Post-ERCP Pancreatitis: Reduction by Routine Antibiotics

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Cholangitis and pancreatitis are severe complications of endoscopic retrograde cholangiopancreatography (ERCP). Antibiotics have been considered important in preventing cholangitis, especially in those with jaundice. Some have suggested that bacteria may play a role in the induction of post-ERCP pancreatitis. It is not clear, however, whether the incidence of post-ERCP pancreatitis could be reduced by antibiotic prophylaxis, as is the case with septic complications. In this prospective study, a total of 321 consecutive patients were randomized to the following two groups: (1) a prophylaxis group (n = 161) that was given 2 g of cephtazidime intravenously 30 minutes before ERCP, and (2) a control group (n = 160) that received no antibiotics. All patients admitted to the hospital for ERCP who had not taken any antibiotics during the preceding week were included. Patients who were allergic to cephalosporins, patients with immune deficiency or any other condition requiring antibiotic prophylaxis, patients with clinical jaundice, and pregnant patients were excluded. In the final analysis six patients were excluded because of a diagnosis of bile duct obstruction but with unsuccessful biliary drainage that required immediate antibiotic treatment. The diagnosis of cholangitis was based on a rising fever, an increase in the C-reactive protein (CRP) level, and increases in leukocyte count and liver function values, which were associated with bacteremia in some. The diagnosis of acute pancreatitis was based on clinical findings, and increases in the serum amylase level (>900 IU/L), CRP level, and leukocyte count with no increase in liver chemical values. The control group had significantly more patients with post-ERCP pancreatitis (15 of 160 in the prophylaxis group vs. 4 of 155 in the control group; $P = 0.009$) and cholangitis (7 of 160 vs. 0 of 155; $P = 0.009$) compared to the prophylaxis group. Nine patients in the prophylaxis group (6%) and 15 patients in the control group (9%) had remarkably increased serum amylase levels (>900 IU/L) after ERCP, but clinical signs of acute pancreatitis with leukocytosis, CRP reaction, and pain developed in four of nine patients in the prophylaxis group compared to 15 of 15 patients with hyperamylasemia in the control group ($P = 0.003$). In a multivariate analysis, the lack of antibiotic prophylaxis (odds ratio 6.63, $P = 0.03$) and sphincterotomy (odds ratio 5.60, $P = 0.05$) were independent risk factors for the development of post-ERCP pancreatitis. We conclude that antibiotic prophylaxis effectively decreases the risk of pancreatitis, in addition to cholangitis after ERCP, and can thus be routinely recommended prior to ERCP. These results suggest that bacteria could play a role in the pathogenesis of post-ERCP pancreatitis. (J GASTROINTEST SURG 2001;5:339-345.)

KEY WORDS: Post-ERCP pancreatitis, antibiotics, prophylaxis

The overall complication rate of endoscopic retrograde cholangiopancreatography (ERCP) is as high as 10%.[1-3] The most important early complications are pancreatitis, cholangitis, bleeding, and perforation. The incidence of bleeding and duodenal perforation is less than 1%, and these complications are associated with therapeutic procedures.[1-3] The incidence of cholangitis is reported to range from 1% to 19%,[1] but in most published studies the incidence of cholangitis is less than 10%.[4] The risk factors for cholangitis consist primarily of failed or incomplete biliary drainage,[4,5] and antibiotic prophylaxis is often

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recommended in these cases. It is not clear whether antibiotic prophylaxis is routinely needed before the ERCP. In the randomized studies a variety of antibiotics have been used to prevent post-ERCP cholangitis, and the results are somewhat contradictory.[6-12] One explanation for these conflicting results may be differences in the selection of antibiotics used, but variations in the patient populations in these studies are another possibility.

The incidence of post-ERCP pancreatitis ranges from zero to 40% because of differences in the criteria used in the diagnosis of pancreatitis. When only prospective studies are taken into account, the incidence of post-ERCP pancreatitis ranges from 5.1% to 7.6%.[4,13-15] The risk factors for post-ERCP pancreatitis have been widely studied and a variety of potential mechanisms of injury during ERCP are suspected; mechanical, chemical, hydrostatic, enzymatic, pharmacologic, and thermal factors may be involved.[14,15] In a large meta-analysis, the following five significant risk factors for post-ERCP pancreatitis were found: suspected dysfunction of the sphincter of Oddi, younger age, precutting sphincterotomy, difficult cannulation, and the number of pancreatic contrast injections.[4] A possible microbiological mechanism for pancreatic injury has also been suggested,[16,17] although to our knowledge no clinical randomized studies have yet been published. Many patients develop hyperamylasemia after ERCP, but only a subset develop clinical acute pancreatitis. The aim of the present study was to evaluate whether antibiotic prophylaxis has any effect on the development of pancreatitis compared with cholangitis after ERCP.

PATIENTS AND METHODS

Between 1993 and 1996, a total of 953 ERCP examinations were performed at Tampere University Hospital. During that time, 321 patients were prospectively randomized into the following two groups on admission to the hospital for ERCP: (1) a prophylaxis group (n = 161) that was given 2 g of cephtazidime (Glazidim) intravenously 30 minutes before ERCP, and (2) a control group (n = 160) that received no antibiotics. All patients admitted for ERCP who had not taken any antibiotics during the preceding week were included. Patients who were allergic to cephalosporins, those with immune deficiency or any other condition requiring mandatory antibiotic prophylaxis, patients with clinical jaundice, and pregnant patients were excluded. In cases where biliary obstruction could not be corrected, antibiotic treatment was continued after the examination (1 g × 2 cephtazidime) both in the prophylaxis group and in the control group. Therefore 6 of these 321 randomized patients were excluded from further analysis. So the final study cohort consisted of 155 patients in the prophylactic group and 160 patients in the control group. Clinical data from these patients, interventions during the ERCP examination, and ERCP diagnoses are presented in Table I.

Methods

The ERCP examinations were performed by or under the supervision of three senior endoscopists using a Pentax ED-3401 duodenoendoscope with nonionic contrast medium (Omnipaque, 180 mg/ml). All patients were given intravenous midazolam (Dormicum, 2.5 to 10 mg) and hyoscinebutylbromide (Buscopan, 20 mg) before ERCP. The choice of antibiotic was based on prevalence and sensitivity data for the most common biliary bacteria (*Escherichia coli*, streptococci, and *Clostridium perfringens*) at our hospital.[18]

Serum samples were collected from all patients just before ERCP, 4 to 8 hours after ERCP, and 18 to 24 hours after ERCP to determine C-reactive protein (CRP) concentrations (normal range 0 to 10 mg/L), alanine aminotransferase (ALT) activity (normal range 0 to 40 IU/L), alkaline phosphatase activity (normal range 0 to 300 IU/L), total bilirubin concentration (normal range 0 to 20 μmol/L), and amylase activity (normal range 0 to 300 IU/L). Additional samples were collected whenever clinically indicated (i.e., if the patient had any signs of complications such as fever, abdominal pain, etc.). The diagnosis of cholangitis was based on a continuously (over 2 days) rising fever, increased CRP level, increased leukocyte count, and increasing liver function values in conjunction with an inflammatory reaction. Blood was drawn for culture when the body temperature exceeded 38.5° C. The diagnosis of acute pancreatitis was based on clinical findings, an increase in serum amylase activity of threefold or more (≥900 IU/L) over the upper normal range, increased CRP level, and increased leukocyte count, and signs of cholangitis were lacking.

The primary end point was the occurrence of cholangitis and pancreatitis during the 7 days after ERCP. In addition, we studied the prevalence of hyperamylasemia (≥900 IU/L) regardless of what other findings were observed.

Statistical Analysis

Before the study, we calculated that with a 5% prevalence of pancreatitis a reduction by half in the study group would be statistically significant with a sample size of 150 in each group. In the final analysis, Fisher's exact test, Mann-Whitney U test, and for-

Table I. Clinical data, interventions, and diagnosis in the study groups

Characteristics	Prophylaxis group (n = 155)	Control group (n = 160)	*P* value
Sex (male/female)	61/94	71/89	NS
Mean age (95% CI)	59 yr (57-62)	63 yr (60-65)	NS
Prior pancreatitis	28	27	NS
Prior cholangitis	10	6	NS
Underlying disease			
Diabetes	13	16	NS
Acute pancreatitis	6	5	NS
Cancer	4	7	NS
Alcoholism	4	4	NS
Cirrhosis	2	2	NS
Preexisting clinical evidence of biliary obstruction	111	108	NS
Mean alkaline phosphatase (95% CI)	386 IU/L (301-471)	408 IU/L (303-513)	NS
Mean bilirubin (95% CI)	70 μmol/L (37-103)	43 μmol/L (24-62)	NS
ERCP interventions			
Choledochal cannulation	112	113	NS
Pancreatic cannulation	84	98	NS
Biliary obstruction	31	29	NS
Pancreatic obstruction	10	13	NS
Sphincterotomy	106	114	NS
Biliary stent placement	10	11	NS
ERCP diagnosis			
Gallbladder stones	31	34	NS
Choledochal stones	32	39	NS
Pancreatic cancer	7	9	NS
Cholangiocarcinoma	5	2	NS
Gallbladder cancer	1	1	NS
Chronic pancreatitis	3	3	NS
Pancreatic pseudocysts	2	4	NS
Adenoma papillae	1	2	NS
Suspected sphincter of Oddi dysfunction	7	4	NS
Stenosis papillae	1	1	NS
Sclerosing cholangitis	3	0	NS
Others	62	61	NS

CI = confidence interval; NS = no significant difference.

ward stepwise multiple logistic regression analysis were used to compare differences between the two study groups; $P < 0.05$ was considered significant.

RESULTS

Nineteen patients (6%) developed pancreatitis and seven patients (2.2%) developed cholangitis after ERCP. Patients in the control group had a greater frequency of both post-ERCP pancreatitis and cholangitis (Table II). Based on the criteria we applied, one patient (7%) in the control group had both post-ERCP cholangitis and pancreatitis, and was included in both complication groups. Among the 19 patients who developed pancreatitis, the mean values (and 95% confidence interval [CI]) for samples collected over a 3-day period following ERCP were as follows: serum amylase activity, 4943 (CI = 2257 to 7628) IU/L; leukocyte count, 15 (CI = 9 to 25) $\times 10^{-3}$ L; and CRP concentration, 111 (CI = 70 to 152) mg/L. Post-ERCP values for ALT, bilirubin, and alkaline

Table II. Complications in the study groups

Complications	Prophylaxis group (n = 155)	Control group (n = 160)	*P* value*
Post-ERCP pancreatitis	4 (2.6%)	15 (9.4%)	0.009
Cholangitis	0	7 (4.4%)	0.009

*Fisher's exact test.

Table III. Risk factors of post-ERCP pancreatitis

	P value*	Odds ratio*	95% confidence interval
Lack of prophylaxis	0.03	6.63	1.23-35.7
Sphincterotomy	0.05	5.60	1.02-30.5
Suspected sphincter of Oddi dysfunction	0.15	6.54	0.52-83.0
Pancreatic duct cannulation	0.16	3.72	0.60-23.5
Age	0.68	0.99	0.95-1.04
Difficult cannulation	0.97	0.97	0.21-4.48

*Forward stepwise multiple regression.

phosphatase did not differ from the levels observed before ERCP. Three patients with pancreatitis (one in the prophylaxis group and two in the control group; no significant difference) had a severe episode according to the prognostic criteria of Ranson and Pasternack.[19] The mean CRP level for these severe cases was 227 (CI = 13 to 441) IU/L. If we use the recently established consensus classification criteria,[20] 10 patients had mild disease, nine patients had moderate disease, and none had severe disease. Two of the 19 patients with pancreatitis, both in the control group, had underlying disease; one patient had diabetes and another had pancreatic cancer. All patients with post-ERCP pancreatitis were treated conservatively and none of them died. Fine-needle aspiration for bacterial culture was not done because infected pancreatic necrosis was not suspected in any of the patients with post-ERCP pancreatitis.

Three of seven patients with post-ERCP cholangitis had positive blood cultures; *Escherichia coli* was found in two patients and streptococci in one patient. Among the seven patients with cholangitis, the mean CRP level was 68 (CI = 20 to 115) mg/L and the leukocyte count was 14 (CI = 9.5 to 24) $\times 10^{-3}$ L. Liver function values were elevated for 3 days after the procedure in the patients with post-ERCP cholangitis compared to levels before ERCP: bilirubin increased from 10 (CI = 5 to 25) to 74 (CI = 7 to 150) μmol/L, ALT from 41 (CI = 29 to 64) to 90 (CI = 35 to 145) IU/L, and alkaline phosphatase from 202 (CI = 79 to 324) to 340 (CI = 203 to 477) IU/L. The mean amylase level in patients with cholangitis was 418 (CI = 62 to 607) IU/L after ERCP. Five of seven patients with cholangitis (all in the control group) had an underlying disease: one had had acute pancreatitis, one had had cholangitis, one had diabetes, and one had both diabetes and pancreatic cancer. All of the patients with post-ERCP cholangitis responded to antibiotic therapy.

Five patients developed other infectious complications: four patients in the control group (cholecystitis in two, pneumonia in one, and urinary tract infection in one) and one patient in the prophylaxis group (cholecystitis). Two patients developed postprocedure bleeding, one in each study group, and one patient in the prophylaxis group had a duodenal perforation. All three patients with post-ERCP cholecystitis were treated surgically, whereas other patients with complications were treated more conservatively. One patient in the prophylaxis group died the day after ERCP; as a result of bleeding from percutaneous transhepatic drainage. None of the patients who had surgery or percutaneous drainage after ERCP developed pancreatitis.

Table IV. Hyperamylasemia (>900 IU/L) in the study groups

	Prophylaxis group (n = 9)	Control group (n = 15)	*P** value
Post-ERCP pancreatitis	4 (44%)	15 (100%)	0.003

*Fisher's test.

A multivariate analysis was carried out of the risk factors for post-ERCP pancreatitis, including those previously considered important,[4] in conjunction with currently studied antibiotic prophylaxis. In this multivariate analysis two factors became independently significant: antibiotic prophylaxis and endoscopic sphincterotomy (EST) (Table III). Sphincterotomy was not performed any more often in patients who developed pancreatitis (8/19 = 42% vs. 86/216 = 29%; $P = 0.16$). Of the patients in the control group who developed pancreatitis, five underwent EST, whereas three patients with pancreatitis in the prophylaxis group underwent EST. Overall, 24 patients developed hyperamylasemia (serum amylase >900 IU/L), whereas 44% of the patients in the prophylaxis group with hyperamylasemia developed clinical acute post-ERCP pancreatitis compared to 100% of patients in the control group (Table IV).

DISCUSSION

Our study indicates that antibiotic prophylaxis can reduce the incidence of both pancreatitis and cholan-

gitis after ERCP. Little attention, however, is paid to the effect of antibiotics on post-ERCP pancreatitis. Niederau et al.[10] studied the influence of prophylactic antibiotic treatment (cephtazidime, 2 g intravenously) on septic complications and found more septic complications in the nonantibiotic group compared to the antibiotic group (8/50 vs. 0/50, $P = 0.01$) but no significant difference in the incidence of post-ERCP pancreatitis between the two groups (3/50 vs. 2/50; $P = 0.2$). In that study the patient population was relatively small, and no data were given for the definition of post-ERCP pancreatitis. In another randomized study Hazel et al.[11] concluded that antibiotic prophylaxis (a single dose of piperacillin, 4 g intravenously) does not significantly reduce the incidence of cholangitis. However, they also found more episodes of cholangitis during the first 48 hours after ERCP in the placebo group compared to the antibiotic group (12/281 vs. 5/270, $P = 0.08$), although the difference was not statistically significant. In the study by Hazel et al.,[11] the incidence of post-ERCP pancreatitis was only 1.8% (10 patients), which is lower than the incidence in other randomized studies.[2-4,13,14] Obviously the focus in any of those studies has not been on the prevalence of post-ERCP pancreatitis.[6-12] Furthermore, the patient population was different in the studies by Niederau et al.[10] and Hazel et al.[11] compared to the present study, where we excluded patients with clinical jaundice because in previous studies they were shown to benefit from antibiotic prophylaxis.[9,10]

In the present study the selection of antibiotic was based on the prevalence of the most common biliary bacteria in our hospital.[18] Cephtazidime is superior to second-generation cephalosporins, because *Pseudomonas* and anaerobes are frequent pathogens in the biliary tree. We found that only one of these biliary bacteria, *Streptococcus faecalis*, is often resistant to cephtazidime. To eliminate this organism we would need to use vancomycin, which might be considered too potent for prophylactic use.

The possible risk factors for post-ERCP pancreatitis have been widely investigated. In univariate analyses many types of potential technical risk factors have been associated with post-ERCP pancreatitis, such as multiple pancreatic injections,[21] hydrostatic injury,[22,23] and thermal injury.[14] Furthermore, some patient-related factors have been associated with post-ERCP pancreatitis including dysfunction of the sphincter of Oddi,[24-26] nondilated common bile duct,[24,25] and young age.[27,28] In a multivariate analysis by Freeman et al.,[4] the most powerful risk factors for predicting post-ERCP pancreatitis were dysfunction of the sphincter of Oddi and "precut" sphincterotomy. Other minor risk factors were difficult cannulation, young age, and number of pancreatic contrast injections.

Different pharmacologic agents that could potentially reduce the frequency of post-ERCP pancreatitis have been investigated; octreotide,[29] nifedipine,[30] and corticosteroids[31] are theoretically potential agents, but the results have been disappointing thus far. Instead, encouraging results in the prevention of post-ERCP pancreatitis have recently been achieved with the use of prophylactic somatostatin[32] and garbaxate, a protease inhibitor.[13] These drugs were not given to our patients. The present study was not double blind or placebo controlled. However, the endoscopist was not aware of whether or not antibiotics had been given. Furthermore, the diagnosis of complications (pancreatitis and cholangitis) was based on strict criteria that included results of laboratory tests. Also, the study data were analyzed by an independent investigator who was not participating in the treatment of these patients. The patients in the study groups were also well matched supporting the successful randomization (see Table I).

It has been shown that bacterial toxins may release cytokines from monocytes, which could result in pancreatitis.[17] It has also been shown that antibiotics increase survival in experimental pancreatitis,[33] but clinical studies focusing on the prevention of pancreatitis by means of antibiotics have not, to our knowledge, been previously published.

Antibiotic prophylaxis seemed to completely eliminate cholangitis in our series (0%). However, we must remember that we excluded the patients who were at highest risk. We found a 2.5% incidence of pancreatitis in the antibiotic prophylaxis group and a 9.4% incidence in the control group, a total of 6%, which is the same level that was found in other randomized studies. In the multivariate analysis (see Table III), the independent risk factors for post-ERCP pancreatitis were lack of antibiotic prophylaxis and sphincterotomy. Also, suspected dysfunction of the sphincter of Oddi and specific pancreatic duct cannulation seemed to increase the risk of post-ERCP pancreatitis, although not statistically significantly. Freeman et al.[4] and Mehta et al.[28] found young age to be a risk factor for development of pancreatitis, whereas we did not. One probable explanation for this difference is the highly selected patient population in our study.

It is always a matter of debate whether the diagnosis of pancreatitis and cholangitis is correct in this as well as in previous studies. There is no "gold standard" for the diagnosis of acute pancreatitis. In severe pancreatitis the diagnosis is well established by contrast-enhanced CT, whereas in mild pancreatitis the sensitivity is limited.[34] A threefold increase in serum amylase above the upper normal range has been considered to have greater than 90% specificity for de-

tecting pancreatitis including mild cases.[35] We know that up to 60% to 70% of patients undergoing ERCP have somewhat elevated serum amylase activity (typically up to twofold) during the first 24 hours after ERCP,[13-15,25] whereas only some patients develop clinical acute post-ERCP pancreatitis. In our study we required an increase in serum amylase activity by at least threefold or more above the upper normal range (≥900 IU/L), an increase in the CRP level, leukocytosis, and clinical signs, whereas early high fever or rising liver function values were not considered in the diagnosis of acute post-ERCP pancreatitis. Interestingly, all patients in the control group who had markedly elevated amylase levels also developed clinical signs of acute pancreatitis, whereas only 44% of patients in the antibiotic group with highly elevated serum amylase activity also had clinical signs of acute pancreatitis. This could mean that antibiotic prophylaxis may reduce the development of pancreatic irritation to clinical acute pancreatitis.

We conclude that antibiotic prophylaxis before ERCP reduces the incidence of both cholangitis and pancreatitis after ERCP, and can thus be routinely recommended. Our results also suggest that bacteria may play a role in the development of pancreatic irritation to clinical acute pancreatitis.

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Discussion

Dr. H.H. Freund (Jerusalem, Israel). What were the indications for the ERCP and were the groups matched in this respect? Also, what type of bacteria grew in cultures from those patients who developed infections? Some of the bacteria that might be seen in post-ERCP patients are bacteria inherent to the endoscope itself. These instruments are very difficult to sterilize. A few months ago we encountered, for example, an outbreak of resistant bacteria which we finally traced to the instruments themselves.

Dr. I. Nordback. The indications for ERCP did not differ between the two groups. The main indication was suspicion of common duct stones, after gallbladder stones were seen on ultrasonography and liver function values were at least transiently elevated at some point during the course of the disease. Bacteria were found in only three patients. In three patients with cholangitis, blood cultures were positive; two grew *E. coli* and one grew streptococci.

Dr. M. Zenilman (Bronx, N.Y.). Is there any experimental evidence that bacteria injected into the pancreatic duct can induce pancreatitis, which would go along with your hypothesis? Also, would it be worthwhile to administer the antibiotics intraductally rather than intravenously?

Dr. Nordback. There is some experimental evidence that bacteria may play some role. In at least one study, sterile bile was injected under extremely low pressure into the pancreas, and no pancreatitis was found. But if the bile was contaminated with *E. coli* and the same pressure was used to infuse the bile into the pancreatic duct, pancreatitis did develop. It would be very elegant to study antibiotic mixed with contrast medium. We did not do that.

Dr. J.P. Chung (Seoul, South Korea). Were the endoscopists blind to the treatment?

Dr. Nordback. The endoscopists and those who treated the patients after the endoscopy did not know whether the patients had been given an antibiotic or not.

Dr. P. Banks (Boston, Mass.). Do you have any imaging data from the patients who were thought to have pancreatitis, and can you tell us something about the severity of the pancreatitis?

Dr. Nordback. We did not perform a CT scan in every patient who had post-ERCP pancreatitis. Three patients developed severe pancreatitis by Ranson criteria and underwent CT scanning, and were found to have acute necrotizing pancreatitis. None of these three patients developed infected necrosis. Two were in the control group and one was in the prophylaxis group.

Dr. Banks. Only those three underwent imaging?

Dr. Nordback. That is correct.

