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Progressive Loss of Pancreatic Function in Chronic Pancreatitis Is Delayed by Main Pancreatic Duct Decompression

A Longitudinal Prospective Analysis of the Modified Puestow Procedure

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Objective
This study evaluated the effect of operative drainage of the main pancreatic duct (MPD) on functional derangements associated with chronic pancreatitis (CP).

Summary Background Data
The author previously reported delayed functional impairment in an evaluation of the impact of operative drainage in patients with CP. The author now reports on a prospective study of 143 patients with this diagnosis.

Methods
Each patient underwent 1) ERCP, 2) the Bentiromide PABA, 3) 72-hour fecal fat test, 4) oral glucose tolerance test (OGTT) and 5) fat meal (LIPOMUL)—stimulated pancreatic polypeptide release (PP). All patients were stratified as mild/moderate (M/M) or severe CP on the basis of a 5-point system that was developed by the author. Patients were studied at 16-month intervals.

Results
All 143 patients underwent initial and follow-up evaluations in a mean follow-up of 47.3 months; 83 of 143 patients had M/M grade at initial evaluation. Eighty-seven patients underwent (MPD) decompression to relieve abdominal pain. In a separate prospective 17 patients with a diagnosis of CP, a grade of M/M and non-disabling abdominal pain were randomized to operative or non-operative treatment; 9 of these randomized patients were operated upon and 8 were not. No patient improved their grade during follow-up; 47 of 83 M/M patients had operative drainage and 36 did not. This grade was preserved in 41 of 47 (87%) operated patients but in only 8 of the 36 non-operated patients (22%). In the randomized trial, seven of nine operated patients retained their functional status in follow-up, whereas only two of eight patients (25%) randomized to non-operation preserved their functional grade.

Conclusions
These data in this large study as well as among a previous randomized sample, support a policy of early operative drainage before the development of irreversible functional impairment in patients with chronic pancreatitis and associated dilation of the main pancreatic duct.

Chronic pancreatitis (CP) is associated with one or all of a triad of abdominal pain, exocrine insufficiency, and endocrine insufficiency. As the disease progresses, the functional deficits result in the clinical entities of pancreatic malabsorption and steatorrhea as well as insulin-dependent diabetes mellitus. Efforts had long been made to prove that operative drainage improved functional status by liberating obstructed pancreatic juice.[1-3] Studies did not provide any evidence of improved function after drainage although occasional anecdotal reports of isolated improvement in one selected endocrine or exocrine functional test have been made.[4,5] Exocrine insufficiency can be properly treated with pancreatic enzyme supplements. The diabetes mellitus of CP can be more challenging due to characteristically wide variations in blood glucose levels. Insulin therapy can stabilize these patients somewhat. Unrelenting abdominal pain, often causing narcotic habituation, has been a greater clinical challenge. The universally recognized singular indication for operation in this patient population has been relief of abdominal pain.[3,6-8] We previously reported on 85 patients in this study population with a minimum of two visits in 68 patients and a mean follow-up of 14 months.[9] Our data provided the first prospective, uniform evaluation of pancreatic function in a controlled population of operated and non-operated patients. In this early report[9] a significant delay in functional impairment was enjoyed by the operated patients.

Operative procedures for the treatment of the abdominal pain associated with CP are classified as either resectional (partial or total pancreatectomy), or decompressive, most commonly represented by the side-to-side longitudinal pancreaticojejunostomy (modified Puestow procedure). Both types of operative procedures control pain successfully in 60–90% of patients.[3,6,8]

One challenge to an organized evaluation of patients with a diagnosis of CP has been the absence of an accepted means of stratifying patients on the basis of severity of disease. For that reason a system for grading the severity of functional impairment of CP patients was developed.[9,10] This system (Table 1) uses an evaluation of morphology (ERCP), two measures of exocrine function (72-hour fecal fat test and the Bentiromide-PABA test) and two endocrine measures (oral glucose tolerance test and lipomul meal-stimulated pancreatic polypeptide release). On the basis of these tests, patients are categorized as either mild/moderate (M/M) grade of CP or severe (S) grade. Patients with a diagnosis of CP underwent initial evaluation and a grade of either mild/moderate (M/M) or severe (S) CP was assigned. A decision was made regarding an operation and operation was performed soon after initial evaluation. Follow-up evaluation was planned for 14–16 intervals after enrollment and thereafter in a longitudinal manner.

