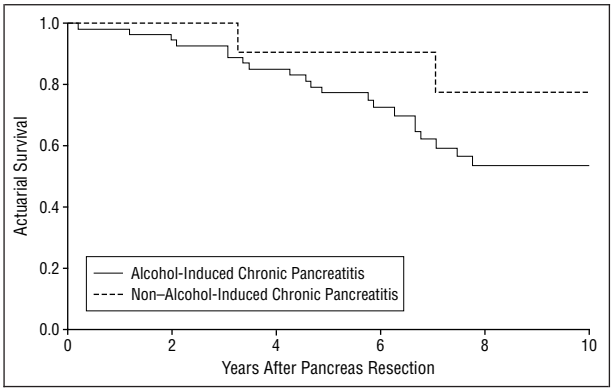

Figure 4. *Actuarial survival after pancreatic resection in patients with alcohol-induced (n=56) or non–alcohol-related (n=12) chronic pancreatitis (Mantel-Cox log-rank test,* P *=.04).*

significantly higher mortality.[16] The most remarkable finding of this study is the almost identical long-term time pattern of endocrine failure, when patients were stratified by cause of CP but more interestingly by type and extent of pancreatic resection. The overall 10-year diabetes-free survival rate of 25% we report compares with the figure of 74% diabetes incidence after a median observation time of 5.7 years in a mixed medicosurgical series of 145 patients.[10] The absence of difference in a Kaplan-Meier analysis of diabetes-free survival according to localization and extent of pancreatic removal has not been previously reported, but it suggests that the eventual development of diabetes is more a reflection of the natural history of the disease than of the amount of pancreatic tissue removed.[17]

Several points of debate exist regarding optimal surgical treatment of CP. Whereas the indications for surgery are reasonably well established, there is still some controversy concerning the timing and the type of surgery to be offered. However, according to conventional wisdom, as a palliative procedure on an already functionally impaired gland, it should be as conservative as possible to limit the occurrence especially of endocrine failure. On the other hand, several local complications of CP are undisputed indications for pancreatic resection, including suspicion of carcinoma, ductal or duodenal compression, venous thrombosis, arterial pseudoaneurysms, and expanding pseudocysts.[1] Intractable pain is the most common symptom leading to surgery, and, in an oversimplified modelization, most surgical teams will perform a derivative procedure in the presence of a dilated pancreatic duct and a resection in the other situation. In this series, pain was present in 61 patients (90%) but was the sole indication for resection in only 3 (4%). The prospects of endocrine failure after surgical resection are of particular concern when the disease is in the body or tail of the pancreas, where most of the endocrine tissue is located. However, if surgical decompression by lateral pancreaticojejunostomy frequently offers pain relief in patients with dilated pancreatic ducts, it might be only temporary and require reintervention[8] because the pathological substrate of pain in CP is multifactorial. Direct and indirect damage to nerves located around and within the pancreatic inflammatory mass plays a significant role in pain generation[18] and is unlikely to be solved by a derivative procedure. Pancreatojejunostomy is of no value in the absence of ductal dilation.[19] On the other hand, distal pancreatectomy and pancreatoduodenectomy have been associated with growing safety and with mortality rates of less than 1%,[20,21] and satisfactory long-term pain control is achieved in more than 90% of patients after resection.[2,22] Our results are in accordance with these data. Long-term analysis of pain control rarely exceeds 5 years in the surgical series[2,22] but is a good reflection of the efficiency of surgery because other factors seem to play a role after longer follow-up. Mixed medicosurgical series[23,24] with median follow-up greater than 10 years report spontaneous achievement of complete pain relief in all patients with advanced CP, independent of a history of surgery, when the pancreas reaches a final state of total "burnout."

It is a striking observation of this study that most patients had experienced several acute bouts of CP, with a history of disease that could be traced to up to 13 years before resection, and had required several percutaneous or open surgical procedures. Although the retrospective nature of this study commands cautiousness in the interpretation, this arguably shows that patients with CP are often deferred late to the surgeon and that a variety of "conservative" surgical procedures are performed, sometimes unnecessarily delaying definitive surgical resection.

This series includes 4 patients who underwent autologous islet of Langerhans transplantation. No conclusion can be drawn from the analysis of this small number of patients, who represent our preliminary experience with the procedure and who remained insulin independent for 1, 3, 4, and 5 years. We have now performed 13 islet autotransplantation procedures after pancreatic resection and have achieved durable or temporary insulin independence in 11 patients who remained insulin independent for more than 6 months. Two years after transplantation, 5 of 9 patients were still insulin independent.[12,25,26] A recent review[27] estimates that approximately 50% of patients undergoing total or subtotal pancreatectomy could be rendered insulin independent by intraportal autologous islet transplantation. In the largest series[11] published so far, the Minneapolis group reports insulin independence in 34% of patients after 2- to 10-year follow-up, but remarkably with no graft failure occurring after 2 years. Moreover, glucose counterregulation and hypoglycemic warning mechanisms have been shown to be markedly improved in islet transplant recipients, even in the absence of insulin independence.[28] As considerable advances have recently been made, notably in islet isolation techniques and primary nonfunction understanding, and are likely to amplify, there is growing optimism regarding the overall improvement of islet autotransplantation results.[13]

Comprehensive analysis of the data presented leads to the conclusion that many patients with severe CP could be offered pancreatic resection earlier in the course of their disease than what is currently observed. Such aggressive attitudes could prevent a patient population already experiencing numerous coexisting pathological conditions from undergoing repeated and sometimes temporary or useless surgical procedures and could of-

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fer long-lasting pain relief to many. Because the extent or localization of resection does not seem to affect long-term development of diabetes, and in view of the increasingly successful results of islet autotransplantation, one could provocatively argue that early, extensive pancreatic resection would provide more and healthier islets for autologous grafting in these patients, who are unrelentingly heading for diabetes of a kind that is particularly difficult to regulate.

Reprints: Thierry Berney, MD, MSc, Diabetes Research Institute, University of Miami, 1450 NW 10th Ave, Miami, FL 33136 (e-mail: tberney@med.miami.edu).

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Quotation

The surgeon who is his own physician, though he often has a fool for a colleague, has the happiness of working in an atmosphere of mutual confidence and admiration.

Sir Heneage Ogilvie

Reference: *Lancet*. 1948;2:1.

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