Renal Cell Carcinoma Metastatic to the Pancreas: Results of Surgical Management

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Metastatic tumors to the pancreas are uncommon. Renal cell carcinoma is one of the few tumors known to metastasize to the pancreas. The purpose of the current report is to evaluate the surgical management and long-term outcome of patients with metastatic renal cell carcinoma. A retrospective review of patients undergoing pancreatic resection for renal cell carcinomas metastatic to the pancreas or periampullary region between April 1989 and May 1999, inclusive, was performed. Time from initial presentation, other metastatic sites, surgical outcomes, and long-term survival were evaluated. During the 10-year time period, 10 patients underwent pancreatic resection for renal cell carcinoma metastases. Of those, six underwent pancreaticoduodenectomy and two underwent distal pancreatectomy, whereas the two remaining patients underwent total pancreatectomy for extensive tumor involvement throughout the entire gland. The mean time from nephrectomy for resection of the primary tumor to reoperation for periampullary recurrence was 9.8 years (median 8.5 years). The range was 0 to 28 years, with one patient presenting with a synchronous metastasis. The mean age of the patients was 61.2 years with 60% of patients being male and 90% being white. Pathologic findings included histologically negative lymph nodes and negative surgical margins in all patients. One patient had tumor involving the retroperitoneal soft tissue, but final margins were negative. The mean live patient follow-up was 30 months (median = 15 months), with eight patients remaining alive. The Kaplan-Meier actuarial 5-year survival was 75%, with the longest survivor still alive 117 months following resection. The patient with retroperitoneal soft tissue involvement died 4 months after resection. The pancreas is an uncommon site of metastasis for renal cell carcinoma, typically occurring years after treatment of the primary tumor. When the metastatic focus is isolated and the tumor can be resected in its entirety, patients can experience excellent 5-year survival rates. The current report suggests that pancreatic metastases from renal cell carcinoma should be managed aggressively with complete resection when possible. (J GASTROINTEST SURG 2001;5:346-351.)

KEY WORDS: Metastatic, renal cell carcinoma, pancreas, periampullary

Metastatic carcinoma to the pancreas from another primary site is uncommon and accounts for approximately 2% of pancreatic malignancies.[1-3] Renal cell carcinomas, along with lung, colon, and breast carcinomas, are among the few tumors known to metastasize to the pancreas.[1-4]

Pancreatic metastases from renal cell carcinoma often present synchronously with widespread metastatic disease, in which case surgical resection is not indicated.[5-8] However, there have been numerous case reports or small series of isolated metachronous pancreatic or periampullary metastases from renal primary lesions treated with surgical resection.[2-4,9-21] The majority of patients in these series survive more than 1 year, but the actual long-term survival is difficult to assess; as many reports are published within 2 years of pancreatic resection.[11,12,15-18,20] The current report spans a 10-year period and evaluates surgical outcomes and long-term survival of patients following resection of isolated pancreatic metastases from renal cell carcinoma presenting both synchronously and metachronously with the primary tumor.

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PATIENTS AND METHODS

A retrospective review of 10 patients undergoing surgical management at The Johns Hopkins Hospital for renal cell carcinoma metastatic to the pancreas or periampullary region was performed. The experience was accumulated over a 10-year period from April 1989 through May 1999. Presenting symptoms, medical history, time from initial presentation, other metastatic sites, surgical outcome, and long-term survival following pancreatic resection were evaluated.

Patients with lesions in the head, neck, or uncinate process of the pancreas and the periampullary duodenum underwent pancreaticoduodenectomy, whereas those with lesions in the body or tail of the pancreas underwent distal pancreatectomy. Total pancreatectomy was reserved for carcinomas extensively involving the gland. All distal pancreatic resections included splenectomy and extended proximally to the superior mesenteric vessels. All resections were standard resections in which only the lymph nodes in the tumor specimen were removed. No patients in the series underwent extended retroperitoneal lymphadenectomy.

All patients in the study had a known primary renal cell carcinoma and the final pathology report on the pancreatic specimen was consistent with renal cell carcinoma. The primary lesions were not reviewed in our pathology department if they had been resected at an outside institution. Patients with both synchronous and metachronous metastases were included in the analysis; however, most patients presented with metachronous lesions having had the primary lesion resected months to years earlier. At the time of surgery, the pancreas or periampullary region was the only site of metastatic disease, but a history of renal cell metastases to other sites with prior resection did not preclude inclusion in the study. All operations were performed with curative intent.

The postoperative mortality and overall incidence of postoperative complications were evaluated. The need for reoperation in the immediate postoperative period was assessed. Delayed gastric emptying, pancreatic fistula, and biliary anastomotic leak were defined by previously reported criteria.[22-24] Wound infection was defined as a positive wound culture and the presence of pus necessitating opening of the wound. Intra-abdominal abscess required radiographic evidence and subsequent positive cultures after percutaneous or operative drainage. Pancreatitis was defined by abdominal pain, an elevated serum amylase level, and CT evidence of pancreatic inflammation. Pneumonia was defined as positive sputum cultures with a corresponding infiltrate on chest radiograph requiring antibiotics. Positive bile cultures, fever, and abnormal liver function tests requiring external biliary drainage and antibiotics defined cholangitis. Perioperative mortality was defined as death during the initial hospitalization or within 30 days of surgery.

Follow-up information was obtained through direct patient contact, review of hospital charts and surgeons' records, and by contacting the United States Social Security Administration. Complete survival information was available for all 10 of the patients.

All continuous data are presented as mean ± standard error of the mean. Survival analysis was performed using the method of Kaplan and Meier.[25] Differences in survival among subgroups were compared using the log-rank test. Significance was accepted at the 5% level.

RESULTS

During the 10-year period of the study, 10 patients underwent pancreatic resection for isolated renal cell carcinoma metastases to the pancreas or periampullary region. The mean age of the patients was 61.2 ± 4.2 years (median 63 years), with the youngest being 31 years and the oldest 78 years. Six of the 10 patients were male (60%) and nine were white (90%). Obstructive jaundice was seen in two patients (20%), nausea and vomiting in two (20%), weight loss in one (10%), and gastrointestinal bleeding in one (10%). The patient with a synchronous pancreatic metastasis presented with hematuria and multiple renal cysts. Two patients had no symptoms at all, with the pancreatic mass being found on routine follow-up radiologic imaging.

The mean time from nephrectomy for resection of the primary tumor to reoperation for pancreatic recurrence was 9.8 years (median 8.5 years; Table I). The range was 0 to 28 years, with one patient presenting with a synchronous lesion. The primary tumor was in the right kidney in five patients and in the left kidney in five patients. In all patients with right-sided renal lesions, the pancreatic metastasis was located in the proximal pancreas necessitating pancreaticoduodenectomy, whereas in those with left-sided venal lesions, two of the five had distal pancreatic metastases.

For their isolated pancreatic recurrences, six patients underwent pancreaticoduodenectomies, four of which were pylorus preserving and two of which were classic resections that included a distal gastrectomy. Five of the six metastases were centered in the head, neck, or uncinate process of the pancreas, whereas the remaining metastasis was in the periampullary duodenum and infiltrated the pancreas. Two patients underwent distal pancreatectomy for metastatic disease in the body or tail of the gland, whereas the final two patients underwent total pancreatectomy (one pylorus

Table I. Time to recurrence, procedure, other metastatic sites, and survival

Patient	Years to pancreatic recurrence	Procedure performed	Previous sites of recurrence	Status	Survival (mo)
1	0	Distal pancreatectomy with left partial nephrectomy	None	Alive	63
2	6	Classic pancreaticoduodenectomy	None	Alive	22
3	7	Classic pancreaticoduodenectomy	None	Dead	4
4	7	Distal pancreatectomy	None	Alive	4
5	8	Pylorus-preserving pancreaticoduodenectomy	None	Alive	117
6	9	Pylorus-preserving pancreaticoduodenectomy	Trachea, tongue, scapula	Alive	22
7	9	Classic total pancreatectomy	None	Alive	8
8	11	Pylorus-preserving pancreaticoduodenectomy	None	Dead	7
9	13	Pylorus-preserving total pancreatectomy	None	Alive	3
10	28	Pylorus-preserving pancreaticoduodenectomy	Right kidney, lung, right hip	Alive	7

preserving and one classic) for lesions diffusely involving the gland. The patient presenting with the synchronous lesion underwent a left partial nephrectomy simultaneous with pancreatic resection.

One woman in the series initially presented with a right-sided renal cell cancer in 1988, which was resected. Prior to developing a pancreatic metastasis in 1997, she had metastases to the base of the tongue, the trachea, and the scapula, all of which were resected. A second woman, who presented with an isolated pancreatic metastasis 28 years after left nephrectomy for her primary tumor, also had three previous isolated recurrences. These occurred in the contralateral kidney, the lung, and the right hip. All were resected in their entirety. The right renal recurrence required only partial nephrectomy leaving the patient with an adequate functioning renal mass. In both patients the pancreas was the only site of metastatic disease at the time of pancreaticoduodenectomy. Another patient underwent a left nephrectomy in 1985. He subsequently had a recurrence in his right kidney and underwent right nephrectomy in 1992, followed by successful renal transplantation in 1994. Of note, one patient had a history of von Hippel-Lindau syndrome.

The postoperative course is shown in Table II. There were no perioperative deaths in the series. Three patients (30%) had postoperative complications. All had undergone pancreaticoduodenectomy. The mean postoperative length of stay was 13.5 ± 4.0 days (median 8.5 days), with a range of 7 to 47 days. One patient developed a pancreatic fistula and a wound infection, one developed delayed gastric emptying following pylorus-preserving pancreaticoduodenectomy, and one patient developed a wound infection. The patient with the pancreatic fistula required reoperation for repair of the disrupted pancreaticojejunal anastomosis. The remaining seven patients had an uneventful postoperative course. No patients developed biliary anastomotic leaks, pancreatitis, pneumonia, intra-abdominal abscess, or cholangitis.

Table II. Postoperative course*

	No. of patients	(%)
Perioperative mortality	0	0
Overall complications	2	20
Specific complications		
Reoperation	1	10
Pancreatic fistula	1	10
Delayed gastric emptying	1	10
Wound infection	2	20

*Postoperative length of stay (mean ± standard error) 13.5 ± 4.0 days.

Table III. Tumor characteristics

Tumor size (mean ± standard error)	4.8 ± 0.9 cm
Positive resection margins	0%
Positive lymph nodes	0%
Retroperitoneal involvement	10%

The tumor characteristics are summarized in Table III. The mean tumor diameter was 5.2 ± 1.0 cm (median 4 cm). All patients were resected with negative surgical margins and histologically negative lymph nodes. The average number of lymph nodes in the resected specimens was 10 (range 0 to 21). One patient had retroperitoneal soft tissue involvement; however, the final surgical retroperitoneal margin was negative.

The mean live patient follow-up of the cohort was 30 months (median 15 months), with eight patients remaining alive at last follow-up. The longest survivor remains alive 117 months after resection. The patient

with soft tissue involvement died 4 months after resection (see Table I). The patient whose status was post renal transplant died 7 months after pancreatic resection from renal failure and complications of immunosuppression, but did not have recurrent renal cell carcinoma. All other patients are alive with no evidence of disease at last follow-up. There is no evidence of further recurrence in either patient with a history of previous recurrence and resection prior to pancreatic resection. The first patient, with resected metastases to the tongue, trachea, and scapula, is alive 22 months after surgery. The second, with metastases to the contralateral kidney, lung, and right hip, is alive 7 months after resection.

DISCUSSION

Approximately one third of patients with renal cell carcinoma have metastases at presentation and another third develop widespread metastatic disease following nephrectomy.[5,6] Some patients with renal cell carcinoma, however, present with late metastases, months to years after resection of the primary tumor. It is estimated that between 2% and 6% of patients with renal cell carcinoma present with isolated metastatic lesions that are amenable to surgical resection.[5-8] Aggressive surgery for these isolated metastases has been shown to significantly improve survival.[3,4,7,8,26-29] Isolated metastases are found in less than 10% of patients with metastatic renal cell cancer. When such isolated metastases are identified, complete resection may contribute to prolonged long-term survival. Carcinoma metastatic to the pancreas is uncommon. When compared to other tumors metastatic to the pancreas, renal cell carcinoma appears to be the most frequently treated with surgical resection. More than 60 cases of pancreatic resections for metastatic renal cell carcinoma have been reported in the literature.[3,15-21] These metastases may present synchronously but tend to present months to years following resection of the primary tumor. Of the many case reports, the time to pancreatic recurrence was often more than 10 years after nephrectomy for the primary disease,* with isolated recurrences reported up to 25 years following resection.[31] The current series is consistent with only one patient presenting with synchronous isolated metastases, whereas the remaining nine patients did not develop a pancreatic recurrence until 5 or more years after resection of the primary lesion. One patient in the series developed a resectable pancreatic metastasis 28 years after initial nephrectomy.

*References 2, 10, 12, 14, 17, 30, 31.

Patients with metastatic renal cell carcinoma present in a variety of ways including complete absence of symptoms, with metastatic tumor noted on routine follow-up, hematuria from a primary lesion, gastrointestinal bleeding, and obstructive jaundice. It is often difficult to distinguish pancreatic metastases from pancreatic primary lesions preoperatively, but in patients with a concomitant renal mass or a history of renal cell carcinoma the diagnosis should be included in the differential.

With the long-term follow-up on many previously published case reports and series being less than 2 years,[11,12,15-18,20] it is difficult to accurately determine long-term survival following pancreatic resection for metastatic renal cell carcinoma. However, the results of these case reports are encouraging with most patients living more than 1 year after resection. Z'graggen et al.[3] reported three patients surviving longer than 20 months, whereas Hirota et al.[15] and Sahin et al.[17] reported patients surviving 22 months and 18 months after pancreatic resection. In 1994 Kierney et al.[28] predicted a 5-year survival rate of 31% for 41 patients undergoing resection for isolated renal cell metastases. With a median follow-up of 3.2 years, this review included metastases to all sites and was not broken down for those with pancreatic recurrence. In a 1999 report by Tuech et al.,[19] five patients were treated with pancreaticoduodenectomy for metastatic renal cell carcinoma, with a mean patient survival of 48 months and 5-year survival of 68%. The current series is the largest series of resected isolated pancreatic metastases from renal cell carcinoma, with long-term follow-up. The 5-year survival rate of 75% in this series is consistent with previous encouraging reports.

One late death in the series, occurring 7 months after pancreatic resection, was not directly related to the renal cell carcinoma. The other patient was noted to have extrapancreatic disease in the retroperitoneum at the time of resection. Despite negative surgical margins, he died of metastatic renal cell carcinoma 4 months after resection.

Some investigators have suggested that patients presenting with metachronous lesions have improved survival over those presenting with synchronous lesions.[26,32,33] In the current series the patient presenting with a synchronous, resectable lesion is alive at 63 months with no evidence of recurrent disease.

Two patients in the series had three isolated metastases prior to pancreatic recurrence. They remain alive and disease free at 22 months and 7 months following pancreatic resection. This suggests that previous recurrences, regardless of site, should not dissuade aggressive management of pancreatic metastases as long as they have been completely resected and patients are otherwise disease free at the time of surgery.

The ability of renal cell carcinoma to present with isolated metastases to unusual sites years after resection of the primary lesion should be remembered when seeing a patient with a pancreatic mass and a history of resected renal cell carcinoma. Long-term survival of patients with renal cell carcinoma metastatic to the pancreas or periampullary region is better than that of patients with resected primary adenocarcinoma of the pancreas[24,34,35] and significantly better than that of patients with tumors metastatic from other sites.[3,4] Patients presenting with isolated renal cell metastases to the pancreas, whether synchronous or metachronous, represent a select group of patients with more indolent renal cell carcinomas. A history of previously resected metastases from other sites should not discourage pancreatic resection, providing the pancreas is the only site of metastasis at the time of surgery. With the increasing safety of pancreatic resection at major centers[34-39] and the improved long-term survival, aggressive management of pancreatic metastases from renal cell cancer is advocated.

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Overexpression of Caspase-1 in Pancreatic Disorders: Implications for a Function Besides Apoptosis

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The caspases are known to play a crucial role in the triggering and execution of apoptosis in a variety of cell types. We assessed the expression of caspase-1 in 42 pancreatic cancer tissue samples, 38 chronic pancreatitis specimens, and nine normal pancreatic tissues by immunohistochemistry and Western blot analysis. We found a clear overexpression of caspase-1 in both disorders, but differences in the expression patterns in distinct morphologic compartments. Pancreatic cancer tissue showed a clear cytoplasmatic overexpression of caspase-1 in tumor cells in 71% of the tumors, whereas normal pancreatic tissue showed only occasional immunoreactivity. In chronic pancreatitis an overexpression of caspase-1 was found in atrophic acinar cells (89%), hyperplastic ducts (87%), and dedifferentiating acinar cells (84%). Although in atrophic cells a clear nuclear expression was found, hyperplastic ducts and dedifferentiating acinar cells showed clear cytoplasmic expression. Western blot analysis revealed a marked expression of the 45 kDa precursor of caspase-1 in pancreatic cancer and chronic pancreatitis (80% and 86%, respectively). Clear bands at 30 kDa, suggested to represent the p10-p20 heterodimer of active caspase-1, were found in 60% of the cancer tissue and 14% of the pancreatitis tissue specimens. Since we found a highly significant correlation between cytoplasm overexpression of caspase-1 in pancreatic cancer and overexpression of the known prognostic factors cyclin D1, epidermal growth factor, and epidermal growth factor receptor, it is plausible that caspase-1 has a yet unknown function in proliferative processes in addition to its well-known role in the apoptotic pathway. (J GASTROINTEST SURG 2001;5:352-358.)

KEY WORDS: Caspase-1, interleukin 1β-converting enzyme, apoptosis, pancreatic cancer, chronic pancreatitis

Caspase-1 was the first described member of a group of cysteine proteases called caspases. Formerly designated interleukin-1β converting enzyme, it was originally characterized by its ability to cleave the inactive precursor of interleukin-1β to generate the active 17.5 kDa proinflammatory cytokine IL-1β.[1] Caspase-1 is expressed in many tissues as an inactive 45 kDa precursor protein (p45) from which the active enzyme is generated by an autocatalytic cleavage process.[2] It was first isolated from the human monocytic cell line THP 1 and because of its similarity in sequence to the death gene product CED-3 of the nematode *Caenorhabditis elegans*, it is regarded as a key enzyme of the apoptotic pathway.[3] At present, more than 10 caspases have been identified and their role in apoptosis is now well known.[4-6]

Overexpression of caspase-1 in rat fibroblasts leads to programmed cell death,[7] and coexpression of the potent caspase-1 inhibitor crmA blocks caspase-1–induced apoptosis.[8] Further, caspase-1 seems to have an important role in Fas-mediated apoptosis and apoptosis following chemotherapy.[4,9,10] However, caspase-1 is not the only protease in the normal apoptotic pathway since thymocytes and macrophages from caspase-1–deficient mice undergo apoptosis normally.[11]

Several new members of the group of caspases have been identified and described. Similar to caspase-1, overexpression of any of these enzymes leads to apop-

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tosis in a variety of cell types.[12-14] We investigated the expression of the apoptosis-related enzyme caspase-1 in pancreatic cancer and chronic pancreatitis. Interestingly, we found a clear overexpression of caspase-1 in pancreatic cancer tissue as well as in chronic pancreatitis specimens.

MATERIAL AND METHODS

Tissue Samples

Pancreatic tissue samples were obtained from 42 patients with pancreatic cancer and 38 patients with chronic pancreatitis who underwent surgery in the Department of General Surgery, University of Ulm. Tissue specimens were taken in accordance with the regulations of the local ethics committee after informed consent was obtained.

The median age of the patients with pancreatic cancer (20 women and 22 men) was 61.8 years (range 38 to 78 years). The group of patients with chronic pancreatitis included 13 women and 25 men. The median age of this group was 52.2 years (range 22 to 73 years). The main indication for pancreatic head resection was long-lasting pain (36 of 38 patients) and obstruction of the common bile duct (19 of 38 patients). In all patients, duodenum-preserving pancreatic head resection was performed. The etiology of chronic pancreatitis was chronic alcohol abuse with alcohol consumption of more than 50 ml per day in all patients.

Tissue samples, collected after surgical removal, were either immediately snap-frozen in liquid nitrogen and stored at −80° C or fixed in 4% formalin for 24 hours at room temperature, then processed, and embedded in paraffin. All 42 pancreatic cancer tissue and 38 chronic pancreatitis tissue samples were used for immunohistochemical analysis. Five normal pancreatic tissue samples from organ donors and four normal pancreatic tissue samples from patients undergoing surgery for pancreatic cancer served as control specimens. Western blot analysis was performed on 20 pancreatic cancer tissue, 14 chronic pancreatitis tissue, and seven normal pancreatic tissue samples.

Immunohistochemistry

Paraffin-embedded tissues were cut into sections 5 μm thick, mounted on slides pretreated with silane, deparaffinized, and hydrated by passing through xylene (3 × 5 minutes), a graded series of isopropanol (1× 100%, 80%, 70%, and 50%) for 5 minutes and distilled water for 10 minutes. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol (30 minutes) between the first two steps of washing with isopropanol. After each step, sections were washed three times with 0.5 mol/L Tris buffer (pH 7.6) for 10 minutes. The tissue sections were covered with 5% normal goat serum (Dako, Glostrup, Denmark) in Tris-buffered saline solution for 60 minutes and incubated overnight with the polyclonal rabbit antihuman caspase-1 antibody (Upstate Biotechnology, Lake Placid, N.Y.) in a dilution of 1:100. For each sample, a corresponding section was incubated in Tris-buffered saline without the primary antibody as a control for nonspecific staining. Additional negative control specimens consisted of normal rabbit serum instead of specific antiserum. Biotinylated pig antirabbit secondary antibody was added for 45 minutes followed by the avidin–biotinylated peroxidase complex for an additional 45 minutes. After washing with distilled water for 10 minutes, staining was achieved by using 3,3′-diamino benzidine. The sections were then counterstained with Mayer's hemalum and mounted. Staining of cyclin D1, epidermal growth factor (EGF), and EGF receptor (EGF-R) was achieved by using the monoclonal antibodies DCS-6 (anti-cyclin D1 oncogene), anti–EGF-R (clone 528 oncogene), and the polyclonal rabbit serum antibody-3 (anti-EGF oncogene), as described elsewhere.[15,16]

Grading of Immunohistochemical Findings

Immunohistochemical findings were scored based on the extent and intensity of staining. All sections were graded by two experienced investigators (M.R. and S.G.) who had no knowledge of the clinical data. At least 10 randomly selected high-power fields were scored on a Zeiss Axioplan 2 light microscope (Carl Zeiss, Inc., New York, N.Y.). The intensity of staining was graded on a four-point scale as follows: 0 = no staining; 1 = weak; 2 = moderate; and 3 = strong. The extent of positive immunoreactivity was graded according to the percentage of stained cells in the region of interest (0 points for 0%, 1 point for <20%, 2 points for 20% to 50%, and 3 points for >50%). An overall score was obtained by multiplying the intensity by the extent of positive staining. Cases with 0 points were considered negative; cases with a final score of 1 to 3 were deemed weakly positive, 4 to 7 moderately positive, and greater than 7 strongly positive.