Table 1. METHODS: 5 POINT SYSTEM TO GRADE SEVERITY OF CP

Test	Threshold	Points Assigned
ERCP	Cambridge "severe"	1
OGTT/insulin	Abnormal hyperglycemia	1
Lipomul PP	Flat response	1
72-hour fecal fat	More than 7 g/24°	1
Benteromide/PABA	Less than 50% absorption	1
		Total 5 points

System for grading the severity of chronic pancreatitis is based upon 5 measures, 0, 1, or 2 points = mild/moderate grade, 3–5 points = severe grade. Each of 5 tests fast stimulated pancreatic polypeptide (PP), oral glucose tolerance test (OGTT), Bentiromide PABA, 72-hour fecal fat (72-h FF), and endoscopicretrograde-cholangiopancreatography (ERCP) are performed. Abnormal results in each test is assessed 1 point.

METHODS

Beginning in September 1984 all patients were included in this study after a diagnosis of CP was established and were referred to the Pancreas Clinic at The University of Texas Medical Branch in Galveston. A total of 143 patients with the diagnosis of CP have been enrolled in an ongoing study that involves a 5–7 day stay in our Clinical Research Center (CRC) for testing. Children and prisoners were not included in this study and without exception all patients who were willing to participate were considered proper candidates for inclusion in the study. ERCP was considered diagnostic in all patients and those patients who were referred without ERCP had that procedure performed in our Surgical Endoscopy Unit.

We continue to use a protocol that was originally approved for use by the Investigational Review Board of The University of Texas Medical Branch. This protocol is reviewed and re-approved on a yearly basis. Signed written informed consent was obtained from all participants. A questionnaire is used to obtain all historical information, such as history of ethanol abuse, history of abdominal pain (character and duration), weight loss, diarrhea, fatty stools, previous operations, previous episodes of pancreatitis, diabetes and need for narcotics. Because there is a possibility of residual effect by supplemental pancreatic enzymes for a period as long as 3 days, we have as a routine stopped all pancreatic enzyme supplements 5 days before admission to the CRC. At midnight before each study, patients are kept without any

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oral intake. On separate days each patient underwent: 1) fatty meal (Lipomul,™ Upjohn Company, Kalamazoo, MI) stimulated release of pancreatic polypeptide (PP), 2) an oral glucose tolerance test (OGTT) with simultaneous measurement of insulin (by radioimmunoassay) and glucose, 3) a Bentiromide PABA test combined with d-xylose test, and 4) a 72-hour fecal fat measure (72-hour FF). Serum levels of lipase, amylase, bilirubin, and alkaline phosphatase were obtained in all patients. No patients were studied during a relapse or exacerbation of an acute inflammatory episode. As a planned part of the protocol a mean interval of 14–16 months was placed between the initial evaluation and the first evaluation and a similar interval was placed between subsequent evaluations.

PROSPECTIVE RANDOMIZED EVALUATION

On the basis of our earlier report,[9] the decision was made to undertake a prospective randomized evaluation of the impact of operative decompression upon functional deficit in patients with CP. A protocol was devised in which the diagnosis of CP was established by ERCP. Patients who had the combination of mild/moderate grade chronic pancreatitis with dilated main pancreatic duct and mild non-debilitating pain were presented with the opportunity to enroll in our randomized protocol. The patients understood that there was no definite functional benefit to be obtained from operation and were given the option of joining this separate protocol. Only the patients who agreed to undergo randomization were included in this protocol. After randomization every other aspect of the protocol was identical to the larger protocol. Patients underwent initial evaluation and grading. After an interval of 14–16 months repeat evaluation for the purpose of grading was performed. The initial plan was to recruit approximately 10 patients in each of the operated and non-operated groups and to follow those patients for several years before undertaking a broader application of the randomization.

GRADING SYSTEM

We have developed and previously described a system for the grading of the severity of disease in patients with CP.[9,10] One morphologic (ERCP), two exocrine (Bentiromide and 72-h FF) and two endocrine (OGTT and fat stimulated PP) tests were used in producing a grading system ranging from 0–5 points as adapted from our previous reports.[9] ERCP tests with advanced changes according to the Cambridge grade[11] were assessed a grade of 1. Patients in whom a pancreatogram could not be obtained by ERCP (either because of ducta, stricture, or technical failure) had an intraoperative pancreatogram performed. Abnormal results in the two endocrine and two exocrine tests were each assessed a point value of 1. Patients with 0, 1, or 2 points were given a grade of mild/moderate CP, and those with 3, 4, or 5 points were designated as severe CP (Table 1).

The Bentiromide-PABA (Chymex,® Adria Laboratories, Dublin, OH) test, commonly referred to as the Bentiromide test, and a simultaneous d-xylose test were performed as previously described.[9,10]

After an overnight fast release of PP was induced by a fatty meal (Lipomul), consisting of 71% fat by weight long-chained triglycerides, at a dose of 1.5 ml/kg body weight. Serial blood samples were obtained for later assay of PP. Release was measured by standard radioimmunoassay methods used in our laboratory.[12]

A standard oral glucose tolerance test with simultaneous measure of circulating insulin-like immunoreactivity and 72-hour FF test were performed as previously described.[9,10] Since September 1984, 143 patients with chronic pancreatitis have been studied at least two times.

CRITERIA FOR OPERATIVE OR NON-OPERATIVE THERAPY

With the exception of the smaller randomized trial that is discussed subsequently, an absolute requirement for all operations was the presence of severe abdominal pain. This pain was of sufficient severity to necessitate repeated hospitalizations, repeated visits to emergency room, and chronic use of narcotics. Often the pain was sufficiently severe to induce weight loss and to restrict the ability of the patient to maintain employment or to conduct normal activities. Certain patients were considered to be candidates for operation because of intermittent attacks that were severe and were not biochemically or clinically consistent with the diagnosis of recurrent acute pancreatitis. In these patients, the indication for operation was only achieved when the frequency and severity were both increasing and disabling. Because a requirement for drainage procedure was a significantly dilated main pancreatic duct, all candidates for operation had advanced abnormalities on ERCP by the Cambridge grading system. A threshold dilatation of 8 mm diameter in the main pancreatic duct was considered to be a requirement for candidacy for operative drainage.

The composition of the group of patients who have not had an operation was scrutinized to optimize the evaluable data. The two groups under analysis are not randomized. The differences that we have observed may not simply be based on the fact that the populations are diverse. The reasons for not operating on patients have included non-dilated MPD, non-disabling pain, patient refusal, and associated cirrhosis.

OPERATIVE PROCEDURE

The operative procedure used in all patients was a modified Puestow procedure, which is a longitudinal side-to-side Roux-en-Y pancreaticojejunostomy as described by Partington and Rochell.[13] Incision along the main pancreatic duct was made in the midbody of the pancreas and extended to the left side of the spine towards the tail of the gland and as far to the right side of the gland as the genu of the main pancreatic duct. Any ductal stones that were encountered were removed. Where indicated, the modified Puestow procedure was combined with a choledochoenterostomy. This was considered to be proper when a typical elongated stricture in the distal (intra-pancreatic) common bile duct was associated with right-sided abdominal pain and persistent elevation of serum alkaline phosphatase to levels > 450 IU/L. Pseudocyst drainage was used in all patients with associated pseudocyst. Patients with a mass affect causing some degree of duodenal obstruction underwent gastrojejunostomy. This latter addition was rarely required.

RESULTS

A total of 143 patients have been enrolled in this protocol. All have had a diagnosis of CP established by ERCP. The mean age of all participants was 43.7 years. There were 95 men and 48 women enrolled in the protocol. Among the 143 patients, 134 or 94% have had a history of ethanol abuse. The remaining 9 patients had a diagnosis of idiopathic chronic CP; 71 patients or almost half of the patients with a history of ethanol abuse are currently drinking. This distribution of continued ethanol abuse was evenly represented in both the operated and the non-operated population (Table 2). The mean duration of diagnosis of CP in this group was 9.2 years. Many have presumed that CP is a result of recurrent episodes of acute pancreatitis, but our data support those of Ammann et al. who have suggested that chronic pancreatitis occurs independent of recurrent acute pancreatitis.[14] Only 34 of our 143 patients had previous hospitalizations for acute pancreatitis.

Table 2. STUDY PARTICIPANTS

Number of patients	143
Mean age	43.7 years
Male/female	95/48
Ethanol abuse	134 patients
Ideopathic CP	9 patients
Currently drinking	71 patients

Population characteristics of patients with the diagnosis of chronic pancreatitis who have been enrolled in the longitudinal study.

One hundred and two of the 143 patients who were enrolled in this protocol had weight loss and weighed less than their ideal body weight; 131 of the 143 patients required narcotics for treatment of chronic abdominal pain at the time of the initial survey. Forty-one of the 143 patients were insulin dependent at initial evaluation. Each of these characteristics were comparably distributed between operated and non-operated patients.