Western Blot Analysis

Frozen pancreatic tissues were finely diced with a surgical blade and washed twice with ice-cold phosphate-buffered saline. The pellet was resuspended in 2 mmol/L Tris (pH 7.2), 0.1 mmol/L EDTA, and 1% Triton X-100 containing the protease inhibitors aprotinin (1 μg/ml), leupeptin (1 μg/ml), pepstatin

(1 μg/ml), N-ethylmaleimid (1 μg/ml), and soybean trypsin inhibitor (10 μg/ml). After swelling on ice for 60 minutes, the samples were dissociated by sonication (10 seconds, 60 watts). The lysates were centrifuged at 16,000*g* for 20 minutes at 4° C. The protein fraction (supernate) was divided into aliquots and stored at −80° C until further analysis. For immunoblotting the lysates were boiled in sodium dodecyl sulfate–gel sample buffer for 5 minutes. Then 30 μg of protein was electrophoretically resolved on denaturing 15% polyacrylamide gels with a 3% stacking gel. Proteins were transferred to nitrocellulose membranes (Schleicher & Schüll, Dassel, Germany) using a transblot apparatus (Phase, Lübeck, Germany). Nonspecific interactions were blocked by overnight preincubation of the membranes with a powdered milk suspension (10% dry milk in phosphate-buffered saline) at 4° C. After incubation of the membranes with monoclonal antibodies, the binding of antibodies was detected using the electrochemiluminescence system (Amersham, Arlington Heights, Ill.). The monoclonal antibody CAL directed against human caspase-1 was a generous gift from Dr. C. Miossec (Hoechst Marion Roussel, Romainville, France). The autocleavage experiments of the monocytic cell line THP 1 were performed as previously described.[17]

Statistical Analysis

Statistical significance was defined as $P < 0.05$. Kaplan-Meier regression analysis was performed for postoperative survival analysis. Chi-square test was used for correlation analysis. All statistical tests were computed using the MedCalc software package (MedCalc Software, Mariakerke, Belgium).

RESULTS

Immunohistochemical Findings

Staining of pancreatic tissue specimens with a polyclonal rabbit antiserum recognizing caspase-1 revealed a marked overexpression of caspase-1 in pancreatic cancer and chronic pancreatitis. Although normal pancreatic tissue showed only occasional slight staining (Fig. 1, *A*), we found predominantly cytoplasmic immunoreactivity of cancer cells in 71% of the pancreatic tumors (Fig. 1, *B*). In primary chronic pancreatitis tissue samples, caspase-1 overexpression was found in atrophic acinar cells, hyperplastic ducts, and acinar cells that appeared to dedifferentiate to form tubular structures. Hyperplastic ducts showed clear cytoplasmic staining in 87% (Fig. 1, *C*). Atrophic acinar cells with pyknotic nuclei stained positive in 89% of the pancreatitis tissues, but the immunoreactivity was predominantly nuclear (Fig. 1, *D*). Dedifferentiating acinar cells showed positive cytoplasmic immunostaining with the caspase-1 antiserum in 84% (Fig. 1, *E*). In chronic pancreatitis tissue, which often surrounds pancreatic carcinoma because of tumor obstruction (Fig. 1, *F*), we also found strong caspase-1 expression, but immunoreactivity differed from that of chronic pancreatitis tissue specimens from patients without malignancy. The staining in tumor-surrounding pancreatitis tissues was generally stronger than that in non–tumor-related pancreatitis tissues, and the distinct distribution pattern found in primary chronic pancreatitis could not be observed. In addition to this tissue-specific staining, a positive immunoreactivity of tissue-infiltrating lymphocytes was found in 73% of the tissues (see Fig. 1, *F*).

Western Blot Analysis

To confirm the overexpression of caspase-1 seen in immunohistochemical staining, Western blot analyses were performed with the monoclonal antibody CAL against human caspase-1. This antibody was developed to detect the 20 kDa subunit of active caspase-1,[18] but also detects the p45 precursor. Pancreatic cancer tissue as well as chronic pancreatitis tissue specimens showed specific bands migrating at 45 kDa (Fig. 2), suggested to be the p45 precursor protein of caspase-1. This band was found in 80% of the cancer tissues and 86% of the chronic pancreatitis tissues.

Lysates from THP 1 cells served as control specimens for active caspase-1. In monocytic THP 1 cells, the p45 caspase-1 precursor is known to be cleaved by an autocatalytic process to the active caspase-1 enzyme when kept at room temperature for 24 hours.[18] In 60% of the cancer probes and 14% of the pancreatitis lysates, and in lysates from the autocleavage experiments of THP 1 cells, a further band at 30 kDa was detectable, which is suggested to represent the active p10-p20 heterodimer of active caspase-1. In pancreatic tissue of healthy organ donors, no signals were obtained using the monoclonal antibody against human caspase-1, suggesting an overexpression of the caspase-1 protein in pancreatic cancer and chronic pancreatitis. Since lysates from pancreatic cancer tissue and chronic pancreatitis specimens also showed the 30 kDa band, it is plausible that caspase-1 is at least partly activated in these disorders.

Correlation With Clinicopathological Features

To assess the clinical importance of caspase-1 overexpression in pancreatic cancer, we correlated the immunohistochemical finding with age, sex, tumor extent, lymph node metastases, distant metastases, and

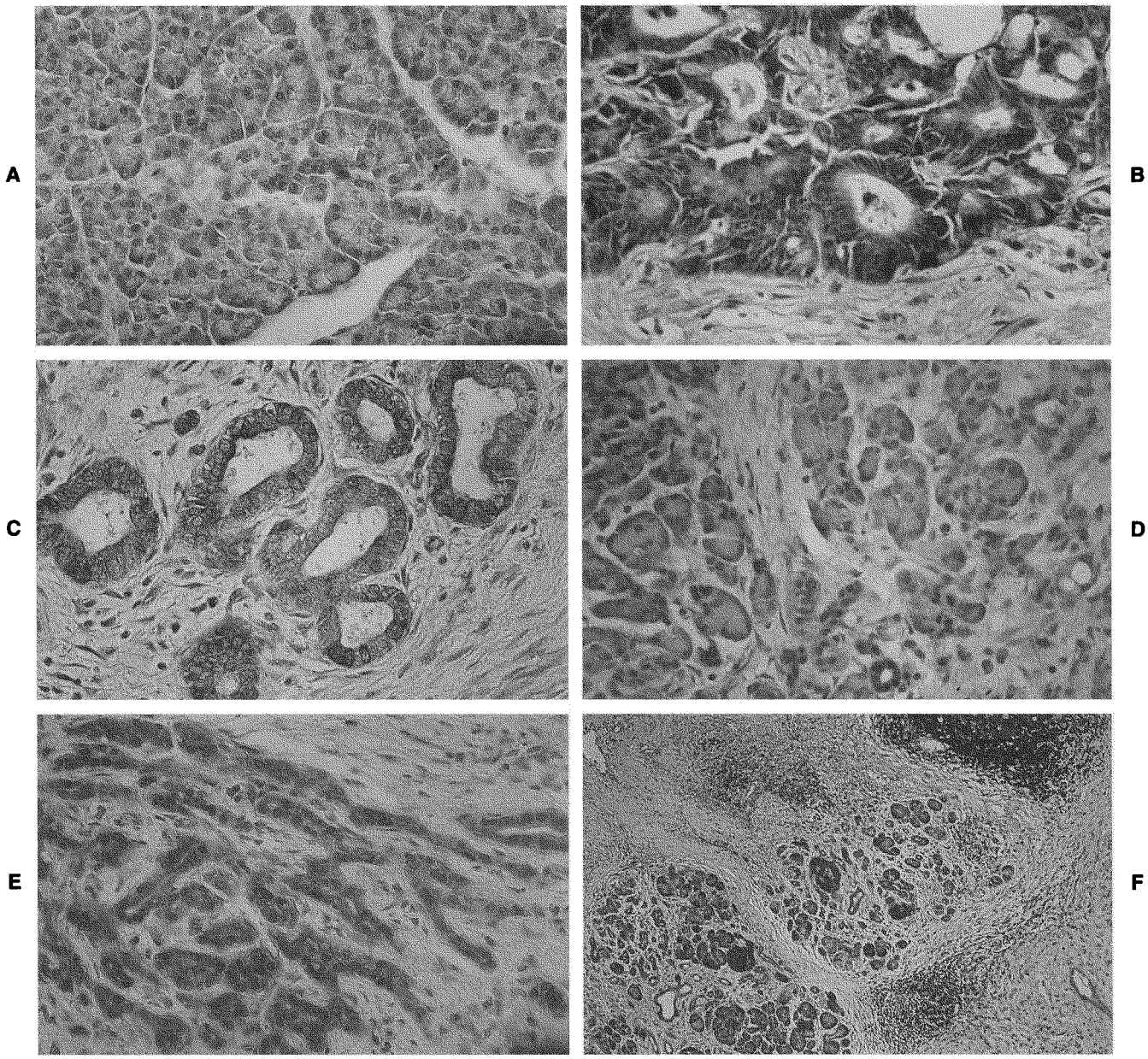

Fig. 1. Immunohistochemical staining of normal pancreatic tissues using the antiserum against human caspase-1. **A,** Normal pancreas showed only occasional slight staining. **B,** Pancreatic cancer cells showed a clear cytoplasmatic immunoreactivity in 71%. **C,** Hyperplastic ducts in chronic pancreatitis tissues also showed cytoplasmic staining in 87% of the tissues, whereas in atrophic acinar cells **(D)** a predominantly nuclear staining could be observed in 89%. **E,** Dedifferentiating acinar cells, which seem to form tubular structures, showed cytoplasmic immunoreactivity in 84%. **F,** This differential expression pattern could not be observed in tumor-surrounding pancreatitis tissue. There nuclear and cytoplasmic staining was found in nearly all pancreatic cells.

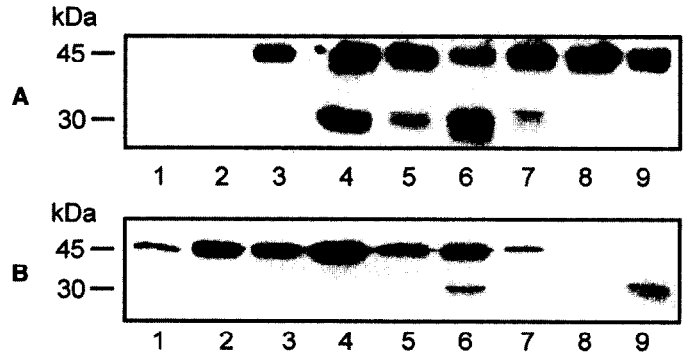

Fig. 2. Western blot analysis of pancreatic tissues with the anti–caspase-1 antibody. The 45 kDa precursor of caspase-1 was found in 80% of the pancreatic cancer tissue samples (**A,** Lanes 3 to 9) and 86% of the chronic pancreatitis samples (**B,** Lanes 2 to 8). In 60% of the cancer specimens and 14% of the chronic pancreatitis tissue samples, the active 30 kDa p10-p20 heterodimer was found. In normal pancreatic tissues (**A,** Lanes 1 and 2), neither the p45 precursor nor the active caspase-1 could be detected. Lane 1 **(B)** and lane 9 **(B)** show the autocleavage probes of THP 1 cells.

grading. No correlation was found between caspase-1 expression and any of these clinicopathologic features. In addition, no statistical difference was found with regard to postoperative survival. Patients with caspase-1–expressing tumors had a median survival time of 12 months, and patients with caspase-1–negative carcinomas had a median survival of 14.8 months (Kaplan-Meier regression analysis, not significant). In patients with chronic pancreatitis, we correlated the expression of caspase-1 with age, sex, onset of disease, need for analgesic drugs, and endocrine and exocrine pancreatic function. As in patients with pancreatic cancer, no correlation with any of the tested features could be found.

Correlation With Cyclin D1, EGF, and EGF-R in Pancreatic Cancer

We recently described the overexpression of cyclin D1, EGF, and EGF-R in human pancreatic carcinoma.[15,16] Comparison of cyclin D1 expression in tumor cells and cytoplasmatic caspase-1 overexpression revealed a highly significant correlation between these molecules ($P < 0.0005$) in our pancreatic cancer tissues. A clear correlation was also found between caspase-1 expression and the expression of EGF and EGF-R ($P < 0.05$ and $P < 0.002$, respectively).

DISCUSSION

Caspases play an important role in the apoptotic pathway in a variety of cell types. However, little is known about the physiologic roles of the different homologues during apoptosis. We assessed the expression of caspase-1 in pancreatic cancer and chronic pancreatitis. Interestingly, immunohistochemical analysis revealed a clear overexpression of this enzyme in both disorders, but also differences in the expression patterns in distinct morphologic compartments. Furthermore, Western blot analysis of pancreatic cancer tissues and chronic pancreatitis tissues showed that caspase-1 is at least partially activated in these diseases.

Caspase-1 is described as a cytosolic protein. However, in our experiments we found a clear nuclear staining with the antibody against human caspase-1 in atrophic acinar cells in chronic pancreatitis specimens. Interestingly, most of the known substrates for caspases in apoptosis are structural or catalytic nuclear proteins the cleavage fragments of which are found in apoptotic bodies.[19] The nuclear immunoreactivity of atrophic acinar cells in chronic pancreatitis may therefore be an indication of ongoing apoptotic processes. In contrast, the marked cytoplasmatic overexpression of caspase-1 in tumor cells can hardly be explained by apoptosis, since some tumors showed caspase-1 expression in nearly all cancer cells. Furthermore, we found a clear correlation between caspase-1 overexpression in pancreatic carcinoma and cyclin D1, which is known to be involved in cellular proliferation and is suggested to contribute to an aggressive behavior in many tumors.[15,20-22] EGF and EGF-R are suggested to play a crucial role in autocrine stimulation of human pancreatic carcinoma.[23] In the pancreatic cancer tissues we investigated, the cytoplasmatic expression of caspase-1 in pancreatic cancer cells also correlated significantly with the expression of EGF and EGF-R. Interestingly, it has recently been shown that EGF is also able to inhibit cell growth and induce apoptosis via caspase-1 induction.[24] However, with regard to the fact that cyclin D1, EGF, and EGF-R overexpression is associated with poor prognosis in human pancreatic cancer,[15,25] it

is hard to believe that these factors could be an indication for the apoptotic state of these tumors.

Chronic pancreatitis is histologically characterized by the destruction of the pancreatic parenchyma, irregular sclerosis, and focal duct cell proliferation.[26] Besides the predominantly nuclear staining with the antibody against caspase-1 in atrophic acinar cells, we found a clear cytoplasmatic overexpression in two other distinct morphologic compartments in chronic pancreatitis—in hyperplastic ducts and in areas with tubularily dedifferentiating acinar cells. Cyclin D1, EGF, and EGF-R are also altered in chronic pancreatitis,[27,28] which lends support to the hypothesis that chronic pancreatitis is a progressive process. Recent observations allude to the causal relationship between EGF and hyperplastic changes of the excretory ducts in pancreatic disorders.[29] Caspase-1 overexpression may thus be a result of induction by EGF. Tumor-surrounding pancreatitis tissues from patients with pancreatic cancer showed a strong positive immunoreactivity with the antiserum against caspase-1, but the differential expression pattern seen in primary chronic pancreatitis could not be observed. Nuclear and cytoplasmatic expression of caspase-1 was found in atrophic acinar cells as well as in duct cells. One explanation for this overexpression may be the dramatic course of the pancreatitis due to tumor obstruction. Another explanation might be that caspase-1 is upregulated through paracrine stimulation with tumor-derived EGF in these cells. Nevertheless, destruction of pancreatic parenchyma due to tumor growth and invasion is likely to be associated with apoptosis of normal pancreatic cells.

In summary, we found a clear nuclear overexpression of caspase-1 in atrophic acinar cells in chronic pancreatitis and tumor-surrounding pancreatitis tissues and a marked cytoplasmatic expression in pancreatic cancer cells and hyperplastic duct cells and dedifferentiating acinar cells in chronic pancreatitis.

CONCLUSION

Overexpression of caspase-1 is a frequent event in pancreatic disorders and its differential expression pattern may reflect two functions of the protease: (1) its participation in the apoptotic pathway in atrophic acinar cells and tumor-surrounding pancreatitis tissue and (2) a probable role in proliferative processes in pancreatic cancer cells and hyperplastic duct cells and dedifferentiating acinar cells in chronic pancreatitis.

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Pancreatic Schwannoma: An Uncommon But Important Entity

Kristi M. Almo, M.D., L. William Traverso, M.D.

The literature contains five single case reports of pancreatic schwannoma—two of the five occurred in patients with von Recklinghausen's disease, and three of the five proved malignant. Within a 3-month period, we resected benign pancreatic schwannomas in two patients without von Recklinghausen's disease. Both patients presented with pain that led to the discovery of a complex pancreatic mass on abdominal CT scan. Pancreatic schwannoma should be included in the differential diagnosis of cystic or solid pancreatic abnormalities on imaging studies. (J GASTROINTEST SURG 2001;5:359-363.)

KEY WORDS: Pancreas, schwannoma, S-100 protein, Whipple

Not all pancreatic neoplasms carry a poor prognosis. In a landmark paper published in June 1970, George Crile, M.D., described his operative treatment of pancreatic malignancies: "When the immediate mortality rate in the diagnosis and radical treatment of non-existent cancers is weighed against the remote possibility of effecting a cure and, also, when the postoperative morbidity is considered, my experience indicates that the average patient has a longer and more comfortable survival after a bypass procedure than after a radical operation."[1] Given the decrease in morbidity and mortality with modern-day pancreatic operations, Dr. Crile himself would likely agree to resection of a pancreatic schwannoma. Nevertheless, his famous quotation regrettably colors the outlook of many physicians regarding pancreatic masses, irrespective of the presence or absence of a tissue diagnosis. For this reason, we recommend that when imaging suggests a localized pancreatic tumor, any patient without significant comorbidity should at least undergo exploratory surgery for possible resection given the increased survival achieved with resected malignancies, the possibility of curing premalignant conditions, and the unfathomable oversight of allowing a benign neoplasm to grow without limits. We report two cases of benign schwannomas arising from the head of the pancreas and mimicking the presentation of either cystic or solid pancreatic malignancies in patients without von Recklinghausen's disease.

CASE REPORTS

Case 1

A 73-year-old healthy, active woman was seen in the emergency department after a single episode of postprandial left upper quadrant cramping, nausea, and vomiting. Initial evaluation included an abdominal ultrasound examination, which showed a cystic mass in the head of the pancreas impinging on the stomach. The patient had no history of pancreatitis, alcoholism, or abdominal pain. Subsequent referral to a gastroenterologist resulted in endoscopic retrograde cholangiopancreatography (ERCP), which revealed a normal pancreaticobiliary tree.

A follow-up CT scan 3 months later showed no change in the cystic mass in the head of the pancreas. At that time, the patient was referred to our institution for endoscopic ultrasound (EUS) and consideration of surgical treatment. EUS demonstrated a hypoechoic, well-demarcated 2.1 × 2.7 cm multicystic lesion in the head of the pancreas with a solid 5 mm rim. The body and tail of the pancreas were normal, as was the pancreatic duct in this area, which measured 1.8 mm. A rapid bolus helical CT scan with directed focus on the pancreas (Fig. 1) again showed a 3 × 3 cm irregular, lobulated, cystic lesion at the junction of the head and body of the pancreas. The mass neither extended beyond the pancreatic margins nor involved the pancreatic ducts. Preoperative chemical values were normal as were tumor markers CA19-9 (<5 [normal <37]) and carcinoembryonic antigen (1.1 [normal <3.0]).

With a preoperative diagnosis of either cystadenoma or cystadenocarcinoma, we performed an exploratory laparotomy. A cystic structure in the head of the pancreas was

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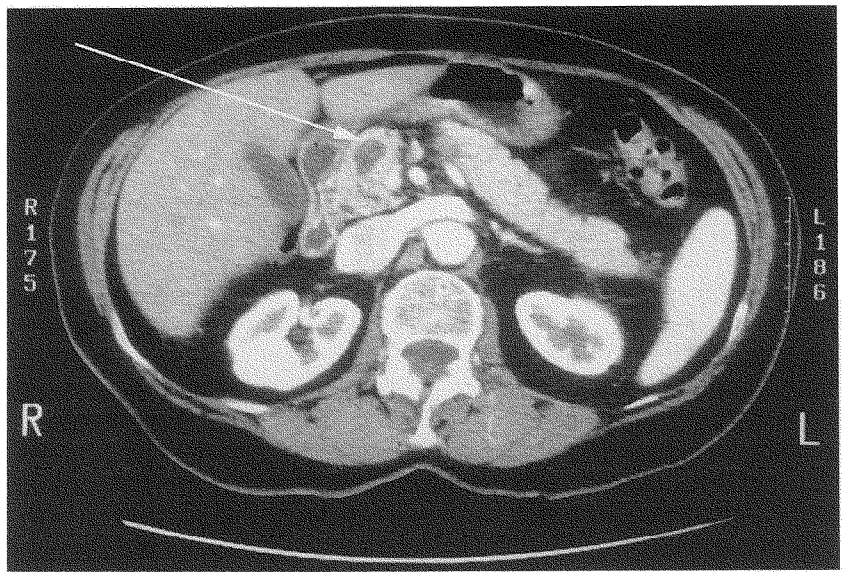

Fig. 1. Helical CT scan with directed focus on the pancreas shows a 3 × 3 cm irregular, lobulated, cystic lesion (arrow) medial to the head of the pancreas. The mass does not appear to extend beyond the pancreatic margins or involve the pancreatic ducts.