During a mean follow-up of 47.3 months, the 143 patients returned for a mean total number of study 3.6 visits. At the time of initial evaluation, 83 patients were classified as mild/moderate CP, whereas 60 patients had advanced to severe CP. Among these groups, 8 patients had 0 points, 14 patients had 1 point, and 61 patients had 2 points. There were 9 patients with 3 points, 22 patients with 4 points, and 29 patients with 5 points. No patient died in the peri-operative period; 87 patients underwent operative drainage of the main pancreatic duct and this was combined with either biliary drainage or gastric drainage when appropriate. Pain relief was achieved in 74 of the 87 operated patients for a rate of 85%. Spontaneous pain relief among the non-operated patients was seen in 1 of 56 non-operated patients for a rate of 1.3%. During the entire length of follow-up, 14 of the 143 patients or 9.8% died. Three of these patients died of adenocarcinoma of the pancreas, each time more than 3 years after enrollment in the protocol suggesting that this is an example of adenocarcinoma associated with the diagnosis of chronic pancreatitis and not simply a misdiagnosis. None of the deaths were related to the pancreatic operations. Six deaths occurred in the non-operated group and 8 deaths occurred in the operated group.

CHANGES IN GRADE AMONG PATIENTS IN THE TWO STUDY GROUPS

In our large population, no randomization process was applied to patients who underwent operation and to those who did not. Among the 60 patients initially graded as severe CP, 40 patients underwent operation and drainage of the MPD and 20 patients with severe disease did not undergo operation. No patient in either the operated or non-operated group who were originally designated as severe CP had sufficient improvement in function in follow-up to achieve a designation of M/M disease. Of the 83 patients initially designated as M/M disease, 47 have had an operative drainage procedure and 36 have not. All operated and non-operated patients have been evaluated in follow-up; 41 of the 47 operated patients had preserved their functional status as M/M CP through the intervals after operation. In the group of 36 patients with M/M disease who did not undergo operation, only 8 of 36 or 22% continue to enjoy that grade of

CP in follow-up testing. Thus only 6 of 47 or 13% of the operated patients with M/M disease underwent a progressive loss of function during the follow-up period, whereas 28 of 36 or 78% of patients who were not operated upon and originally had a designation of M/M CP progressed to severe disease in follow-up (Table 3). The difference in sustained pancreatic function between the group of M/M patients who were operated on (41 of 47, or 87%) and the group who did not undergo operation (8 of 36, or 22%) was significant by Chi-square analysis. The mean follow-up for the group who underwent operation was 49.2 months, and the mean follow-up for the group who were not operated upon was 46.7 months.

RANDOMIZED TRIAL

A total of 17 patients were recruited for the prospective randomized trial. Of these patients, 9 have undergone operation and 8 were randomized to non-operative care. The mean follow-up of this group of patients is 39.2 months. The mean follow-up between the operated and non-operated randomized group was not different. As a requirement of the randomized protocol all patients participating in this protocol were graded as M/M CP at initiation. Thus of the 9 patients with M/M disease who were randomized to operative drainage, 7 patients or 78% continued to reflect this degree of functional impairment in follow-up studies. This number contrasts with the percentage who have retained function in the non-operated randomized group. Among the eight patients with M/M disease who were randomized to non-operative management only two of eight or 25% continued to enjoy this status of pancreatic function in follow-up visits. Only two of nine operated patients who were randomized to this category had progression of the severity of disease over follow-up. Six of eight patients who were randomized to non-operative care advanced to severe chronic pancreatitis during the follow-up period (Table 4).

Table 3. CHRONIC PANCREATITIS

	Follow-Up Mild/Moderate (n = 83)		
	Initial Evaluation	Follow-Up	Progressed To Severe
Operated	47/47	41/47 (87%)	6/47 (13%)
Non-operated	38/36	8/36 (22%)	28/36 (78%)

Eighty-three patients were initially graded as mild/moderate chronic pancreatitis. The changes in severity grade from initial evaluation to follow-up for mild/moderate stage in operated and non-operated patients.

Table 4. CHRONIC PANCREATITIS: PROSPECTIVE EVALUATION OF MILD/MODERATE WITH MINIMAL PAIN

	Initial Evaluation	Follow-Up
Operated	9.9 (100%)	7/9 (78%)
Nonoperated	8/8 (100%)	2/8 (25%)
	Mean follow-up of 39 months	

The change in severity grade from initial evaluation to follow-up for mild/moderate stage chronic pancreatitis in patients randomized to operation or non-operation.

DUCTAL DILATATION

In view of the fact that the scoring system that was employed throughout this study should have successfully categorized patients on the basis of severity of disease, it is necessary to scrutinize the operated and non-operated group regarding other possible factors that might influence the outcome of these studies. One such characteristic is ductal diameter, which is uniformly dilated in the operated patients while a subset of the non-operated patients were not operated specifically because of non-dilated main pancreatic duct. For that reason, this variable was separately evaluated. Small duct chronic pancreatitis was defined as being a duct less than 5.0 mm. Thirty of 143 or 21% of the total population had small duct chronic pancreatitis; 113 patients, 87 of whom underwent operation and 26 of whom did not, had large duct chronic pancreatitis. Once again no patient with large or small duct chronic pancreatitis and a grade of severe CP had improvement in functional status after follow-up. In the subset of patients initially rated as M/M CP, 47 patients with large duct chronic pancreatitis underwent operation. As is previously stated 41 of the 47 or 87% of patients with large duct chronic pancreatitis who underwent operation continue to rate grade (M/M) in follow-up. The 14 patients with large duct chronic pancreatitis and an initial grade of M/M fared poorly. Only 3 of 14 or 21% maintained their functional status in follow-up. The 22 patients with small duct chronic pancreatitis who did not undergo operation and were initially rated as M/M also had an abrupt drop in functional status with only 5 of 22 or 23% maintaining their level of functional impairment in follow-up.

Some have suggested that gland calcification is a favorable prognostic indicator in patients with CP. When gland calcification was correlated with ductal diameter no clear distinction could be drawn. The 87 patients with large duct chronic pancreatitis who underwent operation had calcification noted in 63 patients or 72%. This distribution is not unlike that seen in the patients with large duct pancreatitis who did not undergo operation in

whom 18 of 26 or 69% had calcification of the gland. Among the 30 patients with small duct pancreatitis 26 or 87% had calcification of the gland.

COMPARISON OF THE TWO STUDY GROUPS

Continued ethanol abuse was monitored by an interview only and these data are reliable only in the sense that they have been obtained from each patient in a uniform manner; 71 of the 143 patients had not successfully abstained from alcohol ingestion at the time of initial follow-up. Although a number of patients stated they had successfully recovered from their alcoholism in their follow-up an approximately equal number of patients resumed their ethanol ingestion particularly at third and fourth return visits to the CRC; 43 of 87 operated patients were still abusing ethanol in follow-up; 28 patients who did not undergo operation were still drinking alcohol in follow-up. The progressive loss of function seen in the non-operated patients did not correlate with continued ethanol ingestion.

Serum lipase was the only biochemical measure that appeared to fluctuate significantly during the study period. A high percentage of patients with CP were found to have elevated serum lipase. This elevated pancreatic enzyme correlated poorly with a clinical picture of acute pancreatitis. In our laboratory 190 U/L is the high limit of normal. Mean serum lipase levels were not elevated in patients with severe CP. In the patients with M/M CP, the mean serum lipase level was 970 ± 24 U/L for non-operated patients and 1060 ± 200 U/L in the operative patients. The mean serum lipase level in follow-up for the non-operated patients who were initially classified as M/M CP were also persistently elevated at a level of 860 ± 24 U/L. In contrast, the postoperative mean serum lipase level was 136 ± 84 and these differences were statistically significant. The only other consistent biochemical abnormality was an elevation in alkaline phosphatase, which was seen in 51 patients or 36% of the entire population. In all patients, this abnormality correlated with the presence of distal common duct stricture consistent with chronic pancreatitis and resolved after drainage of the biliary tree. A history of some degree of abdominal pain was present in all patients in the study. Disabling unrelenting abdominal pain was present in all patients in the large group who underwent operation. All of the 17 patients included in the randomized trial had only minor complaints of abdominal pain. Among the patients who did not undergo operation, 40 patients of 56 or 72% had significant abdominal pain. Operative decompression resulted in relief of severe abdominal pain in 74 of 87 or 85%. Many of the patients who underwent operation had a history of substance abuse as reflected in their history of alcoholism and had developed dependence on narcotic analgesics. For that reason, a number of patients were weaned from narcotic analgesics before determining an adequate relief of pain after operation.

Repeated ERCP in postoperative patients revealed patency of the pancreaticojejunostomy in 79 of 87 patients. This number correlates to a 91% patency rate. No correlation could be established in patency and recurrence of abdominal pain. It was assumed that a Cambridge grade of severe changes by ERCP was a fixed finding after operative drainage in spite of the fact that definition of main pancreatic ductal anatomy abnormality is not possible after a pancreaticojejunostomy.