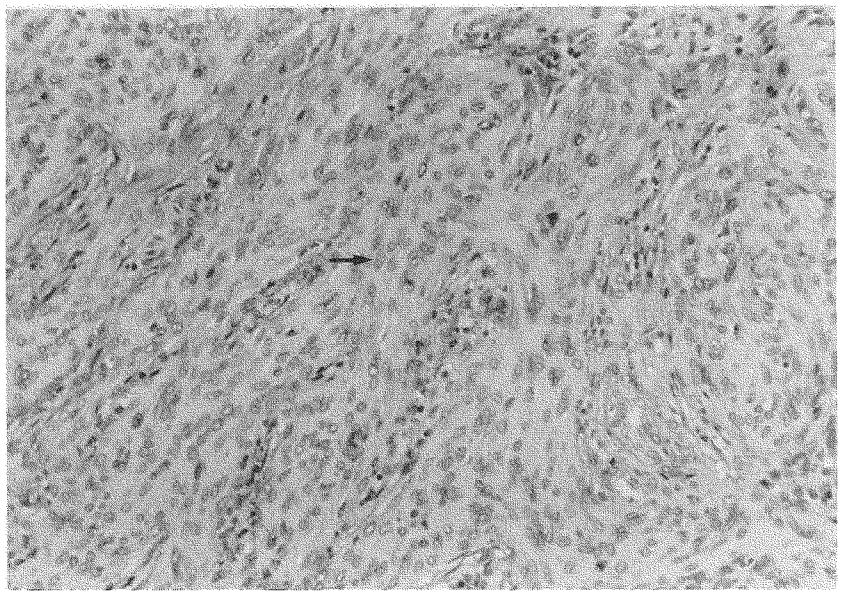

Fig. 2. Microscopic examination of the pancreatic specimen reveals a dense population of spindle cells with bland, short, oval nuclei (black arrow). Growth patterns vary from vesicular to epithelioid areas with a whorling appearance. No significant nuclei atypia or mitotic activity is present.

found to extend posteriorly, pushing on the portal vein at its junction with the splenic vein. After pylorus-preserving pancreaticoduodenectomy, a cross section of the mass confirmed a thick-walled multicystic structure without an epithelium. The mass did not involve the pancreatic duct. Microscopic examination of the thick cyst wall (Fig. 2) revealed a dense population of spindle cells with bland, short, oval nuclei. Growth patterns varied from vesicular to epithelioid areas with a whorling appearance. No significant nuclei atypia or mitotic activity was present. Immunoperoxidase staining with monospecific antisera to S-100, actin, 35BH11 (low-molecular-weight cytokeratin), synaptophysin, human melanin black, epithelial membrane antigen, and panhematopoietic markers (CD21, CD34, CD35, and CD45) resulted in variable positive staining with antibodies to S-100 protein, and negative staining with

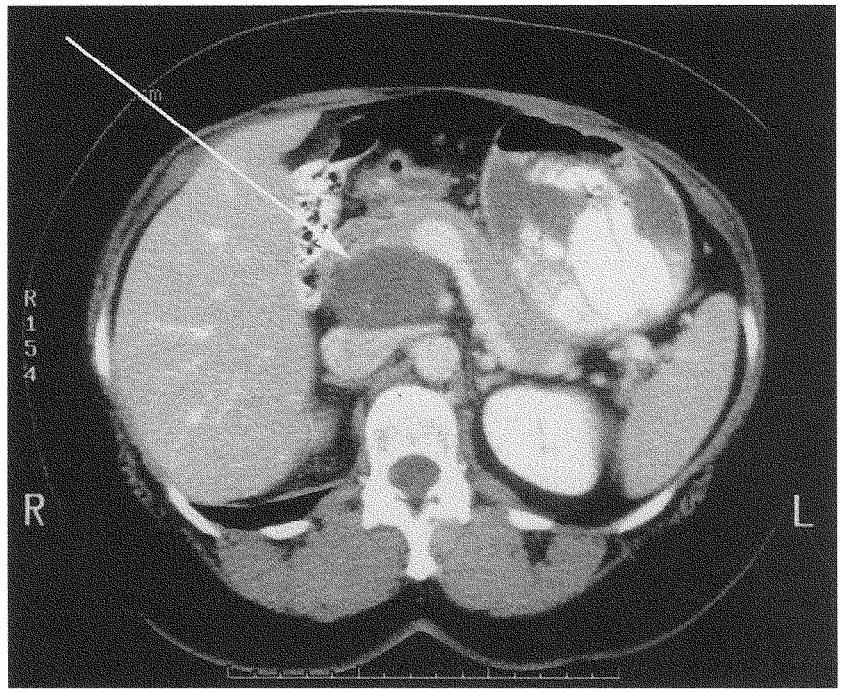

Fig. 3. CT scan showing a 3.5 × 5.0 cm unilocular cystic mass just dorsal to and probably involving the head of the pancreas and uncinate process (arrow), stippled with central calcifications. Only one calcification can be seen on this image; however, the relationship of the mass to surrounding structures is well depicted. The mass partially compresses the underlying inferior vena cava, displaces the portal vein to the left at the splenic vein junction, and displaces the superior mesenteric artery to the left.

the other antibodies. Of particular importance is a negative stain to CD21 and CD35, which argues against the diagnosis of follicular dendritic tumor. The absence of all other markers in the presence of a positive S-100 antibody stain indicates a neurogenic tumor.

Although no postoperative imaging has been performed to assess for tumor recurrence, the patient remains asymptomatic and has had no further episodes of left upper quadrant pain at 17 months' follow-up.

Case 2

A 47-year-old healthy, active woman with no history of pancreatitis, alcoholism, or abdominal pain presented to the emergency department complaining of midback pain of 7 days' duration. Ultrasound imaging demonstrated a 4 cm solid mass in the head of the pancreas stippled with central calcifications. That same day, however, an abdominal CT scan showed a 3 × 5 cm mass that appeared as a *cystic* mass either within or adjacent to the head of the pancreas. After receiving a tapering dose of prednisone with amelioration of her back pain, the patient was referred to our institution for further evaluation of the pancreatic lesion.

ERCP revealed a normal pancreaticobiliary tree. EUS defined a 3.5 × 4.8 cm hypoechoic solid mass with punctate central calcifications. The mass appeared to originate from the head of the pancreas extending cephalad in an exophytic pattern. The pancreas body, tail, and duct were normal. A rapid bolus helical CT scan with directed focus on the pancreas (Fig. 3) showed a 3.5 × 5.0 cm unilocular cystic mass with central calcifications located dorsal to and probably involving both the head of the pancreas and uncinate process. This lesion partially compressed the inferior vena cava, and displaced the portal vein and superior mesenteric artery to the left. Preoperative chemical values were normal.

With a differential diagnosis that included microcystic adenoma, nonfunctional islet cell tumor, acinar cell carcinoma, and papillary cystic-solid tumor, we recommended surgical exploration. At laparotomy, a 5.5 × 4.5 × 4 cm smooth, solid mass in the head of the pancreas protruded posteriorly and remained closely adherent to the proximal 3 cm of the right lateral border of the superior mesenteric artery, which was displaced medially. Cross section of the tumor after a pylorus-preserving Whipple procedure showed a fibrotic, partially calcified nodule with a tan, glistening cut surface. The mass did not involve the pancreatic duct. Microscopic examination revealed an encapsulated tumor with the same dense population of spindle cells, variable growth pattern, and absent mitotic activity similar to Fig. 2. Immunoperoxidase staining resulted in strongly positive staining with antibodies to S-100 protein and negative staining with the other antibodies (i.e., a tumor of neurogenic origin).

At 14 months' follow-up, the patient no longer complains of back pain. Although she has no symptoms of dysphagia or dumping, she does have postoperative diarrhea

Table I. Published reports of pancreatic schwannoma

Reference	Year	Country	Age (yr)	Sex	Presenting symptoms	von Recklinghausen's disease
Moller-Pedersen et al.[7]	1982	Denmark	60	M	Weight loss, back pain	No
Eggermont et al.[4]	1987	Netherlands	40	F	Abdominal pain, jaundice	No
Walsh and Brandspigel[6]	1989	USA	35	F	Abdominal pain, gastrointestinal bleeding	Yes
Coombs[5]	1990	USA	74	F	Melena, anemia	Yes
David and Barkin[8]	1992	USA	46	M	Abdominal pain	No
Almo 1	2000	USA	73	F	Abdominal pain	No
Almo 2	2000	USA	47	F	Back pain	No
AVERAGE			54	71% F	86% Pain	29%

*AWD = alive with disease; AWOD = alive without disease.

with a 40-pound weight loss. Blood studies, including liver function tests, complete blood count, and thyroid-stimulating hormone, were normal. Upper and lower endoscopy with biopsies ruled out celiac sprue and colitis, respectively. A Gastrografin upper gastrointestinal study with small bowel follow-through showed normal transit. Although results of infectious stool studies proved normal, an elevated fecal fat level suggested mild steatorrhea with a 24-hour stool weight of 747 g (normal 200 to 500 g/day), and fecal fat measuring 14.9 g (normal 0.0 to 6.0 g/day). Conceivably, a pancreaticoenteric stricture might have developed. We performed an end-pancreatico-to-side-jejunal stump anastomosis approximating mucosa to mucosa with interrupted 5-0 Maxon sutures over a 3 Fr Geenan stent, and closing the outer seromuscular envelope with interrupted 3-0 silk Lembert sutures. Alternatively, neurogenic diarrhea may be postulated as a cause; however, the proximal-most 3 cm of the superior mesenteric artery was skeletonized 180 degrees along the right lateral border. This noncircumferential dissection should not result in neurogenic diarrhea.[2] The patient's diarrhea has lessened after changing her proton pump inhibitor to an H_2 blocker. Additionally, she was given a 2-week course of antibiotic therapy and pancreatic enzyme supplements. One or two days a week, the patient currently has two to three nonbloody, nonmalodorous, moderate-volume loose stools. An abdominal CT scan has not been performed, but there is no clinical evidence of recurrent disease.

DISCUSSION

Schwannomas are uncommon spindle cell tumors derived from neural crest cells that generally present as multiple masses found in the extremities and trunk of patients with von Recklinghausen's disease. Ten to 15% of these tumors are malignant.[3] Benign schwannomas, also called neurilemomas or neurinomas, comprise 65% of all neurogenic tumors.[2] The most common locations for both benign and malignant schwannomas, in descending order of frequency, involve lower extremities, upper extremities, trunk, head and neck, retroperitoneum, mediastinum, pelvic area, and rectum.[4]

The current literature describes five separate reports of a single case each of pancreatic schwannoma, all of which have been treated surgically (Table I). Two tumors, one probably benign and one malignant, presented with melena and anemia in patients with von Recklinghausen's disease.[5,6] The other three schwannomas, one benign and two malignant, presented with pain in patients *without* von Recklinghausen's disease.[4,7,8] The two tumors in our patients join the one benign schwannoma in the latter group of patients without von Recklinghausen's disease. From this review of all currently identified pancreatic schwannomas, we could not find one reliable preoperative predictor of a tumor's pathology or malignancy. The presence or absence of von Recklinghausen's disease, the patient's age or sex, presenting symptoms, tumor image, and tumor location were not helpful in identifying a pancreatic schwannoma preoperatively.

Immunoperoxidase staining of the specimen proved key to a definitive diagnosis of pancreatic schwannoma. S-100 protein is a highly acidic, water-soluble protein with an affinity for calcium. S-100 protein, initially thought to be specific to the nervous system, has subsequently been identified in extranervous tissues.[9] Microscopic examination and immunoperoxidase staining of pancreatic schwannomas will demonstrate spindle cells, which stain positive with S-100 antibodies—and at the same time stain negative to all other tumor markers—thereby confirming the neurogenic origin of the tumor.

Malignant	Tumor image	Tumor location	Operation	Follow-up (mos)	Patient status*
Yes	Cystic	Body/Tail	Cystgastrostomy	4	AWD
Yes	Solid	Head	Whipple	9	AWOD
?	Solid	Head	Whipple	24	AWOD
Yes	Solid	Head	? Whipple	?	?
No	Cystic	Uncinate	? Local excision	?	?
No	Cystic	Head	Whipple	17	AWOD
No	Cystic	Head	Whipple	14	AWOD
43%	58% Cystic	71% Head	71% Whipple	14	

Table II. Partial differential diagnosis of pancreatic neoplasms

Pancreatic mass	
Cystic on CT	**Solid on US**
Neoplastic	Adenocarcinoma
Serous or mucinous	Acinar cell carcinoma
Cystadenoma	Adenosquamous cell carcinoma
Cystadenocarcinoma	Islet cell tumor
Papillary cystic-solid	Chronic pancreatitis
Intraductal papillary mucinous tumor (IPMT)	Metastases
	Renal cell carcinoma
Pseudocyst	Non-Hodgkin's lymphoma
Uncommon cysts	Breast cancer
(congenital, parasitic, etc.)	Colon cancer
Schwannoma	Schwannoma

CT = computed tomography; US = ultrasound.

As implied by Table II, whether a pancreatic neoplasm appears cystic or solid on preoperative imaging studies, *schwannoma* should be added to the differential diagnosis. Pancreatic schwannoma, benign perhaps 60% of the time, adds to a growing list of benign pancreatic tumors. We thus offer encouragement to frightened patients whose caregivers oftentimes lead them to believe that a pancreatic lesion is synonymous with death. In an era with a much-improved operative success rate as compared to that of 30 years ago during the career of Dr. Crile, we applaud the proactive surgeon's efforts to provide every patient with the opportunity for further tumor workup and an attempt at resection.

CONCLUSION

Although we do not believe that pancreatic schwannomas represent *common* pancreatic lesions, we do believe that they might exist with a higher frequency than heretofore recognized.

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Effect of Platelet-Activating Factor Antagonists (BN-52021, WEB-2170, and BB-882) on Bacterial Translocation in Acute Pancreatitis

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Bacterial translocation is an important source of pancreas infection in acute pancreatitis. The effect of platelet-activating factor (PAF) in the pathogenesis of acute pancreatitis has been proved in various studies. The aim of this study was to determine whether potent PAF antagonists influence bacterial translocation in acute pancreatitis. Acute pancreatitis was induced in 62 Wistar rats by injection of 2.5% sodium taurocholate into the biliopancreatic duct. The rats treated with PAF factor antagonists received intravenous injection of WEB-2170 (10 mg/kg), lexipafant (5 mg/kg), and BN-52021 (5 mg/kg) 30 minutes before induction of acute pancreatitis. Six hours after induction of acute pancreatitis, bacteriologic cultures and histologic scoring of tissues were performed. There was a statistically significant reduction in bacterial translocation to the mesenteric lymph nodes and liver but not to the pancreas of the rats treated with PAF antagonists. No significant increase in the intestinal bacterial population of any group was found. There were no statistical differences between the pancreatic histologic scores of the groups. PAF antagonists reduced bacterial translocation to distant sites other than the pancreas, preventing the bacterial dissemination that occurs in the early phase of acute pancreatitis and may have beneficial effects on the evolution of this disease. (J GASTROINTEST SURG 2001;5:364-370.)

KEY WORDS: Acute pancreatitis, bacterial translocation, platelet-activating factor

It is well recognized that acute pancreatitis is associated with a systemic inflammatory response syndrome. The development of this syndrome is mediated by cytokines such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF), and platelet-activating factor (PAF), the levels of which are greatly increased within 24 hours of the onset of this disease.[1,2] During this inflammatory process, intra-acinar phospholipase A_2 is activated, and promotes the synthesis of PAF (1-0-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) from the cell membrane.[3] This is known to act as an independent mediator of shock, sepsis, and multiorgan failure.[4]

In spite of its participation in normal pancreatic gland function, several experimental studies have demonstrated that PAF potentiates local pancreatic injury, increases serum levels of amylase and lipase, and works as a primary inflammatory mediator in pancreatic gland inflammation.[1] The use of PAF antagonists in experimental models of acute pancreatitis can ameliorate the effects of PAF, significantly reducing the magnitude of the systemic inflammatory response syndrome that occurs in this disease.[5,6] Moreover, PAF is known for its vasoactive properties, which in the mesenteric region cause vasoconstriction and tissue hypoperfusion, which may subsequently induce gastrointestinal mucosal ulceration.[7] In turn, this may promote bacterial or toxin translocation from the intestinal lumen.[4]

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Bacterial translocation in acute pancreatitis has been shown to occur in several studies.[8,9] We have previously demonstrated that, experimentally, bacterial translocation to mesenteric lymph nodes, pancreas, and liver occurs early after the induction of acute pancreatitis.[10] The aim of this study was to analyze the effects and possible modes of action of several PAF antagonists (WEB-2170, lexipafant, and BN-52021) on bacterial translocation following experimental induction of acute pancreatitis.

MATERIAL AND METHODS

Animals

Seventy-three adult male Wistar rats, weighing 220 to 280 g, were housed in individual cages. Temperature was kept at 22° to 28° C, a 12 hour light-dark cycle was maintained, and all rats were fed a diet of standard rat chow and water ad libitum. The experimental protocol was approved by the Ethics Commission of the Hospital das Clinicas, São Paulo University.

Platelet-Activating Factor Antagonists

Three different PAF antagonists were used in this experiment: (1) WEB-2170 (8(R,S)-6-2-clorophenyl)-8,9-dihydro-1-methyl-8-(4-morpholinylcarbonyl)-4H,7H-cyclopenta(4,5)thienol[3,2-f] [1,2,4]triazolo [4,3-a][1,4]) (Boehringer-Ingelheim, Mannheim, Germany); (2) BB-882 (lexipafant, (S)-4-methyl-2-{methyl-[4-(2-methylimidazo {4,5-c} pyridin-1-yl-methyl)-benzene sulphonyl]-amino} pentanoic acid ethyl ester) (British Biotech Pharmaceuticals, England); and (3) BN-52021 (3-t-butyl-hexahydro-4,7b,11-trihydroxy-8-methyl-9H-1,7a-epoxymrthano-1H,6aH-cyclop) (Henri Beaufour-Ipsen Institute Research Laboratories, Le Plessis Robinson, France).

Induction of Acute Pancreatitis

In brief, rats were operated on under aseptic conditions, using ketamine anesthesia (0.1 mg/100 g). Median duration of anesthesia was 2 hours. The pancreas was exteriorized through a midline abdominal incision. The proximal end of the bile duct was clamped at the level of the hilum of the liver and cannulated using a 19G polyethylene catheter (Biotecno, Saõ Paulo, Brazil) through the duodenal wall. Acute pancreatitis was induced by intraductal retrograde injection of 2.5% sodium taurocholate (Sigma Chemical, St. Louis, Mo.) to a total dose of 0.1 ml/100 g body weight, without pressure control. Duration of injection was 0.1 ml/min. In the sham-operated group, sodium taurocholate injection was omitted, but the surgical procedure was otherwise identical to that of the experimental groups, including biliary pancreatic duct cannulation.

Experimental Design

Animals were divided into five experimental groups as follows: Group I (sham operation) = 10 rats subjected to the same procedures as experimental rats but without induction of acute pancreatitis; group II (control) = 12 rats with induction of acute pancreatitis; group III = 15 rats treated with WEB-2170 (10 mg/kg) intravenously 30 minutes before induction of acute pancreatitis; group IV = 14 rats, treated with lexipafant (5 mg/kg) intravenously 30 minutes before induction of acute pancreatitis; and group V = 11 rats treated with BN-52021 (5 mg/kg) intravenously 30 minutes before induction of acute pancreatitis.

Six hours after surgery (sham operation or induction of acute pancreatitis), the rats were weighed and reanesthetized with ketamine (Parke-Davis, São Paulo, Brazil). A midline thoracoabdominal incision was made using an aseptic technique, and the animals were sacrificed by transcardiac exsanguination.

Measurement of Pancreatitis

The presence of ascites was determined by inspection of the peritoneal cavity at laparotomy. This was the only clinical measure used to assess the severity of pancreatitis because it is only produced in severe acute pancreatitis and is an indirect measure of increased vascular permeability.

Following midline incision, tissue samples were harvested from all mesenteric lymph nodes, the left lobe of the liver, and the head of the pancreas. Cecal contents and free peritoneal fluid were sampled using sterile cotton swabs. All samples were weighed prior to determination of bacterial growth. The samples were homogenized in test tubes containing brain-heart-infusion broth. All media for aerobic cultures were incubated at 37° C for 48 hours. An automatic system was used to perform blood cultures (Vitek System, bioMérieux, Inc., St. Louis, Mo.) over 5 days. All isolated aerobic bacteria were identified and counted by standard procedures. Bacterial counts were expressed as colony-forming units per gram.

Fragments of pancreas, mesenteric lymph nodes, liver, and duodenum were fixed immediately in 10% formaldehyde solution, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for light microscopy. Coded sections of pancreas were analyzed and graded blind for the presence of acute inflammatory changes. Each of the following five vari-

ables was assigned a grade of 0 to 4 (total maximum score = 20 as an index of the severity of tissue injury[11]): edema, acinar necrosis, fatty necrosis, inflammation, and perivascular infiltration.

The mucosa of the duodenum was similarly graded for the presence or absence of inflammation or ulceration. Lymph nodes were examined for the presence of follicular hyperplasia and sinus histiocytosis, and the liver parenchyma was examined for periportal inflammation, hepatocellular necrosis, and Kupffer cell hyperplasia. In these organs, changes were simply classified as present or absent.

Statistical Analysis

The proportion of animals with ascites or positive cultures was expressed as a function of the total. In some cases, because of technical problems, the total number of tissues studied was slightly less than the total number of rats in each group. A positive culture was considered to be indicative of significant tissue infection when there were more than 10^3 colony-forming units per gram of tissue. Different groups were then compared using K-proportion and Fisher's exact tests. Values for cecal bacterial overgrowth were compared between groups using the Kruskal-Wallis one-way analysis of variance, following normalization of data by $\log^{10}$ transformation.

To compare individual "inflammation" scores from the histologic analysis of pancreatic tissue, Kruskal-Wallis one-way analysis of variance was used. A similar analysis of variance was used to analyze total pancreatic histology scores. To compare the histology scores of other tissues (duodenal, lymphatic, and hepatic) the K-proportion test was used, and for analysis between individual groups, Fisher's exact test was used. In all analyses, $P < 0.05$ was taken as the level of significance.

RESULTS

The incidence of ascites in the control group was significantly greater than that in the sham-operated group ($P < 0.05$, Fisher's exact test) (Table I). A significant decrease in the incidence of ascites was noted in animals in group IV, which had been pretreated with lexipafant ($P < 0.05$, Fisher's exact test).

A significantly increased rate of positive bacterial cultures was obtained from the liver, pancreas, mesenteric lymph nodes, and peritoneal cavity in the control group in comparison to the sham-operated group (Table II). There were no significant differences in the incidences of positive blood cultures among all groups (Table II). The incidences of bacterial translocation from the gut to extraintestinal sites such as liver and lymph nodes, but not to the pancreas, were decreased in animals from the groups treated with WEB-2170, lexipafant, and BN-52021. In addition, in group IV bacterial translocation to the peritoneal cavity was also reduced (Table II).

Table I. Incidence of ascites

Group	Ascites*
I	0/10†
II	8/11
III	11/15
IV	4/14‡
V	6/11

*Number of rats in each group with ascites, expressed as a proportion of the total.
†Group I vs. group II: $P < 0.05$.
‡Group IV vs. group II: $P < 0.05$.

Table II. Bacterial translocation to liver, mesenteric lymph nodes, pancreas, peritoneal cavity, and blood*

Group	Liver	Pancreas	MLN	Peritoneum	Blood
I	1/9†	3/10†	2/10†	2/10†	2/10
II	9/12	9/11	9/11	11/12	5/12
III	3/13†	13/15	2/15†	13/15	4/15
IV	3/13†	9/13	5/14†	6/13†	8/14
V	1/11†	6/11	1/11†	6/11	1/11

MLN = mesenteric lymph nodes.
*Proportion of rats with positive cultures from tissue culture studies.
†$P < 0.05$ vs. group II (control).

There were no significant differences in the number of intestinal bacteria among the groups. Bacteriologic analysis revealed a predominant presence of gram-positive bacteria in the liver, pancreas, peritoneal cavity, and blood but not in the mesenteric lymph nodes (Table III).

Small bowel inflammation and ulceration were observed in all experimental groups (Table IV). Follicular hyperplasia and sinus histiocytosis were seen in mesenteric lymph nodes (see Table IV). The intestinal and mesenteric lymph node changes were not significantly reduced by treatment with PAF antagonists. Histologic analysis of the liver showed a significant increase in Kupffer cell hyperplasia in the hepatic lobules of rats pretreated with WEB-2170 and BN-52021 (see Table IV). There were no significant differences in pancreatic histologic grades between any of the groups (Table V).

Table III. Type and incidence of bacteria identified per tissue of all animals (sham + control + treated groups*)

Bacteria/tissue	Liver (n = 58)	Pancreas (n = 60)	MLN (n = 61)	Peritoneum (n = 61)	Blood (n = 62)
S. viridans	24%	43%	18%	18%	16%
E. faecalis	3%	35%		20%	2%
E. coli		5%	38%	7%	2%
S. aureus	10%	2%		3%	
F. breve	3%	10%		15%	14%
S. epidermidis	3%	5%	5%		2%
Other	9%	2%	5%	3%	

*$P > 0.05$, sham vs. control vs. treated groups.

Table IV. Results of morphologic analysis: Frequency of histologic changes*

	Intestine		MLN		Liver			
					Portal	Lobules		
Group	I	E	FH	SH	I	I	N	KH
I (n = 10)	4†	1	3	1	0	1	0	5
II (n = 12)	12	7	11	6	0	0	0	6
III (n = 15)	15	9	14	14	3	0	0	13†
IV (n = 14)	13	4	13	12	3	1	0	6
V (n = 11)	10	3	10	10	2	0	0	10†

MLN = mesenteric lymph nodes; n = total number of rats in each group; I = inflammation; E = erosion; FH = follicular hyperplasia; SH = sinus histiocytosis; N = necrosis; KH = Kupffer cell hyperplasia.
*The number of animals with histologic changes is tabulated for each group according to the tissue studied.
†$P < 0.05$ vs. group II (control).

Table V. Pancreatic histologic grading*

Group	E	AN	H	FN	IPI	Total
I (n = 10)	1.9 ± 0.2	0.1† ± 0.1	0† ± 0	0 ± 0	0.6† ± 0.2	2.6† ± 0.3
II (n = 12)	1.9 ± 0.3	3.6 ± 0.1	1 ± 0.1	0.6 ± 0.1	2.2 ± 0.3	9.6 ± 0.5
III (n = 15)	2 ± 0.2	3.3 ± 0.2	0.5 ± 0.1	0.5 ± 0.1	2.2 ± 0.2	8.5 ± 0.6
IV (n = 14)	2.4 ± 0.1	3.2 ± 0.2	0.7 ± 0.1	0.7 ± 0.1	2.6 ± 0.3	9.6 ± 0.7
V (n = 11)	2.4 ± 0.1	3.6 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	2.8 ± 0.2	10.5 ± 0.3

n = total number of rats in each group; E = edema; AN = acinar necrosis; H = hemorrhagic necrosis; FN = fatty necrosis; IPI = inflammation and perivascular infiltration.
*Mean ± standard error of pancreatic tissue morphologic grading in each tissue per group.
†$P < 0.05$ vs. group II (control).

DISCUSSION

Knowledge of the pathophysiology of acute pancreatitis has increased considerably in the past few years. The earliest events of acute pancreatitis occur in acinar cells where enzyme activation may lead to acinar cell damage.[12] This is followed by a systemic inflammatory response mediated by cytokines such as IL-1, IL-6, IL-8, TNF, and PAF.[13] The inflammatory process evolution can induce multiple organ failure and death. PAF appears to be one of the key mediators and is released from many cells, including endothelial cells, macrophages, neutrophils, and platelets, resulting in cell activation and subsequent synthesis of other cytokines.[14]

Phospholipase A_2 and elastase play fundamental roles in the development of the glandular inflammatory process in acute pancreatitis. Catalytic activity of phospholipase A_2 releases lyso-PAF, a PAF precursor, from the cell membrane, in a calcium-dependent reaction, to form PAF.[1] Elastase induces a systemic inflammatory reaction by stimulating the synthesis of TNF from activated macrophages.[15] Low plasma concentrations of antiproteases (α_1-proteinase, α_1-chemotrypsin) decrease the synthesis of PAF, indicating that some plasma proteases are involved in PAF biosynthesis induced by cytokines.[13] Such a protease has recently been characterized and shown to be an elastase synthesized by endothelial cells after stimulation by IL-1 or α-TNF.[13] This evidence confirms that the interaction of PAF, cytokines, and proteases is important in the pathogenesis of acute pancreatitis.[16]

Several authors have emphasized the participation of PAF in the pathogenesis of acute pancreatitis. Intravenous injection of PAF increases serum amylase levels and causes histologic pancreatic changes similar to those produced by cerulein injection.[17] An analogous study showed that PAF serum levels were increased in lung tissue, proportional to the severity of the lesion, following only 6 hours of acute pancreatitis.[18] The same group demonstrated that the level of acinar PAF correlated with the Ca^{++} level, and that this was important in the pancreatic injury induced by cerulein.[19] It is thus recognized that it is not only pancreatic enzymes that participate in the pathogenesis of acute pancreatitis, but also chemical mediators of the systemic inflammatory process. These are responsible for intestinal lesions, possibly related to bacterial translocation, which may cause pancreatic and systemic septic complications. Several investigators have shown that mucosal gastrointestinal injury may be caused by PAF. Bowel ulceration, the presence of intestinal bacterial overgrowth, endotoxins, and an increase in permeability of the mucosal barrier have been identified experimentally as positive factors that favor the occurrence of bacterial translocation.[20,21]

The exact role of different PAF receptors is far from being resolved, and there is inadequate information about the action of currently available PAF antagonists. For this reason we used the following three structurally distinct antagonists in this study: BN, a tarpenoid compound; WEB, a modified diazepinic compound that lacks central action; and lexipafant, an imidazolyl derivative. Doses of PAF antagonists used in this study were chosen from those previously reported. The dose of 2 mg/kg BN-52021 has been shown to significantly reduce pancreatic edema induced by intravenous injection in rats.[22] The dose of 5 mg/kg WEB-2170 has been shown to significantly inhibit edema in rat bronchi induced by intratracheal injection of PAF.[23] A dose of 5 mg lexipafant ameliorated pulmonary vascular permeability when administered after the induction of acute pancreatitis.[24]

The present study demonstrated a decrease in bacterial translocation to the liver and mesenteric lymph nodes, but not to the pancreas, in rats treated with PAF antagonists. However, only lexipafant was able to reduce bacterial translocation to the peritoneal cavity. Since bacterial translocation has been shown to correlate with the severity of pancreatic lesions,[10,25,26] the reduction in translocation to distant sites induced by PAF antagonists could theoretically be due to their effects on pancreatic lesions. However, the histologic analysis of pancreatic tissue showed that the grade of inflammatory process was not affected by any PAF antagonists and remained similar in all study groups, although it is possible that the short duration of the current study (6 hours) may have resulted in the absence of pancreatic histopathologic changes. Liu et al.[27] reported similar results in a recent study in a rat model of acute pancreatitis using lexipafant pretreatment. After 48 hours, they observed a decrease in bacterial spread to distant sites but no difference in severity of histologic pancreatic lesions.

The decrease in bacterial translocation to the mesenteric lymph nodes and the liver, but not to the pancreas, of animals treated with PAF antagonists cannot be easily explained. We speculate that the intensity of the pancreatic inflammatory process achieved in this model, not modified by PAF antagonists, could enhance bacterial survival in this tissue. However, the Kupffer cell hyperplasia found in animals treated with WEB-2170 and BN-52021, but not in those treated with lexipafant, suggests that these cells may have some action in preventing bacterial circulatory dissemination.

Some investigators have emphasized the importance of impaired intestinal barrier function in the mechanism of bacterial translocation.[8,28] In this study we observed that PAF antagonists had no effect in reducing the degree of intestinal mucosal inflammation

and erosions, and had no effect in altering the intestinal bacterial counts between groups. These findings suggest that other factors are involved in promoting bacterial translocation in acute pancreatitis. In addition to the degree of gland injury, bacterial translocation in acute pancreatitis probably depends on a number of complex pathophysiologic alterations, for example, hypotension, prolonged fasting, paralytic ileus, endotoxemia, lowered immunologic resistance, and increased intestinal permeability.[29]

Abdo et al.[30] noted that vascular permeability was increased in an experimental model of acute pancreatitis, and that this effect was promoted by the generation of oxygen free radicals secondary to the local inflammatory process. It is known that PAF potentiates the effects of IL-10 in the production of free radicals, and that these can modify intestinal mucosal permeability.[31] In fact, the increase in intestinal permeability associated with the severity of acute pancreatitis has been suggested by others to be a factor in bacterial translocation.[25] Andersson et al.[32] observed an increase in intestinal endothelial permeability and an increased permeability of the mucosal barrier. They concluded that in acute pancreatitis, circulatory insufficiency and systemic alterations in the capillary barrier led to tissue infection, and consequently to organ failure.

In an attempt to evaluate the effects of lexipafant, in changing intestinal permeability, the same group,[33] using a model of taurocholate-induced pancreatitis, observed that this antagonist was capable of hindering permeability changes and decreasing the frequency of capillary thrombosis in intestinal villi. These investigators concluded that lexipafant was a potential agent for preventing pancreatitis-associated gut barrier dysfunction.

The decreased ascites observed in this study in animals pretreated with lexipafant suggests a possible effect of this antagonist in decreasing vascular permeability. It is known that ascitic fluid contains substances capable of activating intracellular adhesion molecules (ICAM-1) in the pancreas and lung, and is also capable of activating macrophages and secreted factors that induce apoptosis, such as TNF, for example.[34,35] Thus the reduction in vascular permeability induced by lexipafant may have a beneficial role in reducing the systemic inflammatory response syndrome in acute pancreatitis.

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Necrotizing Pancreatitis During Pregnancy: A Rare Cause and Review of the Literature

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Acute pancreatitis is an uncommon cause of abdominal pain during pregnancy, and rarely progresses to the necrotizing form of the disease in this clinical setting. Hyperlipidemia is an infrequent cause of acute pancreatitis. Whereas only 100 cases of hyperlipidemia-induced necrotizing pancreatitis have been reported in the literature to date, all of the cases were mild in severity and responsive to conservative medical management. Herein we present a case of life-threatening necrotizing pancreatitis, which developed in a hyperlipidemic pregnant woman and required multiple peripartum pancreatic necrosectomies. Additionally, we review the evaluation of pregnant patients with abdominal pain, the pathophysiology of hyperlipidemia-induced necrotizing pancreatitis, and the operative care of this challenging group of patients, revisiting an innovative technique for management of the retroperitoneum. (J GASTROINTEST SURG 2001;5:371-376.)

KEY WORDS: Necrotizing pancreatitis, hyperlipidemia, gestational pancreatitis

Acute pancreatitis during pregnancy can be a life-threatening emergency, resulting in significant fetal and maternal mortality.[1] Although most pregnant women with acute pancreatitis have associated gallstones, less common causes such as trauma, drugs, and ethanol ingestion have also been reported.[2,3] A small number of pregnant women with acute pancreatitis have an associated hyperlipidemia, usually hypertriglyceridemia.[1,4] Whereas approximately 100 cases of hyperlipidemia-induced acute pancreatitis during pregnancy have been reported in the medical literature, in all of the cases to date the pancreatitis was mild in severity and responsive to conservative medical management. There are no published reports of hyperlipidemia-induced necrotizing pancreatitis during pregnancy that required operative management. Herein we present a case of necrotizing pancreatitis in a pregnant woman, a review of the literature, and guidelines for surgical intervention.

CASE REPORT

A 33-year-old gravida 3, para 0, therapeutic abortion 2 woman of Chinese descent presented at 31 weeks' gestation with persistent nausea, vomiting, and progressive mid-epigastric abdominal pain. Her medical, surgical, and family histories were all unremarkable. Pertinent physical findings at the time of admission included a normal temperature, sinus tachycardia (125 beats/min), and abdominal findings of a normal gravid uterus and mild epigastric tenderness. She had no eruptive xanthomas, or evidence of a Grey Turner's or Cullen's sign. The patient's plasma was grossly lipemic, with a triglyceride level greater than 6600 mg/dl (Table I). Serum electrolytes and hemoglobin levels were normal, with a white blood cell count of 12.8×10^6 cells/L and a lipase level of 6548 U/L. The patient had a Ranson score of 7 and an APACHE II score of 14. An abdominal ultrasound examination revealed ascites, and diffuse pancreatic enlargement, without evidence of gallstones or dilated intra- or extrahepatic bile ducts.

During the evaluation of the patient's abdominal pain, the fetus developed cardiac decelerations and a breech presentation was noted. Because of signs of fetal distress, an emergency cesarean section was performed through a vertical midline incision. The patient was delivered of a healthy baby girl with Apgar scores of 4, 6, and 8, at 1, 5, and 10 minutes, respectively.

The patient's postpartum clinical course deteriorated despite aggressive fluid resuscitation and medical management. During the first 24 hours following the cesarean section, although the patient received 14 liters of intravenous fluid to maintain normal cardiac filling pressures, blood pressure, and urine output, a base deficit of 9.5 persisted. She also became increasingly obtunded. An abdominal

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Table I. Selected laboratory values

	Normal values	Admission	Initial OR	Discharge
WBC (10^3 cells/L)	4-11.6	12.8	11.0	6.3
Glucose (mg/dl)	65-165	201	121	117
LDH (U/L)	110-220	743	N/A	N/A
AST (U/L)	10-50	35	39	55
Ca^{2+} (mg/dl)	8.5-10.5	5.0	4.3	8.5
Base deficit (mmol/L)	0-2.0	9.5	10.4	0.9
Amylase (IU/L)	20-110	779	814	107
Lipase (U/L)	30-270	6548	4958	287
TG (mg/dl)	10-150	6640	669	271

WBC = white blood cells; LDH = lactic dehydrogenase; AST = aspartate aminotransferase; Ca^{2+} = total calcium; TG = triglycerides; N/A = not available.

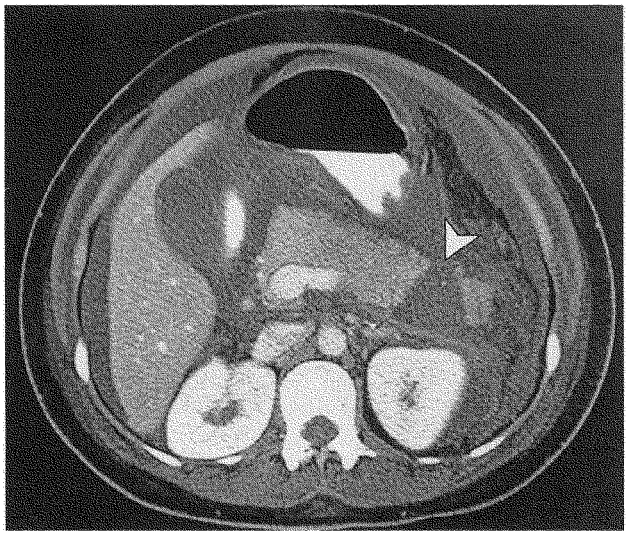

Fig. 1. Abdominal CT scan highlights wedge-shaped defect in the tail of the pancreas (white arrow).

computed tomography (CT) scan revealed ascites, generalized anasarca, peripancreatic fluid, and a wedge-shaped area within the tail of the pancreas that failed to enhance with intravenous contrast (Fig. 1), yielding a CT severity index of 4.[5-7]

Because of continued clinical instability and a tensely distended abdomen (transvesicular abdominal compartment pressure 26 mm Hg), the patient was taken back to the operating room for an exploratory laparotomy on day 1 following the cesarean section. Intraoperatively, 3 liters of pancreatic ascites (amylase >24,000 U/L), fat necrosis, diffuse saponification within the lesser sac, and a necrotic segment within the tail of the pancreas were encountered, corresponding to the findings on the CT scan. A blunt necrosectomy was performed, intraoperative cultures were taken, and the abdomen was irrigated. In addition, a transverse flank laparostomy incision was fashioned in the anterior axillary line, two finger breaths below the left costal margin. The pancreatic bed and lesser sac were packed with latex Penrose drains, which exited the left flank laparostomy, effectively "marsupializing" the retroperitoneum. Given the elevated abdominal compartment pressures, the fascia was left open and the abdominal cavity was closed using a composite vicryl and marlex mesh.

Postoperatively the patient's clinical course stabilized, and her lipid levels normalized. Additional operations included revision of the marlex mesh closure on postoperative day 2, removal of the mesh with placement of retention sutures on postoperative day 7, and final closure of the abdominal fascia 11 days after the initial pancreatic debridement. She resumed enteral feeding on postoperative day 17. Irrigation (hydrodebridement) of the retroperitoneum via the flank laparostomy incision continued for an additional 4 weeks, with permanent removal of the Penrose drains on postoperative day 28. The flank laparostomy incision subsequently closed by secondary intention.

On discharge from the hospital, the patient was clinically stable, with normalization of her laboratory profile (see Table I). In addition, she was tolerating a low-fat diet with no evidence of abdominal pain, or endocrine or exocrine insufficiency. The patient was discharged on the antihyperlipidemic agent gemfibrozil, and returned with her infant daughter to China in good condition.

DISCUSSION

This case represents the successful management of life-threatening necrotizing pancreatitis during pregnancy. The patient presented during her third trimester with classic signs and symptoms of acute pancreatitis. After emergency cesarean section, she developed a necrotizing form of pancreatitis and subsequently underwent aggressive surgical management with multiple debridements of the retroperitoneum. Grossly lipemic serum suggested an associated hyperlipidemia. Although hyperlipidemia-induced necrotizing pancreatitis during pregnancy is rare, it highlights several important points regarding the diagnosis and treatment of pregnant women with ab-

dominal pain, the pathophysiology of hyperlipidemia-induced acute pancreatitis, and the diagnosis and treatment of necrotizing pancreatitis in the peripartum period.

The complaint of abdominal pain during pregnancy is relatively common. Emergency abdominal surgery in this group of patients, however, is relatively uncommon. Citing Swedish Registry data, Mazze and Kallen[8] reported that abdominal surgery was performed in 1331 of 720,000 pregnant women, for an incidence of approximately 1 in 500. Of causes unrelated to pregnancy, the most common indications for abdominal surgery during pregnancy are appendicitis and gallstones.[9] In the Swedish retrospective series, 778 in 720,000, or 1 in 1000, appendectomies were performed in pregnant women. Appendicitis was confirmed in 65% of the cases, for an incidence of 1 in 1500,[8] and in most series is associated with an increased fetal loss, ranging from 15% to 20%. Cholelithiasis was the second most common indication for abdominal surgery in pregnant women, with a reported incidence of approximately 1 in 1000.[3] Interestingly, biliary abnormalities were found via ultrasound in a much higher percentage of pregnant patients than in those who ultimately required cholecystectomy. Maringhini et al.[10] reported asymptomatic stones in 2.5% to 10% and sludge in 30% of pregnant patients, suggesting that pregnancy may predispose to gallbladder disease.

In contrast to appendicitis and cholecystitis, acute pancreatitis rarely complicates pregnancy. Acute pancreatitis complicated 1 in 3300 pregnancies at a large public hospital in Dallas, Texas,[11] whereas in Southern California 1 in 1500 women were affected.[12] Other published reports cite incidences ranging widely from 1 in 1000 to 1 in 12,000 live births.[13,14] Although uncommon, the associated morbidity and mortality are significant, with one study citing 37% and 14%, respectively.[15] Similarly, Glasgow et al.[9] reported a fetal loss rate associated with gallstone pancreatitis as high as 20%.

Of the small percentage of women who develop acute pancreatitis during pregnancy, an even smaller percentage have an associated hyperlipidemia. The exact incidence is not known. Gallstones are clearly the most common cause of pancreatitis during pregnancy, followed in frequency by trauma, alcohol ingestion, drugs, viral infection, and, finally, hyperlipidemia.[2,3]

The association of hyperlipidemia with pancreatitis during pregnancy was first reported in 1818.[16] By 1970 a total of only 101 reports had been published, the vast majority of which were case studies. Table II details more recent published reports.[17-25] Miller et al.[23] published one of the largest retrospective studies wherein they followed 35 patients with hyperlipidemia for 1 to 11 years. Fifty-four percent of women had recurrent abdominal pain and 29% developed pancreatitis. They found that although mild pain occurred frequently when patients had plasma triglycerides in the 2000 to 5000 mg/dl range, triglyceride levels over 6000 mg/dl were often associated with severe pain, hospitalization, and unnecessary diagnostic studies and operations. Cessation of oral intake combined with intravenous fluids was associated with clinical improvement within 48 hours. Although this report did not characterize the contribution of pregnancy to the clinical setting of hyperlipidemia-induced pancreatitis, it did recognize and document an important complication of hyperlipidemia. Several recent case reports and anecdotal papers have attempted to more definitively describe the pathogenesis, progression, and treatment of hyperlipidemia-induced pancreatitis during pregnancy.

Pregnancy itself may cause patients to become predisposed to hyperlipidemia-induced pancreatitis. Many women develop gestational hyperlipidemia largely because of the increased estrogen levels during pregnancy. In fact, it appears that some degree of hyperlipidemia during pregnancy is normal. This so-called "physiologic hyperlipidemia of pregnancy" is associated with a two- to fourfold increase in plasma triglycerides and a 10% to 50% increase in plasma cholesterol at term. These changes are thought to represent a generalized increase in substrate mobilization, both for the placenta and for the growing fetus.[1,26] Much like the development of gestational diabetes, clinically significant hyperlipidemia characteristically occurs in the third trimester when lipid clearance is outpaced by synthesis and release. The rise in plasma lipids appears to parallel increases in plasma estrogen levels. Since the trend of increasing lipid levels during pregnancy resembles that found during treatment with sex hormones, a hormonal basis for gestational hyperlipidemia is suspected.[27] Thus the hyperlipidemia of pregnancy is one of many changes in maternal physiology designed to support the fetus that can also stress maternal lipid homeostasis, resulting in skin lesions, fatty changes in the liver, and pancreatitis. For this reason it is imperative to differentiate between the physiologic and pathologic hyperlipidemia of pregnancy. Although Miller et al.[23] found that triglyceride levels above 6000 mg/dl were associated with severe abdominal pain and pancreatitis, unfortunately there were not enough conclusive data to provide an absolute upper limit of normal for the plasma lipid concentration during pregnancy.

Several published papers during the past decade suggested that pregnant women with genetic defects

Table II. Hyperlipidemia-induced pancreatitis during pregnancy

Reference	Year	No. of patients	Study design	Etiology	Treatment	Notes
Miller et al.[23]	1979	35	Retrospective review	Hyperlipidemia	Bowel rest; intravenous fluids	Pancreatitis resolved
Weinberg et al.[22]	1982	1	Case report	Hyperlipidemia	Low-fat diet	Focus on diet, TPN Pancreatitis resolved
De Chalain et al.[25]	1988		Case report	Hyperlipidemia (LPL activity low for patients 2 and 3)	Medical, low-fat diet	Patient 1: Hemorrhagic → death Patient 2: Mild Patient 3: Mild
Sanderson et al.[27]	1991	1	Case report	Hyperlipidemia	Medical, low-fat diet	Pancreatitis resolved
Swoboda et al.[17]	1993	1	Case report	Hyperlipidemia	(a) Plasmapheresis (b) Immunospecific apheresis	Relatively mild pancreatitis managed by chronic extracorporeal removal of lipoproteins
Ma et al.[24]	1994	4	Case report	Chylomicronemia (partial LDL deficiency)	Plasmapheresis, low-fat diet	DNA sequencing done
Saravanan et al.[18]	1996	1	Case study	Hyperlipidemia	Plasma exchange	Pancreatitis resolved with two consecutive plasma exchanges
Keilson et al.[4]	1996	2 (sisters)	Case report	Hyperlipidemia (LPL defect gly188 → glu)	Low-fat diet, cholestyramine	Sister 1: CT showed hemorrhagic pancreatitis Sister 2: Needed multiple postpartum pancreatic debridements
Steinberg et al.[21]	1996	1	Case report	Hyperlipidemia (LPL deficiency trp421 → arg his421 → arg)	Medical, low-fat diet	Authors found that increased uptake of triglyceride-rich lipoproteins by macrophages is aided by apoE enrichment
Suga et al.[19]	1998	1	Case report	Hyperlipidemia (LPL deficiency missense of exon 8)	Dietary intervention	Pancreatitis resolved, delivered healthy baby
Knobell et al.[15]	1998	1	Case report	Hyperlipidemia	Medical, zero-fat diet	Pancreatitis gradually resolved

LPL = lipoprotein lipase; LDL = low-density lipoprotein; TPN = total parenteral nutrition.

in lipid metabolism are at an even higher risk for acute pancreatitis during pregnancy. For example, more than 30 mutations have been identified in the lipoprotein lipase gene in women with gestational pancreatitis.[4,24,28] The lipoprotein lipase gene, which codes for a 474 amino acid enzyme, is crucial for regulating triglyceride levels. Ma et al.[24] reported a ser172 → cys mutation in a pregnant East Indian woman with pancreatitis. Her overall lipoprotein lipase activity was 27 nmoles/min (normal 230 nmoles/min), resulting in a 10-fold increase in plasma triglycerides. Interestingly, lipoprotein lipase activity increased to 138 nmoles/min immediately post partum, with rapid normalization in plasma triglycerides. Apolipoprotein deficiencies also may be involved in gestational hyperlipidemia, interfering with the hepatic clearance of circulating lipoproteins.[21,29] In all likelihood, additional genetic causes of hyperlipidemia will be identified with the potential for future DNA screening.