Weight loss is common in this disease. Some degree of weight loss was elicited by history in 134 of the 143 patients or 94%. When the mean percentage of ideal weight for each patient was calculated the mean percentage ideal weight among all patients was below 100%. The mean percent ideal body weight in the patients with M/M disease was 92 ± 21% for the non-operated patients at initial assessment and this measure was 84 ± 22% in follow-up. The mean percent ideal body weight for the 47 patients with M/M CP who underwent operation was 72 ± 14% at initial assessment and rose to 98 ± 17% in postoperative evaluation; 34 of the 36 non-operated patients with M/M disease had had significant weight loss at initial evaluation and lost a mean of 2.2 kg in the follow-up period. In contrast 47 of 47 patients with M/M disease who underwent operation had significant weight loss preoperatively and 31 of 47 or 66% were equal to or above their ideal body weight after operation and all patients had gained some weight since operation. Both operated and non-operated patients were treated properly for their insulin needs and for enzyme supplementation. The most common reason for continued nutritional deficit in the non-operated patients was pain after eating although a large number of the non-operated patients and of the operated patients before their operation appeared to have a resistance to nutritional supplementation which was only overcome in the operated patients after their pancreatic duct decompression.

Abnormal oral glucose tolerance has previously been shown by us to be seen commonly even in patients with early disease.[15] In spite of this fact, abnormal OGTT was distributed equally between the two groups; 32 of the 47 operated patients with M/M disease or 69% had an abnormal OGTT and 23 of the 36 non-operated M/M patients or 64% had abnormal OGTT. A flat response to Lipomul meal stimulated PP release was far more specific. This abnormality was never observed in patients with M/M disease. For that reason, we have previously stated[9,10] and continue to believe that this endocrine measure is the most specific marker for a severe disease.

Again this abnormality was evenly distributed between the two groups of severe chronic pancreatitis patients. No patient who had a flat response in PP release after Lipomul meal corrected that abnormality and had normal rises in PP after a meal in follow-up studies. Clinical steatorrhea was highly correlated with abnormal 72-hour FF; 22 of the 60 patients with severe disease or 37% had a history of steatorrhea and 26 patients had abnormal 72-hour FF. Steatorrhea was also specific for severe disease.

Main pancreatic duct pressures were measured in 67 of the 87 patients who were operated upon. The mean pancreatic duct pressures among all those measured was 21 ± 3.6 cm of H_2O. When this information is divided among the patients who sustained recurrence of their abdominal pain after their operation there is some significance to these measures. Among the 67 patients who have had ductal pressures measured intra-operatively 58 have had complete pain relief and 9 of these patients have sustained pain recurrence. The mean main pancreatic duct pressure among the 58 patients who had pain relief is 25 ± 4.9 cm of H_2O. Normal values are thought to be between 10 and 12 cm of H_2O. Among the 9 patients with pain recurrence the mean main pancreatic duct pressure was 9.5 ± 1.5 cm of H_2O. This difference is statistically significant.

DISCUSSION

Our report in 1988[9] was the first documentation of any functional advantage to be gained by main pancreatic duct drainage. This study raised the question of whether the groups were truly comparable. We have attempted to address this issue by means of our small group of controlled randomized patients with disease characteristics that were highly comparable. We have continued to work with the original group of patients with chronic pancreatitis and have now enrolled 143 patients who have been both evaluated initially and seen at intervals of 15 months follow-up. A mean follow-up for the entire population of 47.3 months offers some more interpretable data. Our data in this report support the initial observations made in 1988.[9] We have again shown that operative decompression in patients with M/M CP serves to arrest the progressive loss of function in a high percentage of patients. Some degree of functional derangement will progressively appear in these patients, but our data leave little question that the rate of loss of pancreatic function is considerably delayed by this intervention. Although it is appealing to think that liberating the obstructed pancreatic juice in the characteristically dilated pancreatic duct will result in enhanced exocrine function. We have been unable to provide data to support this supposition. One may speculate on the basis of our data, however, that persistent obstruction of the main pancreatic duct and presumably high pressures with the parenchyma of the pancreas play a role in the continued loss of function in this disease. In that sense decompression of the main pancreatic duct may simply arrest a process that otherwise inexorably proceeds to loss of function with both steatorrhea and diabetes mellitus. Our data are consistent with other reports[6–8] with regard to relief of severe abdominal pain. Our success in that regard (85%) compares favorably with previous reports. These data support the time-honored indication for operative decompression of the main pancreatic duct in CP which has been for the relief of disabling unrelenting abdominal pain. Our data further suggest, however, that preservation of both endocrine and exocrine function represents a significant and achievable goal of main pancreatic duct decompression in patients who have not yet sustained complete loss of function. Our data specifically support the previous studies supervised by Reber which have documented a rise in main pancreatic duct pressures induced by ethanol and have shown repeatedly that high intraductal pressures result in permeability in the pancreatic parenchyma to macromolecules and to progressive diminution in function caused by these elevated pressures.[16]

Our measures of pancreatic duct pressure intraoperatively document the presence of persistently elevated main pancreatic duct pressures in these patients. Our data also suggest that patients with less dilated main pancreatic duct have lower intraductal pressures and have poor results in relief of abdominal pain by decompression. This absence of high intraductal pressures in patients without main pancreatic duct dilatation suggest the possibility that a separate mechanism of pain and perhaps of progressive functional derangements may be operative. We have found a significant elevation in serum lipase levels in patients with M/M severity of disease. This observation was unexpected and correlated poorly with acute symptoms. Operative decompression of the main pancreatic duct resulted in a consistent fall in serum lipase levels towards normal. We have speculated that elevated lipase levels may be a reflection of ongoing subacute inflammation. The decrease in serum lipase that is seen after pancreatic duct decompression may reflect a reversal of this ongoing subacute inflammation process. Our data are insufficient to prove or disprove this mechanism, but the observation would seem to be consistent with the universal perception that pancreatic enzyme elevations reflect some degree of inflammation or of cell death.

Our original plan had been to limit the prospective randomized trial to 20 patients with the knowledge that a long follow-up would be necessary to identify any difference, and not wishing to subject a large number of patients to an operation which might prove to be unnec-

essary. In view of this fact we limited the enlistment to the prospective randomized trial to 17 patients, 9 of whom underwent operation and 8 of whom did not. Each of these patients were graded as M/M severity of disease at initial evaluation. We feel confident about the results of this subset who have now had a 39-month mean follow-up. Only two of the nine operated patients have progressed to severe disease whereas six of the non-operative patients have sustained a significant degree of functional derangement over the follow-up period. These data, combined with our larger group greatly fortified the observation that pancreatic duct decompression serves to protect pancreatic endocrine and exocrine function.

Studies on the impact of any therapeutic measure in the treatment of chronic pancreatitis have been challenging because of the absence of a universally accepted means of stratifying patients. A second difficulty is created by the fact that the majority of patients with this disease have a diagnosis of ethanol abuse and tend to be somewhat unreliable for follow-up. In our previous report[9] we perfected a grading system to be used in our study and hopefully to be applied broadly as a means of differentiating patients on the basis of functional derangement. We have used this measure in a number of previous reports.[9,10,12] A uniform adoption of a system for evaluating the patients with this diagnosis should be adopted. The consistent data that has been easily gathered and generated by our studies would argue in favor of this methodology.

Previous studies that have attempted to prove any change in function after pancreatic duct decompression have been based on largely isolated observations. Three studies had attempted to define an improvement in function after operative pancreaticojejunostomy.[1-3] One study simply looked at the somewhat imprecise measure of clinically apparent diabetes or clinically apparent pancreatic malabsorption.[1] A second study also evaluated ten patients, looking at C-14–labeled fat absorption.[2] These studies were performed 1–2 months after operation. Finally, a report from Japan[3] simply looked at the development of severe uncontrolled diabetes in patients after a variety of operative procedures for the diagnosis of CP. One report from Spain included a total of 70 patients with a diagnosis of chronic pancreatitis. "Improvement in steatorrhea" in four patients after operation, in three patients after alcohol abstinence, and in one patient after pseudocyst drainage was documented. The authors draw special emphasis to the combination of abnormal Bentiromide PABA tests with high serum trypsin levels.[4] Interestingly this elevation in serum trypsin may have similar importance to our finding of elevated serum lipase levels. Finally a recent study using endoscopically placed pancreatic stents has shown in 12 patients out of a total population of 120 with chronic pancreatitis that C-14 triolein breath test was improved in patients with stent placement. No long-term follow-up was available on these patients. In addition, the studies were limited to this one test of exocrine function. Only our study from 1988[9] has documented delayed loss of pancreatic exocrine and endocrine function after pancreaticojejunostomy. In an invited lectureship at the 1991 American Pancreatic Association Hans Beger reported preservation of pancreatic function in a higher percentage of patients after operation compared with those who have not undergone operation (Beger H, personal communication).