Because of the rarity of the disease and lack of prospective data, the treatment for acute pancreatitis during pregnancy is unclear. Citing data from nonpregnant patients with acute edematous pancreatitis, or citing anecdotal case reports, several early studies have advocated medical management, consisting of the restitution of third-space losses, bowel rest, and supportive care. In keeping with the natural history of acute edematous pancreatitis, patients generally did well. Historically, surgery has been reserved for severe cases in which patients were taken to the operating room in profound shock, having failed all nonoperative efforts to control the disease. There are few data to guide treatment when cases progress to severe (necrotizing) acute pancreatitis. Based on prohibitively high mortality rates following the surgical management of necrotizing pancreatitis in nonpregnant patients, some investigators are even more tentative in promoting operative intervention in the pregnant patient with necrotizing pancreatitis.[30]

Herein we revisit an innovative and safe surgical treatment for necrotizing pancreatitis in the peripartum period—namely, marsupialization of the retroperitoneum. Initial blunt necrosectomy of the pancreatic bed through a midline incision is followed by marsupialization of the retroperitoneum through a separate flank laparostomy incision. This technique allows adequate and ready exposure to the evolving pancreatic and retroperitoneal necrosis, without repetitive violation of the peritoneal cavity. Preliminary analysis of an ongoing prospective study at our institution suggests that operative treatment of necrotizing pancreatitis via retroperitoneal marsupialization can significantly reduce the morbidity and mortality of this frequently lethal condition. In contrast to reported mortality rates of 15% to 40%,[31-33] the overall mortality rate at our institution over the past 8 years has been less than 5% (unpublished data).

CONCLUSION

Acute pancreatitis, pregnancy, and hyperlipidemia comprise a clinical triad that demands rapid diagnosis and treatment to minimize fetal and maternal mortality. Hyperlipidemia is a rare cause of acute pancreatitis and must be recognized during pregnancy, especially in those women with known defects in lipid metabolism. If diagnosed early, bowel rest, intravenous hydration, and slow progression to a nonfat diet are often adequate interventions. In the rare patient who develops pancreatic necrosis, such as the woman presented in this report, operative management may be warranted. We believe that aggressive surgical management can be safely performed in this setting. The method of retroperitoneal marsupialization via flank laparostomy incisions is a safe alternative to standard repeat laparotomies and may be a useful adjunct to the surgical management of this complex and challenging pancreatic disease.

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Mediators for Fat-Induced Ileal Brake Are Different Between Stomach and Proximal Small Intestine in Conscious Dogs

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Our aim was to determine the mechanisms by which intraileal fat alters proximal gastrointestinal motility—the ileal brake. Five mongrel dogs with ileal Thiry-Vella fistulas were equipped with strain gauge force transducers on the upper gut to measure contractile activity. Ileal infusions of 115 mmol/L oleic acid and triglyceride were studied in dogs with extrinsically innervated and extrinsically denervated Thiry-Vella loops. Plasma concentrations of peptide YY and total glucagon-like immunoactivity were measured. Oleic acid but not triglyceride inhibited postprandial contractions in the gastric antrum in dogs with innervated and denervated Thiry-Vella loops. Postprandial duodenal and jejunal motility was inhibited by oleic acid regardless of extrinsic denervation to the loops ($P < 0.05$), but triglyceride inhibited small intestinal motility only in dogs with innervated Thiry-Vella loops. Intraileal oleic acid but not triglyceride increased plasma concentrations of peptide YY and total glucagon-like immunoactivity in dogs with innervated and denervated Thiry-Vella loops. Intraileal oleic acid inhibits gastric and small intestinal motility possibly via increased plasma concentrations of peptide YY and enteroglucagon. Intact extrinsic innervation is necessary for intraileal triglyceride to inhibit small intestinal motility. (J GASTROINTEST SURG 2001;5:377-382.)

KEY WORDS: Enteroglucagon, extrinsic nerves, oleic acid, peptide YY

The feedback mechanism by which the presence of nutrients in the ileum inhibits upper gastrointestinal motility and transit has been called the ileal brake.[1] The inhibitory response of upper gastrointestinal motility differs with the nutrients infused into the ileum. Fat infused into the ileum as oleic acid or medium-chain triglycerides inhibits jejunal motility, whereas protein and carbohydrate have no effect in humans.[2] Other investigators, however, reported that protein, fat, and carbohydrate all have similar inhibitory effects on upper gastrointestinal motility in dogs.[3] These contrasting results may be secondary to differences in species or in caloric content, osmolality, or pH of the test solutions evaluated. Nevertheless, it is generally accepted that fat is the most appropriate test nutrient for study of the ileal brake.

The ileal brake may be mediated by humoral and/or neural factors. Plasma concentrations of peptide YY (PYY), enteroglucagon (EG), and neurotensin are increased during infusion of oleic acid and triglyceride into the ileum.[2] Among these peptides, several studies have suggested that PYY is the most likely humoral mediator of the ileal brake.[4,5] Although the role of EG or neurotensin in the ileal brake remains controversial, intraileal infusion of Intralipid delayed small bowel transit but was not associated with altered plasma concentrations of EG or neurotensin.[6] Support for neural mediators of the ileal brake also exists. Extrinsic denervation of the ileum blocked the inhibitory effect of intraileal lipid on upper gastrointestinal motility in rats.[7] Also, naloxone, 5-HT_3 antagonist, adrenoceptor antagonist, and cholecystokinin an-

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tagonist blocked the inhibitory effect of the ileal brake.[8-11]

The aim of this study was to attempt to define the mechanisms by which upper gut motility is altered by hormonal and neural factors. Our hypothesis was that inhibition of gastric motility is mediated by increased serum concentrations of PYY and EG, whereas external innervation of the ileum is more important in mediating the inhibition of small intestinal motility. The specific aim of the present study was to determine the mechanisms by which infusion of oleic acid and triglyceride into extrinsically innervated and extrinsically denervated ileal loops alters gastric and small intestinal motility and plasma levels of PYY and EG.

MATERIAL AND METHODS

Preparation of Animals

Five mongrel dogs of both sexes were used. Anesthesia was induced with intravenous thiopental (25 mg/kg; Tanabe Seiyaku Co., Ltd., Osaka, Japan) and maintained with inhaled halothane (Takeda Chemical Industries, Osaka, Japan). Four strain gauge transducers (F-12IS, Star Medical, Inc., Tokyo, Japan) were sutured onto the upper gut to measure contractile activity of the circular muscle layer. The first transducer was positioned on the gastric body opposite the splenic hilum, and the second on the antrum 4 cm proximal to the pylorus. The third transducer was sewn to the duodenum at the level of the main pancreatic duct, and the fourth was sewn to the jejunum 10 cm distal to the ligament of Treitz. Thiry-Vella loops were constructed from the distal ileum composed of one fourth of the total length of the jejunoileum and ending 10 cm from the ileocecal junction. Continuity of the alimentary tract was reestablished by an end-to-end ileoileal anastomosis. After the experiments were completed in the dogs with innervated (normal) Thiry-Vella loops, all dogs were reoperated, and the extrinsic nerves innervating the Thiry-Vella loop were transected by meticulously removing all connective tissue around the arteries and veins supplying the loop. The dogs were housed in individual cages and fed a mixture of solid and canned food (ED-1, Oriental Yeast Co., Tokyo, Japan; and Vita One Crux, Japan Pet Food Co., Tokyo, Japan), 30 g/kg body weight. Two weeks was allowed as a recovery period after each operation.

Recording of Gastrointestinal Motility

Upper gastrointestinal motility was recorded on a multichannel recorder (MS-0836, Graphtec Co., Tokyo, Japan), and on a computer (PC-9801BX, Nippon Electric Co., Ltd., Tokyo, Japan) by connecting the wires from the transducers to the amplifier (MS08S, Star Medical).

Experimental Protocol

All experiments were begun in interdigestive phase 1 after at least one complete migrating motor complex cycle was recorded (two phase 3 contractions). A 14 F Foley catheter (Create Medic Co., Ltd., Yokohama, Japan) was introduced into each end of the Thiry-Vella loop, the balloons were inflated with 3 ml distilled water to prevent test solutions from exiting the loop, and the catheter at the distal end of the loop was clamped. The test solution or 150 mmol/L NaCl was warmed to 40° C and infused into the Thiry-Vella loop through the proximal catheter at 1.5 ml/min for 60 minutes. The test solution consisted of either intralipid (Pharmasia AB, Stockholm, Sweden), 90 ml of which contained 9 g soybean oil or oleic acid (115 mmol/L). Blood samples were collected from a peripheral upper extremity vein 5 minutes before feeding and at 15, 30, 45, 60, 90, and 120 minutes after feeding. The 400 g of canned food (this canned food had a volume of 600 ml and contained 10% protein, 5% lipids, and 82% water, and 85 calories per 100 g) was given immediately after the start of infusion of saline or test solution into the ileal loop. Blood samples were collected in ice-chilled glass tubes containing ethylenediaminetetraacetic acid (EDTA) and aprotinin (NT-EA0205, Nipro Co., Osaka, Japan); the plasma was separated and stored at −30° C until assay. The same experiment was repeated twice, and the mean of the two studies was regarded as a representative value for that dog. The administration of intraileal solution was performed once a day in a random order. The intraileal solution was not washed after each experiment.

Measurement of Peptide

Glucagon-like immunoreactivity was measured by radioimmunoassay using antiserum G25 as reported previously,[12] and immunoreactive PYY with a PYY radioimmunoassay kit (RIK-7173, Peninsula Co., Belmont, Calif.). All serum was measured in a duplicate assay. The integrated outputs of these peptides were calculated by the cumulative incremental responses of glucagon-like immunoreactivity and PYY (0 to 120 minutes).

Data Analysis

Motor activity was quantitated as the motor index by totaling the areas between the baseline and contractile waves at all transducer sites using a commer-

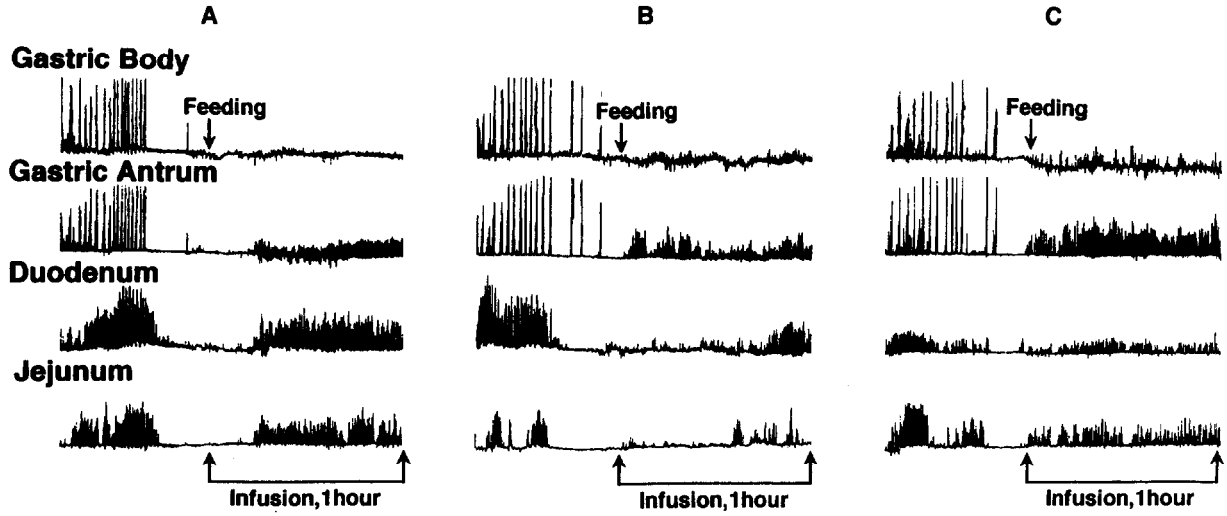

Fig. 1. Postprandial contractile waves with infusion of various solutions into innervated ileal Thiry-Vella loops. **A,** Saline; **B,** Oleic acid; **C,** Triglyceride.

Table I. Effect of ileal infusion of oleic acid and triglyceride on postprandial motor index in dogs with innervated and denervated Thiry-Vella loops

	Control	Oleic acid	Triglyceride
Innervated			
Antrum	1.39 ± 0.17	0.77 ± 0.07*	1.56 ± 0.18
Duodenum	1.50 ± 0.22	0.70 ± 0.14*	0.83 ± 0.12*
Jejunum	1.61 ± 0.21	0.76 ± 0.18*	0.96 ± 0.15*
Denervated			
Antrum	1.76 ± 0.25	0.91 ± 0.06*	1.59 ± 0.30
Duodenum	2.14 ± 0.26	1.02 ± 0.03*	1.93 ± 0.33
Jejunum	2.10 ± 0.38	0.62 ± 0.14*	1.89 ± 0.34

Values are mean ± standard error; n = 5 dogs.
*P <0.05 indicates significant difference compared to control values.

cial computer program (Eight Star, Star Medical). The motor indexes in the first postprandial hour were expressed as a ratio with the mean motor indexes for the interdigestive phase 3 contractions. All values are expressed as mean ± standard error. Values were compared using a paired t test with correction for multiple comparisons; P values <0.05 were regarded as significant.

RESULTS

Effects on Motility

In dogs with extrinsically innervated Thiry-Vella loops, phase 3 contractions were observed at intervals of 121 ± 21, 126 ± 22, 132 ± 18, and 118 ± 20 minutes in the gastric body, antrum, duodenum, and jejunum, respectively. Feeding interrupted this interdigestive pattern, and contractile activity assumed a postprandial pattern of regular phasic contractions. These patterns of motor activity were not altered after extrinsic denervation of the ileal Thiry-Vella loops.

Intraileal saline had no apparent effect on the pattern of postprandial upper gastrointestinal motility or on the motility indexes in either group (Figs. 1, *A* and 2, *A*). In contrast, infusion of oleic acid into innervated loops significantly inhibited postprandial contractions in the antrum, duodenum, and jejunum (Fig. 1, *B* and Table I), whereas triglyceride inhibited postprandial contractions in the duodenum and jejunum but had no effect on antral contractions (Fig. 1, *C* and Table I).

In dogs with extrinsically denervated loops, oleic acid also inhibited postprandial contractions in the gastric antrum, duodenum, and jejunum (Fig. 2, *B* and Table I). However, infusion of triglyceride did not alter contractile activity at any site (Fig. 2, *C* and Table I).

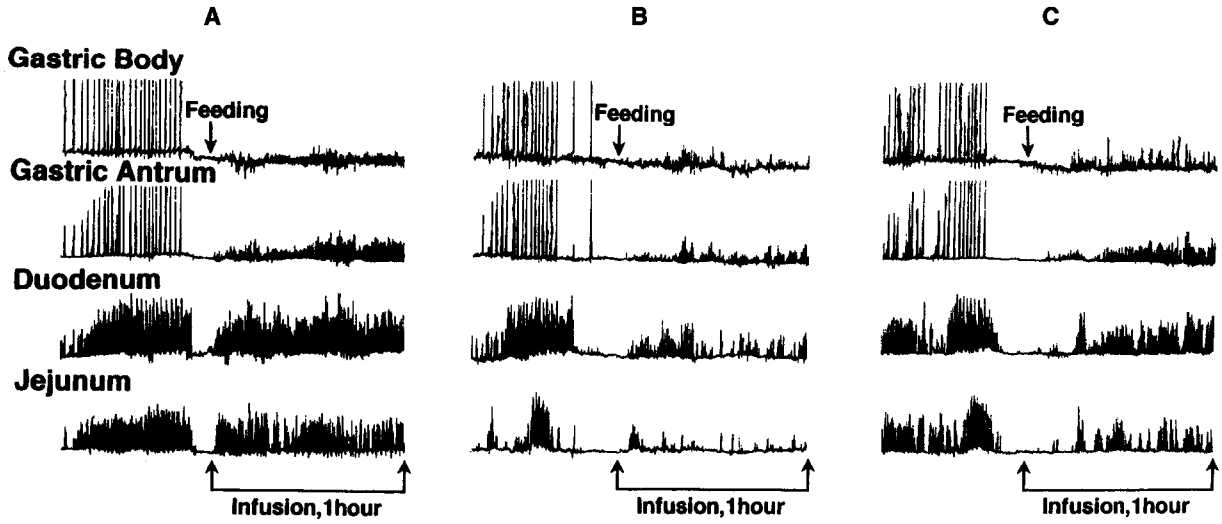

Fig. 2. Postprandial contractile waves with infusion of various solutions into denervated ileal Thiry-Vella loops. **A,** Saline; **B,** Oleic acid; **C,** Triglyceride.

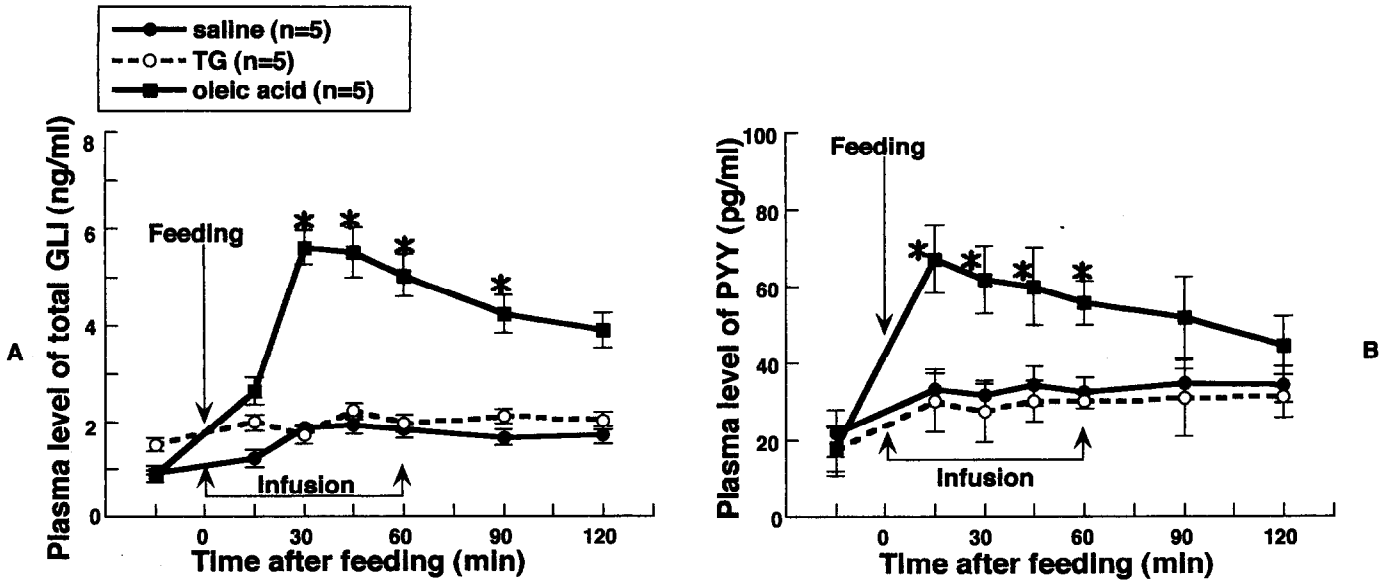

Fig. 3. Changes in plasma level of total glucagon-like immunoreactivity **(A)** and peptide YY **(B)** during ileal infusion in dogs with innervated Thiry-Vella loops. Values are mean ± standard error; n = 5 dogs. *P <0.05 compared to saline infusion.

Table II. Changes in total response of total glucagon-like immunoreactivity (GLI) and peptide YY (PYY) during ileal infusion in dogs with innervated and denervated Thiry-Vella loops

	Control	Oleic acid	Triglyceride
Innervated			
GLI (120 min · ng/ml)	199 ± 18	513 ± 46*	238 ± 20
PYY (120 min · ng/ml)	3930 ± 512	6440 ± 1020*	3530 ± 785
Denervated			
GLI (120 min · ng/ml)	162 ± 23	534 ± 53*	224 ± 30
PYY (120 min · ng/ml)	3250 ± 353	6070 ± 816*	3440 ± 591

Values are mean ± standard error; n = 5 dogs.
*P <0.05 compared to control values.

Effect on Hormones

Infusion of oleic acid into extrinsically innervated Thiry-Vella loops increased postprandial plasma concentrations of PYY and total glucagon-like immunoreactivity compared to control values at 15 to 60 minutes and 30 to 90 minutes, respectively (Fig. 3). Integrated outputs of PYY and glucagon-like immunoreactivity for 120 minutes after feeding were increased compared to NaCl infusion (Table II). Infusion of triglyceride into these innervated loops did not alter postprandial plasma concentrations of PYY or glucagon-like immunoreactivity compared to NaCl infusion at any time point after feeding; integrated responses were not altered by intraileal infusion of triglyceride in dogs with innervated Thiry-Vella loops (see Table II). The effects of intraileal infusion of oleic acid or triglyceride into extrinsically denervated loops on PYY and EG did not differ from the effects on innervated loops.

DISCUSSION

In the present study we infused lipid into ileal Thiry-Vella loops to study the mechanism of the ileal brake. We used this model rather than infusing lipid into the intact ileum, which has continuity with the rest of the bowel, for two reasons. First, ileal loops are free from pancreatic juice and bile. We were able to see the pure effect of intraileal triglyceride on upper gastrointestinal motility in our model, which is not possible in a model where triglyceride infused into the ileum must be digested into fatty acids because of pancreatic juice and bile, which come from the proximal small intestine. Second, lipid infused into the ileum did not reach the colon in our model. It is known that a "colonic" brake also exists, in addition to the ileal brake.[13] It is possible that lipid infused into the intact ileum enters the colon and induces both ileal and colonic brakes.

We showed that the postprandial motor response of the gastric antrum to intraileal fat did not differ between dogs with innervated and denervated ileal Thiry-Vella loops; ileal infusion of oleic acid significantly inhibited postprandial antral contractions, whereas triglyceride infused into the ileal loops had no effect on these contractions. Intraileal infusion of oleic acid showed an inhibitory effect on duodenal and jejunal motility in dogs with innervated and denervated Thiry-Vella loops. However, the motor response in the duodenum and jejunum to intraileal triglyceride was different between dogs with innervated and denervated Thiry-Vella loops; intraileal infusion of triglyceride, which significantly inhibited duodenal and jejunal motility in dogs with innervated ileal Thiry-Vella loops, showed no effect in dogs with denervated ileal Thiry-Vella loops. Plasma concentrations of PYY and total glucagon-like immunoreactivity were increased during intraileal infusion of oleic acid, but not triglyceride, both in dogs with innervated and denervated Thiry-Vella loops. Previously we reported that PYY and glicentin, a major component of EG, significantly inhibited antral motility.[14] Taking all these findings into account, it might be said that different intraileal fats inhibit upper gastrointestinal motility through different mechanisms between the stomach and proximal small intestine. Inhibition of gastric and small intestinal motility induced by intraileal oleic acid, at least in part, must depend on an increase in PYY or total glucagon-like immunoreactivity and is not related to ileal extrinsic nerves. Intact extrinsic innervation is necessary for intraileal triglyceride-induced inhibition of small intestinal motility.

In this study we found that plasma concentrations of PYY and total glucagon-like immunoreactivity were increased during intraileal infusion of oleic acid. Most of the total glucagon-like immunoreactivity is considered to be released from the intestine; pancreatic glucagon is only 5% to 10% of the total glucagon-like immunoreactivity.[15] Therefore total glucagon-like immunoreactivity must represent EG. It is likely that PYY is one of the mediators for the ileal brake based on our present results and previous reports.[4,5] We believe that EG must also be involved in the ileal brake as a humoral factor. Previously we reported that intravenously injected glicentin, a major component of EG, significantly inhibited postprandial contractions in the gastric antrum similar to PYY.[14] Furthermore, it was confirmed that plasma levels of EG are increased during ileal infusion of oleic acid.

The role of neural factors in the ileal brake has been reported in several articles. Systemic administration of naloxone, 5-HT_3 antagonist, adrenoceptor antagonist, or cholecystokinin-receptor antagonist was reported to block the effect of a fat-induced ileal brake.[8-11] Surgical extrinsic denervation of the ileum also abolishes the inhibitory effect of intraileal fat on small intestinal motility.[7]

However, there was no study showing the role of ileal extrinsic nerves in the enhanced release of peptide during intraileal fat infusion. We found that ileal extrinsic nerves are not important in the oleic acid–induced release of PYY and EG. Intraileal triglyceride inhibits proximal small intestinal motility but not gastric motility through extrinsic nerves innervating the loop, and this phenomenon was considered to be independent of peptide release. Although we could not determine which receptor on the mucosa was involved in this triglyceride-induced response from the present results, involvement of mechanoreceptors in ileal mu-

cosa is unlikely because infusion of saline into the ileum had no effect on duodenal and jejunal motility. Triglyceride in the ileum must stimulate osmoreceptors or chemoreceptors, and this stimulus would be transmitted through extrinsic nerves. Why infusion of triglyceride into innervated ileal loop failed to inhibit gastric motility also remains undetermined.

Our model might be slightly different from the physiologic state in the sense that the ileal loop atrophied in the absence of intraluminal contents. We performed all studies within 4 weeks after surgery to minimize this effect, and intraileal infusion of oleic acid was potent enough to increase serum levels of peptides in dogs with innervated and denervated Thiry-Vella loops. Thus we believe that stimuli obtained by infusion of lipids into Thiry-Vella loops are as strong as those obtained by infusion of lipids into intact normal ileum. It also would be good to perform transection and reanastomosis of arteries and veins feeding the loop as a method of extrinsic denervation. We consider that almost all extrinsic nerves are denervated because a method such as ours that removes all tissues except for arteries is reported to be satisfactory by the other investigators.[16]

In the present study, we closed the distal end of the loop to prevent test material from exiting the loop. We used this method to allow the intraileal fat to come in contact with mucosa for a long period and to obtain stronger stimuli than if the distal end were left open. With our method we might be looking at the effects of increased intraileal pressure as well as the effect of fat coming in contact with mucosa on upper gastrointestinal motility. We believe this is unlikely because intraileal saline did not show any effect on upper gastrointestinal motor activity. It is also possible that fat but not saline will stimulate the secretion of mucus and increase the volume of intraileal material; we cannot deny the possibility that an increase in intraileal volume by fat could, at least in part, contribute to the inhibitory effect on upper gastrointestinal motility.

The concentration of oleic acid used in this study (115 mmol/L) was much higher than the physiologic concentrations in canine ileum. In fact, 15 mmol/L oleic acid significantly inhibited intestinal transit.[17] We used oleic acid in high concentrations to obtain an apparent effect on upper gastrointestinal motility. We may need to look at the effects of lower doses of oleic acid.

CONCLUSION

Ileal perfusion with oleic acid into an enterically isolated Thiry-Vella loop inhibits gastric and small intestinal motility, possibly through increased plasma levels of PYY and EG. Ileal infusion of triglyceride inhibits small intestinal motility but not gastric motility through, in large part, extrinsic nerves innervating the ileum, and this phenomenon is independent of increased plasma levels of PYY or EG.

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Results of Salvage Abdominoperineal Resection for Recurrent Anal Carcinoma Following Combined Chemoradiation Therapy

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Combined chemotherapy and radiation therapy is the standard treatment for epidermoid carcinoma of the anal canal. Failures are often not associated with distant recurrence and are therefore potentially amenable to salvage abdominoperineal resection. The aim of this study was to review our experience with abdominoperineal resection following failure of chemoradiation therapy for epidermoid carcinoma of the anus. Between 1980 and 1998, 17 patients underwent salvage abdominoperineal resection following failure of chemoradiation therapy. Four patients were excluded from survival analysis because resection was performed with palliative intent. Survival curves were based on the method of Kaplan and Meier, and univariate analysis of predictive variables was performed using the log-rank test. Twelve patients underwent abdominoperineal resection for persistent disease and five patients for recurrent disease. No operative deaths occurred, but local complications including perineal wound infection and wound breakdown was seen in 8 of 17 patients and 6 of 17 patients, respectively. Patients undergoing omental flap reconstruction (n = 3) or no pelvic reconstruction (n = 5) had a higher incidence of perineal breakdown compared to those undergoing muscle flap reconstruction (n = 9) ($P < 0.05$). The median follow-up time for the patients operated on with curative intent was 53 months. The 5-year actuarial survival was 47%. Potential prognostic factors that were not found to have an impact on survival included margin status of resection, sphincter invasion, and degree of differentiation. Only pathologic tumor size greater than 5.0 cm ($P < 0.001$) and age over 55 years ($P < 0.05$) adversely affected survival. Selected patients with recurrent or persistent anal carcinoma following chemoradiation therapy can be offered salvage abdominoperineal resection. This operation is associated with a high incidence of local wound complications, and muscle flap reconstruction should be considered when possible. Prolonged survival can be achieved in some patients following salvage resection for epidermoid carcinoma of the anal canal. (J GASTROINTEST SURG 2001;5:383-387.)

KEY WORDS: Anal, epidermoid, recurrence, abdominoperineal resection

Epidermoid cancer of the anus accounts for 1% to 2% of large bowel malignancies and 2% to 4% of anorectal malignancies.[1,2] Combined chemotherapy and radiation therapy, introduced in 1974 by Nigro et al.,[3] is considered the standard treatment with overall survival rates of 60% to 80%.[4-6] However, local failure can occur in up to 30% of patients treated with curative intent.[7-11] These recurrences are often localized and therefore potentially amenable to salvage therapy.[12] However, concern about increased morbidity from such a procedure following chemoradiation, as well as the unclear long-term outcome in these patients, has curbed the enthusiasm for aggressive surgical therapy. The aim of this study was to evaluate our experience with abdominoperineal resection (APR) following failure of chemoradiation therapy (CRT) for epidermoid carcinoma of the anus.

MATERIAL AND METHODS

Patients

From January 1, 1980 to December 31,1998, eighteen patients underwent APR at Johns Hopkins Hospital following failure of initial CRT. One patient was excluded because of concomitant vulvar carcinoma. Hospital discharge data, medical records, and tumor

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registry information were reviewed for these 17 patients. Histologic diagnosis was confirmed in all cases. Eight patients were initially treated with CRT at Johns Hopkins Hospital, whereas the other nine patients were treated at other hospitals. Four patients were excluded from survival analysis because they underwent APR with palliative intent. Of these patients, one patient was HIV positive with bulky disease, one patient had known iliac nodal metastases prior to resection, and two patients had liver metastases identified at the time of operation.

Statistics

Univariate analysis of predictive variables was performed using the log-rank test. A P value <0.05 was considered statistically significant. Survival curves were calculated from the time of APR and were based on the method of Kaplan and Meier.[13] Analysis of perioperative morbidity was performed by means of Fisher's exact test.

RESULTS

Patient Characteristics

The study included nine men and eight women ranging in age from 34 to 73 years. Mean age at diagnosis was 54 years. Initial staging of patients and the type of CRT are shown in Table I. External beam radiation therapy was used with an average dose of 5275 cGy (3400 to 6000 cGy). Patients were also classified by disease-free interval following CRT. Persistent disease (n = 12) was defined as malignancy was documented by repeat biopsy within 6 months following completion of CRT. Disease was defined as recurrent (n = 5) when an initial post-treatment biopsy was normal and a recurrence was identified by repeat biopsy more than 6 months following completion of CRT.

Table I. Characteristics of patients undergoing salvage abdominoperineal resection

	Characteristics
Demographics	
Total patients	17
Age >55 years	8
Males:Females	8:9
Initial tumor stage	
Stage I	1
Stage II	11
Stage IIIa	1
Stage IIIb	4
Degree of differentiation	
Grade I	4
Grade II	4
Grade III	7
Nongraded	2
Type of chemotherapy	
5-FU/MMC	13
5-FU	1
5-FU/cisplatin	2
5-FU/MMC/LV	1
Disease interval	
Residual (<6 mo)	12
Recurrent (>6 mo)	5
Type of operation	
Abdominoperineal resection only	15
Pelvic exenteration	2
Operative intent	
Curative	13
Palliative	4
Reconstruction type	
None	5
Rectus abdominis flap	4
Gracilis flap	5
Omental flap	3
Specimen pathology	
Margin positive	7
Perianal node positive	3
Sphincter muscle invasion	6
Adipose tissue involvement	8
Tumor size >5.0 cm	4
Iliac nodes positive	1
Liver metastases	2

5-FU = 5-fluorouracil; MMC = mitomycin C; LV = leukovorin.

Operative Data

All patients underwent a complete proctectomy with permanent colostomy; two of them also had a posterior pelvic exenteration. One patient was found to have external iliac nodal involvement preoperatively and underwent resection with palliative intent. Two other patients were found to have isolated solitary liver metastasis at the time of surgery, one of whom had a concomitant liver resection.

Reconstruction of the pelvis and the perineum was performed using a variety of techniques. Primary skin closure without reconstruction or pelvic floor closure was performed in five cases. In three cases, an omental pedicle alone was placed within the pelvis. The remaining nine patients had a muscle flap reconstruction—four using vertical rectus abdominis muscle and five using gracilis muscle (Table II). The mean blood loss was 430 ml (range 150 to 1000 ml). The average operative time was 4.6 hours (range 2.5 to 14 hours). Other concomitant resections were performed in eight patients. These included a variety of pelvic exenterations including posterior vaginectomy (n = 7), partial vulvectomy (n = 1), and prostatectomy/cystectomy/seminal vesicle resection (n = 1). In two

Table II. Local wound complications

Type of reconstruction	No.	Infection	Breakdown	Overall complication	Percent
None	5	3	1	3	60
Rectus abdominis	4	1	0	1	25
Gracilis muscle	5	2	2	3	60
Omental pedicle	3	2	3	3	100

patients, deep pelvic lymph node dissection was performed, but none of the patients had an inguinal lymphadenectomy.

Pathology

The pathologic data are also presented in Table I. In three patients, no residual tumor was found on the surgical specimen. In eight patients, tumor involvement of perineal and/or perirectal fat was found on the pathologic specimen, and in seven patients, there was tumor involvement of the margins. Tumor was found to have invaded the sphincter muscle in six patients. In four patients, the pathologic tumor size was greater than 5.0 cm and perianal lymph nodes were involved in three patients.

Postoperative Complications

There were no postoperative deaths in this group of patients. The average hospital stay was 14 days. Local wound complications were seen in 10 (59%) of 17 patients, including perineal wound infection (n = 8) and wound breakdown (n = 6). Local complications varied significantly with the type of reconstruction (see Table II). The local complication rate for primary closure was 60% (3 of 5 patients). Reconstruction with an omental pedicle had a similarly high rate of wound breakdown/infection (3 of 3 patients). Muscle flap reconstruction had a lower complication rate. Only one (25%) of four patients developed local wound complications when a vertical rectus abdominis muscle was rotated into the perineum.

Long-term Outcome

The median follow-up time was 53 months for the patients operated on with curative intent. The overall and disease-free survival curves following salvage APR are shown in Fig. 1. The median overall survival was 33 months with an actuarial 5-year overall and disease-free survival of 47% and 44%, respectively.

On univariate analysis of factors predicting long-term outcome, race, sex, and tumor grade (poorly differentiated vs. other) had no statistical influence on survival or recurrence. Similarly, tumor stage at initial diagnosis (T3 or T4 vs. T1 or T2), lymph node status at initial diagnosis, perianal adipose tissue involvement, positive vs. negative margins, and the presence of residual vs. recurrent disease were all shown to have no impact on survival. Interestingly, only pathologic tumor size greater than 5.0 cm ($P = 0.0002$) and age over 55 years ($P = 0.04$) had a significant negative influence on survival. The impact of pathologic nodal status (at the time of resection) could not be examined because none of the patients undergoing resection with curative intent had histologically positive nodes.

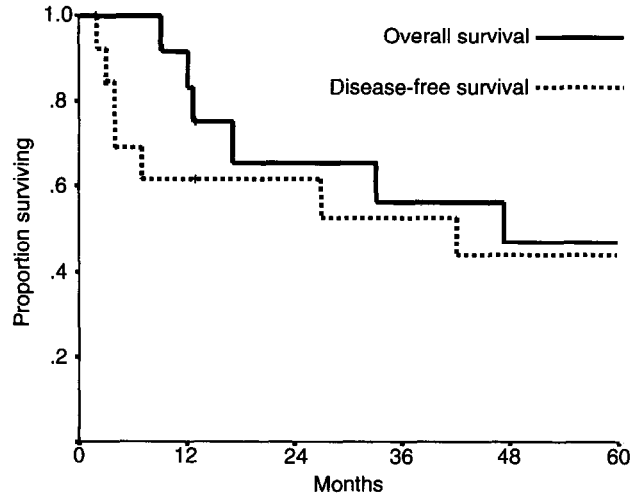

Fig. 1. Actuarial overall and disease-free survival in patients undergoing salvage abdominoperineal resection with curative intent (n = 13).

At the time of the last follow-up, five patients had no evidence of disease, one was alive with disease, and seven had died of their disease. Of the four patients operated on with palliative intent, all died within 6 months. Of the eight patients who had a recurrence following resection with curative intent, five developed their initial recurrence within the pelvis or inguinal nodes alone, whereas three patients had concomitant pelvic and liver recurrences. Adjuvant therapy was not administered to any patient following resection. Among those patients who had a recurrence, four were treated with further chemotherapy, principally cisplatin-based regimens.

DISCUSSION

Since the initial report by Nigro et al.,[3] a combination of chemotherapy and radiation therapy has become the principal treatment modality for epidermoid carcinoma of the anal canal, with observed 5-year survival rates ranging from 60% to 80%.[4-6] In selected cases, surgical resection is considered the treatment of choice for salvage therapy for failure following CRT. Our study supports this general approach, with a 47% 5-year survival rate for those operated on with curative intent. The small sample size of this study limited the ability to perform meaningful statistical analysis of prognostic factors. This study failed to demonstrate clear predictors of long-term outcome in these patients, including margin status, tumor stage, and disease-free interval following CRT. Only large tumor size and advanced age were associated with decreased survival.

Several other small retrospective series have examined the question of salvage APR (Table III). Ellenhorn et. al.[12] reported on a series of 38 patients with a 5-year survival rate of 44%. They found that only the presence of inguinal adenopathy, pelvic wall fixation, and perirectal adipose tissue involvement was correlated with worse survival. In two other reports, Pocard et al.[14] and Zelnick et al.[15] reported 5-year survival rates of 33% and 24%, respectively, for patients similarly treated with aggressive surgical therapy.

Residual or persistent disease compromises 10% to 15% of the failures of CRT, and another 10% to 15% of patients have disease that recurs after a complete response.[11] In this study, 12 (70%) of 17 patients were operated on for residual disease. There was no difference in survival between patients with persistent versus recurrent disease. These results are similar to those in other studies.[12,16] Pocard et al.[14] reported a trend toward improved survival for patients with residual tumor (72% vs. 29%), although the differences were not statistically significant. Interestingly, 86% of patients in that study had radiation therapy alone as their initial treatment.

Three patients had no residual disease at the time of salvage resection, in spite of documented persistence or recurrence on biopsy. One explanation may be that the preoperative biopsy resulted in complete excision of the site of recurrence. Alternatively, these cases may represent patients in whom a continued response was achieved with CRT after the biopsy. Although no statistical difference in survival or local recurrence was seen in these patients compared to those with residual disease, inclusion of these cases may partially explain our encouraging results.

The incidence of local wound complications is high following salvage APR for epidermoid cancer compared to resections for rectal carcinoma. Even in patients treated for rectal cancer following CRT, wound complication rates are reported to be between 3% and 5%.[17] Clearly, the differences are due to the extent of CRT, including differences in radiation fields, as well as the timing of the resection relative to radiation therapy. In this series, the perineal wound infection rate was 41% and wound breakdown was seen in 35% of cases. Interesting observations regarding pelvic and perineal reconstruction are seen in these patients. Those patients undergoing muscle flap reconstruction appeared to have a lower wound complication rate. Although omental flap reconstruction was performed in only three patients, wound complications were seen in all of them. In one report in which 76% of patients underwent omentoplasty, no perineal wound breakdown was seen.[14] Ellenhorn et. al., using only primary closure or open wound packing, reported a 30% perineal wound complication rate.[12]

Table III. Summary of reported series of long-term outcomes following salvage abdominoperineal resection for anal carcinoma

Reference	No. of patients	Median survival (mo)	5-year survival (%)
Zelnick et al.[15] (1992)	9	20	24
Ellenhorn et al.[12] (1994)	38	41	44
Pocard et al.[14] (1998)	21*	35	33
Current study	13†	33	47

*Radiation therapy alone.
†Thirteen of 17 treated with curative intent.

Eight of the 13 patients operated on with curative intent developed recurrent disease following resection. Five had a local recurrence, and the other three had concurrent distant metastatic disease. In addition to salvage APR, other therapeutic options have been suggested following recurrence or persistence of cancer after CRT. Some studies suggest that some patients can be salvaged with further chemotherapy, particularly platinum-based therapy.[2] Given the high recurrence rate and potential for postoperative morbidity, salvage chemotherapy should be considered.

CONCLUSION

Based on the preceding results, salvage APR should be considered in patients with persistent or recurrent disease following initial CRT for epidermoid carcinoma of the anal canal. For those patients who have

only localized disease, or when palliative therapy is being considered, APR can result in long-term survival in selected patients. When performing resection in these cases, strong consideration should be given to muscle flap reconstruction in order to avoid wound complications.

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Ischemic Colitis in Young Adults: A Single-Institution Experience

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Ischemic colitis is not well characterized in the young adult population, despite its commonness in older patients. The aim of this study was to investigate the demographics, etiology, clinical features, and prognosis of ischemic colitis in young adults. We conducted a retrospective study of 39 young adults (<50 years of age) diagnosed with ischemic colitis over a period of 9 years (1990 to 1998). The mean age at diagnosis was 38 ± 2 years (range 18 to 49 years); the female:male ratio was 1.8. Fifty-two percent (13 of 25) of women were using oral contraceptives at the time of diagnosis. Other potential associations identified were vascular thromboembolism (4 of 39), vasoactive drugs (4 of 39), hypovolemia (4 of 39), and vasculitis (2 of 39); 19 patients (49%) had no identifiable predisposing factors. Dominant presenting symptoms were abdominal pain (77%), bloody diarrhea (54%), and hematochezia (51%). Most patients were diagnosed at colonoscopy, and most disease was left sided. Twenty-nine patients were successfully managed with intravenous fluids, broad-spectrum antibiotics, and bowel rest; 10 patients required surgery. There was one disease-related death in the operative group. We found a strong female predominance and an association with oral contraceptive use, but almost half of the patients did not have an identifiable etiology. Mortality from ischemic colitis in this patient population is low. (J GASTROINTEST SURG 2001;5:388-392.)

KEY WORDS: Ischemic colitis, young adults, oral contraceptives

Ischemic colitis is the end pathophysiologic result of a lack of blood flow to the colon, and as such has diverse etiologies. Thus it is logical that the incidence, pathophysiologic mechanisms, and etiologic factors may differ between age groups. The majority of cases have been shown to predominantly affect the elderly and debilitated, with a male gender predominance.[1,2] The disease is seen less commonly in young adults, and only a few studies to date have focused on this age group.

PATIENTS AND METHODS

Mayo Clinic medical records of young adults (<50 years of age) with biopsy-proved ischemic colitis over a 9-year period (1990 to 1998) were identified. Charts were reviewed for demographic information, possible associated factors, clinical presentation, treatment, complications, and outcome. All of the patients included in the study were culture negative for infectious forms of colitis. Patients with other types of colitis (inflammatory, lymphocytic, or bacterial) were excluded.

RESULTS

Thirty-nine patients diagnosed with ischemic colitis whose medical records were available for review were identified for the 9-year study period. The mean follow-up period was 21 ± 3 months (range 2 days to 77 months). Mean age at the time of diagnosis was 37.8 ± 1.3 years (range 18 to 49 years). Twenty-five (64%) of 39 patients were female, giving a female:male ratio of 1.8. Thirteen (52%) of the 25 women were using oral contraceptives at the time of diagnosis, and four patients were concomitantly taking ergotamine products for migraine headaches. Other identifiable etiologic factors identified were vascular thromboem-

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Table I. Etiology of ischemic colitis in young adults

	No.
Oral contraceptives	13
Vasoactive medications (ergotamine products)	4*
Low-flow state (hypovolemia, dehydration)	4†
Collagen vascular disease	2
Vascular thrombosis	4
Unidentified etiology	19

*All of them used oral contraceptives.
†Three of them also used oral contraceptives.

Table II. Distribution of disease in our patient population

	No. (%)
Right colon	2 (5)
Transverse colon	5 (13)
Descending colon	11 (28)
Rectosigmoid colon	16 (41)

Table III. Presenting symptoms of ischemic colitis in young adults

	No. (%)
Abdominal pain	30 (77)
Bloody diarrhea	21 (54)
Hematochezia	20 (51)

bolism (4 of 39), low-flow state with hypovolemia (4 of 39), and vasculitis (2 of 39). Some patients had more than one predisposing factor (Table I). Nineteen patients (49%) had no identifiable etiology. Concurrent diseases were found in 15 patients (38%) and included cardiovascular disease, diabetes, hypothyroidism, and renal failure; most had only one associated disease. Given these small numbers, a direct correlation between these medical conditions and ischemic colitis could not be established.