In our previous report[9] we have identified a consistent improvement in nutritional status after main pancreatic duct drainage. We have become increasingly convinced by this observation in our larger follow-up. Not only have we continued to find a significant improvement in nutritional status in operated patients compared with non-operated patients, but we have repeatedly made the observation that pre-operative patients who have had significant nutritional deficit and have been treated with nutritional supplementation have appeared to be refractory to any nutritional supplement. Only after operative drainage have these patients been able to benefit from the dietary supplements. We equally distribute pancreatic enzyme supplements where required in both the operated and non-operated groups.

We are unable to provide any data to document this phenomenon beyond the effect on ideal body weight. Some degree of increased metabolic rate, which is induced by the subacute inflammatory process, may be reversed by operative drainage. Operative drainage consistently results in improved nutritional status in patients, apparently independent of improved pancreatic enzyme supplementation.

We have presented data to show that with the exception of ductal diameter all other significant variables are equally distributed between the two groups. Specifically the presence of gland calcification, beta cell dysfunction, weight loss, pancreatic serum enzyme levels, distal common bile duct stenosis, continued ethanol abuse, or ethanol abstention have all been comparably distributed between the two groups. As we stated in our earlier report the standard indication for operative drainage in CP, that of unrelenting abdominal pain, continues to be well treated by this procedure. Although no data supports such a practice, there continues to be some sentiment in favor of delaying operative drainage until complete or near complete functional derangements have occurred. On the basis of our small prospective evaluation and our large longitudinal evaluation of the impact of operative drainage on pancreatic function we continue to support a policy of early operation in CP patients before signifi-

cant loss of function. Our data support the concept that high intra-ductal pressure may contribute to both the ongoing loss of function and perhaps to an ongoing level of subacute inflammation, which restricts utilization of nutritional substrates. We finally believe the consensus should be reached regarding a system for grading the severity of chronic pancreatitis so that similar studies may be compared.

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Discussion

DR. JOSEF E. FISCHER (Cincinnati, Ohio): Dr. Nealon, that's a very fine presentation in a very difficult group of patients and my first response to the paper is, I believe the paper and I believe the data. The question as to what to do in the urban setting with the chronic alcoholic who has severe pancreatitis and takes resources and repeated hospitalizations as well as heads for the final burn-out stage with pancreatic insufficiency is a very difficult one. Many of your patients, I think 134 out of 143, were drinking at the time of randomization and I believe that on the slide that you showed 71 of those who survived were identified as continued to drink after the randomization and after treatment. It is remarkably difficult to tell when these patients have stopped drinking and one can always assume even if the patient tells you that they have, that they probably have not. And so my first question about the data is, how did you assess, if you did, on whether or not the patient stopped drinking and were there any tests, blood alcohol levels taken at random, when they did show up, or any other way in which you attempted to judge whether or not they stopped drinking? Secondly, as a corollary of that, is there any relationship between their improvement and the maintenance of the mild-to-moderate chronic pancreatitis status of the patients as related to their stopping drinking? In other words, one of the great stimuli in my experience to a patient stopping drinking is a great big scar on their abdomen. And did the patients that got operated on experience a lower rate of recidivism and a lower rate of alcoholism than those patients who did not, and is it possible that this is, in part, responsible for the results as you presented them? The third question really has to do with rates of hospitalization. And I know you have this data in the manuscript, and I'd like to ask you a question about this because Robert Hummel who is a fourth year resident and the son of one of our members, Robert Hummel, Jr., has reviewed a number of patients at our hospital with chronic pancreatitis who have undergone a variety of procedures for alcoholic pancreatitis in an effort to answer the question as to whether or not operation does anything to change their course from the standpoint of utilizing resources — if I may have the slide, please, of this — and found that in a selected group of patients in whom we had careful follow-up that the difference in preoperative and postoperative admissions per year decreased to a statistically significant extent — next slide, please — and that that difference probably was best in the pancreatico-jejunostomy as opposed to a whole series of other operations were not as effective, but the numbers of patients are too small for this to achieve statistical significance. My third question to you is, do you have such data, because I know this is one of the things that you started out to study, and what does it show?

DR. DANA ANDERSEN (Chicago, Illinois): I think that any pancreatic surgeon carries the bias that operative drainage of a dilated pancreatic duct benefits the patient and helps to effectively reduce pain. But we are compelled to apply the scientific method to discover the truth and certainly that method requires data. And these are the best data that have ever been assembled to answer important treatment questions in patients with chronic pancreatitis. Dr. Nealon has established with cer-