The distribution of disease was heavily weighted toward the left side of the colon, with 69% of patients having ischemia in either the rectosigmoid (n = 16) or the descending colon (n = 11). Only five patients (13%) had ischemia of the transverse colon, and two (5%) had ischemia of the ascending colon (Table II).

Presenting symptoms were generalized; patients complained of acute abdominal pain (77%), bloody diarrhea (54%), and hematochezia (51%) (Table III). Thirty-five patients were diagnosed at colonoscopy, based on findings of edema, erythema, submucosal hemorrhage, and epithelial necrosis. The initial management of these patients consisted of bowel rest, broad-spectrum antibiotics, and intravenous hydration; 29 had satisfactory resolution of disease with no further attacks or long-term sequel such as stricture development during the follow-up period (21 ± 3 months). Two patients in this group died of unrelated disease distant to the episodes of ischemic colitis. The 10 operatively treated patients included the six in whom nonoperative treatment was unsuccessful, as well as four patients diagnosed at exploratory laparotomy. The most common indication for surgery was perforation in five patients followed by deterioration and no clinical improvement in three patients, stricture in one patient, and multiple polypoid masses simulating colonic neoplasm in another patient. The female:male ratio in the operated patients was similar to that seen in the overall study population (1.5 [6:4]). Colon resection was performed in all 10. Seven patients underwent segmental colon resection, two patients underwent subtotal colectomy, and one patient underwent abdominoperineal resection. Eight patients had primary anastomosis, and two received ileostomies. There was one death from sepsis among patients undergoing surgery; the remainder recovered uneventfully.

DISCUSSION

Colonic ischemia affecting young people has been recently recognized in the literature as a relatively distinct clinical entity,[3] and is noted to be an uncommon phenomenon.[4-8] Similar to ischemic colitis in the elderly, the manifestations and clinical courses of these patients were diverse. In contradistinction to the elderly population, the majority of our patients were female, the onset of symptoms was acute, and the associated mortality was only 3%. Our diagnosis was based on the following criteria: acute onset of symptoms as already described; characteristic findings compatible with ischemic colitis as shown by colonoscopy; confirmation that histologic findings in tissue biopsy obtained by colonoscopy or in surgery were consistent with those of ischemic colitis; and negative bacterial cultures in the feces for species of *Salmonella*, *Shigella*, *Vibrio*, *Clostridium difficile*, *Campylobacter*, and *Yersinia*.

Most cases of ischemic colitis occur in the elderly population, more often in men, and are often associated with underlying problems such as cardiovascular disease, diabetes mellitus, renal failure, and hematologic diseases.[1,2] In almost half of these patients, no specific cause was recognized and the "spontaneous" episodes were viewed as localized forms of nonocclusive ischemia. The presentation is variable, reflecting

the fact that ischemia is the final manifestation of multiple pathophysiologic processes. Elderly patients may present with an indolent course and nonspecific complaints that may be attributed to underlying diseases rather than ischemic colitis.[9] The subtlety of the clinical presentation may contribute to a delay in diagnosis,[10] and chronic or relapsing disease may result in the formation of strictures as ischemic areas heal.[11] Fulminant sepsis and multiple organ system failure may result from full-thickness colonic gangrene or perforation, and contribute to the reported high mortality rate of greater than 50% in elderly patients.[12]

The etiology of ischemic colitis may be categorized as occlusive or nonocclusive, the latter being more common. Nonocclusive ischemia is the result of hypoperfusion in the absence of mechanically obstructed blood flow, and is commonly due to hypovolemia or congestive heart failure. Low-flow states may be exacerbated by the following: small vessel atherosclerotic disease, the remarkable sensitivity of the colonic vasculature to the renin-angiotensin axis, and vasoconstrictive drugs such as exogenous catecholamines and cocaine.[4,6,7,9,13-22] Ischemic colitis due to nonocclusive disease may have mild symptoms, or even be subclinical,[23] but more severe disease may be seen as well, especially if underlying factors such as hypovolemia and hemorrhage are not corrected. Occlusive ischemia is a result of complete or partial obstruction of blood flow through the colon vasculature, usually caused by emboli and thrombosis. Affected areas in the colon are usually contiguous, and disease is typically focal in nature. Similar patterns are seen in blunt and penetrating trauma,[24,25] and in right colon ischemia secondary to cecal dilatation.[14,26]

Clinical Presentation

The clinical presentation of abdominal pain, hematochezia, and bloody diarrhea is similar to presentation in the elderly[20]; anorexia, nausea, and vomiting have also been described. Most of our patients, as well as other younger patients reported in the literature, have a relatively more acute onset of symptoms than that seen in the elderly, in whom a more insidious onset is more likely.[12]

Location of Disease

The sites of involvement are fairly consistent in published studies across age groups. Our data, with 69% of cases occurring on the left side of the colon, are similar to the 75% incidence of left-sided lesions in a study of more than 1000 cases and the 78% incidence in another report; both reports included patients of all ages.[18,27] The patients in the series of Matsumoto et al.[21] (all ages) all had left-sided disease. The incidence was evenly distributed between the right and left sides in only one report that focused on elderly patients.[9]

Endoscopic Appearance

Colonoscopic findings in our patients included edema, erythema, patchy superficial ulceration, submucosal hemorrhage, mucosal necrosis, and colonic strictures. Although findings in our patients did not correlate with eventual operation, others have assessed the severity of the disease endoscopically. Signs of reversible ischemia include mucosal hyperemia, friability, and mucosal erosions.[5,17,19] As ischemia progresses, pale mucosa with areas of petechial hemorrhage, erythema, and flat nonconfluent ulcerations can be seen, and more advanced disease is heralded by progressively darker mucosa, deeper more confluent ulcerations, and mucosal sloughing.[9,12,26,28] Strictures from healing of transmural ischemia may be present in 10% to 50% of patients,[14,29] and may be more common in elderly patients with the disease.[20] A rare endoscopic finding in ischemic colitis is a submucosal mass mimicking neoplasia; neoplastic disease unrelated to ischemic colitis may also be present, as was seen in one of our patients.[8,30]

Associated Factors

In nearly half of our patients, no causative etiology was identified. In the remainder, the most interesting association was that of oral contraceptives and ergot alkaloid preparations with ischemic colitis in young adult women. Our study confirms both the female predominance among young adults with ischemic colitis and the association with oral contraceptives noted in other studies.[6,9,17,18] Among the 39 million women aged 15 to 44 years who were practicing contraception in 1995, 10.4 million (27%) used oral contraceptives.[31] Among our 25 female patients, 13 (52%) were using oral contraceptives at the time of the diagnosis of ischemic colitis. This odds ratio indicates a relative risk of 4.8 for the occurrence of the disease among the users of oral contraceptives (Fig. 1). The proposed mechanism is a hypercoagulable state,[6,32] and hyperplasia of arterial endothelium.[33] Four of the patients who were using oral contraceptives were also taking ergot alkaloid preparations for relief of migraine headaches. Although no direct correlation can be established from our data, this is an intriguing association, as ergot alkaloids cause vasoconstriction. Other identified factors were vascular thromboembolism and low-flow state secondary to hypovolemia.

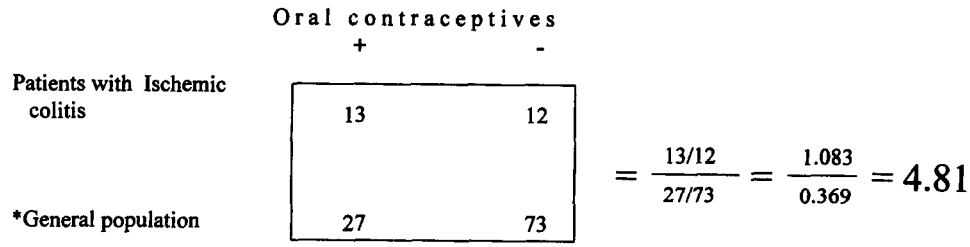

Fig. 1. Oral contraceptives and ischemic colitis. The odds ratio indicates a fivefold relative risk of ischemic colitis in young women while they are taking oral contraceptives. (*General population data from Picinino LJ, Mosher WD. Trends in contraceptive use in the United States 1982-1995. Family Planning Perspectives 30:4-10,46, 1998.)

Treatment

Almost three fourths of our patients had transient, reversible, mild ischemic colitis, which responded well to hydration and intravenous antibiotics; Deana and Dean[27] reported a series of 18 young adults, all of whom behaved similarly. The remaining one fourth of these patients had a more serious course, requiring surgery and a colonic resection, and one patient died as a direct result of this disease. It is worthwhile noting that 17% of patients undergoing initial nonoperative management eventually required laparotomy, with perforation being the most common indication for surgery. Thus it would seem worthwhile to argue for the early involvement of a surgeon in the evaluation and management of these patients.

Prognosis

The prognosis in elderly patients is poorer, and probably reflects a higher incidence of more severe disease and a higher operative rate in addition to the detrimental effects of age and concurrent disease. The incidence of operative intervention is higher in elderly patients, ranging from 50% to 72%, and the operative mortality rate in these patients may be as high as 65%.[8-10] There was one death (3%) directly attributed to colon ischemia in our series; this patient had developed ischemic colitis and sepsis after cardiopulmonary bypass. Other investigators have reported similarly low mortality rates in young adults with ischemic colitis.[5,17,19]

CONCLUSION

Ischemic colitis in young adults represents a distinct clinicopathologic entity that appears to be milder, more transient, and has a lower mortality than its counterpart in the elderly. Occurring more frequently in women, ischemic colitis is associated with the use of oral contraceptives, but half of the patients may have no identifiable predisposing factors. As such, a high index of suspicion in patients with abdominal pain, hematochezia, and bloody diarrhea is warranted. Although most young adults with ischemic colitis respond well to nonoperative therapy, an unpredictable subset will require surgery. Thus close monitoring of patients undergoing conservative treatment is recommended, as is early surgical consultation. The overall prognosis in these patients is excellent.

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Iron Deficiency Suppresses Ileal Nitric Oxide Synthase Activity

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Intestinal motility disorders are more common in women of childbearing age who are prone to iron deficiency anemia. The neurotransmitters nitric oxide (NO) and acetylcholine (ACh) play a key role in ileal smooth muscle relaxation and contraction, respectively. Iron-containing heme is known to be a cofactor for nitric oxide synthase (NOS), the enzyme responsible for NO production. Therefore we tested the hypothesis that iron deficiency would downregulate ileal NOS activity without affecting the ileum's response to ACh. Twelve adult female prairie dogs were fed either an iron-supplemented (Fe+) (200 ppm) (n = 6) or an iron-deficient (Fe−) (8 ppm) (n = 6) diet for 8 weeks. Ileal circular muscle strips were harvested to measure responses to ACh and electrical field stimulation. Under nonadrenergic noncholinergic (NANC) conditions, Nω-nitro-L-arginine (L-NNA), an NOS inhibitor, and VIP_{10-28}, a vasoactive intestinal peptide (VIP) inhibitor, were added prior to electrical field stimulation. NANC inhibitory responses are expressed as a percentage of optimal relaxation from EDTA. The excitatory response to ACh was similar in both groups (1.1 ± 0.3 N/cm² vs. 1.5 ± 0.3 N/cm², $P = 0.45$). The inhibitory response to electrical field stimulation under NANC conditions was greater in the Fe+ group (34.7 ± 2.9%) compared to the Fe− group (23.9 ± 3.2%; $P < 0.01$). L-NNA eliminated the inhibitory response in the Fe+ group (0.02 ± 0.02%) but not in the Fe− group (8.38 ± 2.15%; $P < 0.01$). VIP_{10-28} led to greater relaxation in the Fe+ animals (45.8 ± 6.6%) than in the Fe− animals (23.4 ± 5.8%; $P < 0.05$). Both L-NNA and VIP_{10-28} had no inhibitory response (0.02 ± 0.02%) in the Fe+ animals, whereas the Fe− animals had some residual inhibition (2.54 ± 1.04%; $P < 0.05$). These data suggest that ileal NANC relaxation is due to NOS and that iron deficiency results in (1) decreased NANC relaxation, (2) a compensatory relaxation due to a non-NOS, non-VIP mechanism, and (3) a normal excitatory response. We conclude that iron deficiency suppresses ileal NOS activity. (J GASTROINTEST SURG 2001;5:393-400.)

KEY WORDS: Ileum, nitric oxide synthase, motility, iron deficiency

Intestinal motility disorders such as irritable bowel syndrome are more common in women of childbearing age who are prone to iron deficiency anemia.[1] The etiology of intestinal motility disorders has not been fully elucidated; however, abnormal ileal smooth muscle motility has been implicated.[2] Ileal smooth muscle motility is regulated by excitatory and inhibitory neurotransmitters. Acetylcholine (ACh) plays a key role in ileal smooth muscle contraction, whereas nitric oxide (NO) produced by nitric oxide synthase (NOS) is a key component of ileal smooth muscle relaxation. Iron-containing heme is known to be a cofactor for NOS.[3] However, the role of iron deficiency and its effects on ileal neurotransmitters has not been studied. Therefore we tested the hypothesis that iron deficiency would downregulate ileal NOS activity without affecting the ileum's ability to respond to ACh.

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MATERIAL AND METHODS

Twelve adult female black-tailed prairie dogs *(Cynomys ludivicianus)*, weighing approximately 1 kg each, were obtained from Joe Bill Rogers (Lubbock, Tex.). Animals were housed three to a cage in a light (6 AM to 6 PM)– and temperature (22° C)–controlled room. The prairie dogs were randomly divided into two experimental groups (n = 6 per group) and given free access to pellets that were either iron supplemented (control) (200 ppm) or iron deficient (8 ppm) (Teklad Test Diets, Harlan Sprague-Dawley, Inc., Madison, Wis.) for 8 weeks. The diet compositions have been reported previously.[4] The groups did not differ in terms of mean body weight (1048 ± 36 g) or weight range (883 to 1336 g) at the initiation of the study. All protocols for these animal studies were approved by the Medical College of Wisconsin Animal Care Committee.

Hemoglobin Determination

At the initiation of their protocol diets, the prairie dogs were anesthetized with ketamine/xylazine (50 to 100 mg/kg ketamine; 10 mg/kg xylazine intramuscularly). One milliliter of blood was aspirated percutaneously from the saphenous vein and stored in a Microtainer tube (Becton Dickinson, Franklin Lakes, N.J.) containing EDTA. Hemoglobin was determined by means of a commercially available kit. This procedure was repeated 8 weeks later 18 hours prior to tissue procurement.

Tissue Procurement

Following an overnight fast, the prairie dogs were anesthetized as above, and a midline laparotomy was performed followed by an ileectomy of 4 cm in length starting at 8 cm proximal to the cecum. The specimens were cut along the longitudinal axis and rinsed in ice-cold modified Krebs solution consisting of (mmol/L) NaCl, 116.6; $NaHCO_3$, 21.9; KH_2PO_4, 1.2; glucose, 5.4; $MgCl_2$, 1.2; KCl, 3.4; and $CaCl_2$, 2.5, which had been bubbled with 95% O_2/5% CO_2 for 30 minutes. The mucosa was scraped off, and four circular smooth muscle strips per specimen were then cut approximately 1 mm wide and 5 mm long.

In Vitro Muscle Bath Experiments

Muscle strips were mounted in a 3 ml muscle bath containing Krebs solution bubbled with 95% O_2/5% CO_2 and maintained at 37° C. The strips were allowed to equilibrate at 0.1 g tension for at least 45 minutes. Following equilibration, optimal length was determined by response to 10^{-5} mol/L ACh with 0.3 to 0.8 g tension. Nonadrenergic noncholinergic (NANC) conditions were obtained by using propanolol, atropine, and phentolamine, each at 10^{-6} mol/L. All four muscle strips were exposed to electrical field stimulation (EFS) under NANC conditions. The electrical field was generated using a Grass SD9 stimulator (Grass Instrument Co., Quincy, Mass.) at 150 volts, 20 pps, and 1.0 msec duration for 30 seconds. After rinsing, two of the four muscle strips underwent treatment with the NOS inhibitor Nω-nitro-L-arginine (L-NNA) (10^{-4} mol/L) for 10 minutes, and then L-NNA and the vasoactive intestinal peptide (VIP) inhibitor VIP_{10-28} (10^{-5} mol/L) were each followed by EFS. The remaining two muscle strips underwent treatment with VIP_{10-28} (10^{-5} mol/L) for 10 minutes followed by EFS. At the conclusion of the experiments, all four muscle strips were treated with 20 mmol/L EDTA to determine their maximal relaxation. Signals were recorded on a Grass 7D polygraph with a Grass FT03C transducer (Grass Instrument Co.). Excitatory responses were measured as magnitude from baseline. Inhibitory responses were measured as greatest negative deflection during EFS compared to baseline values. Typical responses are shown in Fig. 1. Muscle responses were quantified using WINDAQ/EX computer software (Dataq Instruments, Inc., Akron, Ohio).

Western Blot Analysis

For analysis of expression of neuronal (n)NOS protein, ileal tissue from prairie dogs was homogenized

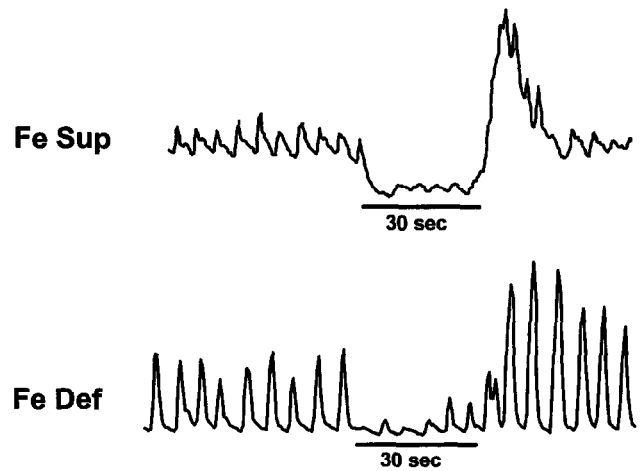

Fig. 1. Representative polygraph recordings of circular ileal smooth muscle strips in iron-supplemented *(Fe Sup)* and iron-deficient *(Fe Def)* prairie dogs. Phasic contractions were seen prior to electrical field stimulation (solid bar). During electrical field stimulation, relaxation was observed followed by off-contractions.

in 2 mmol/L EDTA, 2 mmol/L EGTA, 250 mmol/L sucrose, 50 mmol/L 3-[N-morpholino] propanesulfonic acid, 1 μg/ml leupeptin, 1 μg/ml antipain, 1 μg/ml aprotinin, and 20 μmol/L phenyl methylsulfonyl fluoride, pH 7.4. The whole-cell lysates were centrifuged at 16,000 rpm for 15 minutes. The supernate was assayed for total protein concentration (Bio-Rad Laboratories, Inc., Hercules, Calif.). One hundred micrograms of ileal protein from each specimen were analyzed by 7.5% SDS-PAGE (Bio-Rad Laboratories) and electroblotted onto a membrane (Hybond ECL nitrocellulose, Amersham Pharmacia Biotech, Piscataway, N.J.). The membranes were blocked in buffer containing 10 mmol/L Tris, pH 7.5, 100 mmol/L NaCl, 0.1% Tween 20, 2% bovine serum albumin, and 3% nonfat dry milk for 1 hour at room temperature and then incubated with a monoclonal mouse anti-nNOS antibody (Transduction Laboratories, San Diego, Calif.) at 1:2500 dilution overnight at 4° C. After washing, the immunoblots were incubated with the secondary antibody, goat antimouse immunoglobulin–horseradish peroxidase (Santa Cruz Biotech, Santa Cruz, Calif.), at a dilution of 1:5000 for 1 hour at room temperature and developed with ECL substrate (Amersham Pharmacia Biotech). Blots were exposed to x-ray film and quantified using densitometry (Scion Corp., Frederick, Md.). Finally, the membranes were rinsed and reblotted with a monoclonal mouse anti–β-actin antibody at 1:1000 dilution for 1 hour at room temperature. After washing, the immunoblots were incubated with goat antimouse secondary antibody and developed as described above. Data were normalized to β-actin to control for loading errors and expressed as a percentage of prairie dog brain nNOS to control for variations between multiple gels. Prairie dog brain and liver were used as positive and negative control specimens, respectively. Unless otherwise noted, all reagents and chemicals were purchased from Sigma-Aldrich (St. Louis, Mo.).

Statistics

Data are expressed as mean ± standard error of the mean (SEM). Statistical analyses were performed using SigmaStat Statistical Software (SPSS, Inc., Chicago, Ill.). Differences in muscle bath responses, hemoglobin, and protein levels were tested for statistical significance by one-way and two-way analysis of variance, and Mann-Whitney U test as appropriate. A P value of <0.05 was considered statistically significant.

RESULTS

No significant differences in final body weight were observed between the iron-supplemented and iron-deficient groups (1052 ± 40 g vs. 1076 ± 41 g, respectively). Hemoglobin values did not differ between the two groups prior to the initiation of the test diets. The iron-deficient prairie dogs were found to have significantly lower blood hemoglobin levels than the iron-supplemented animals (14.4 ± 0.5 g/dl vs. 16.4 ± 0.7 g/dl; $P<0.05$) after 8 weeks on the respective diets.

Muscle Bath—Excitatory Response. The response to ACh at optimal length did not differ between iron-supplemented and iron-deficient animals (1.1 ± 0.3 N/cm vs. 1.5 ± 0.3 N/cm^2) (Table I).

Muscle Bath—Inhibitory Response. Under NANC conditions, the ileum of iron-supplemented animals demonstrated more relaxation compared to iron-deficient animals (31.7 ± 2.9% vs. 23.9 ± 3.2%; $P<0.05$) (Table I and Fig. 2). When L-NNA was added, iron-supplemented ileal relaxation was completely abolished, whereas iron-deficient ileum still partially relaxed (0.02 ± 0.02% vs. 8.38 ± 2.15%; $P<0.01$) (Table I and Fig. 2). When VIP_{10-28} was added, iron-supplemented ileum experienced increased relaxation compared to NANC alone (45.8 ± 6.6% vs. 34.7 ± 2.9%; $P<0.05$), whereas iron-deficient ileal relaxation was

Table I. Muscle bath results

	Iron supplemented	Iron deficient	*P* value
Excitatory response			
ACh (10^{-5} mol/L)	1.1 ± 0.3	1.5 ± 0.3	0.45
Inhibitory response			
NANC (10^{-6} mol/L)	34.7 ± 2.9	23.9 ± 3.2	<0.05
NANC + L-NNA (10^{-4} mol/L)	0.02 ± 0.02	8.38 ± 2.15	<0.01
NANC + VIP_{10-28} (10^{-5} mol/L)	45.8 ± 6.6	23.4 ± 5.8	<0.05
NANC + L-NNA + VIP_{10-28}	0.02 ± 0.02	2.54 ± 1.04	<0.05

Values are mean ± SEM.
ACh expressed as N/cm^2; all others expressed as percentage of optimal relaxation from EDTA.

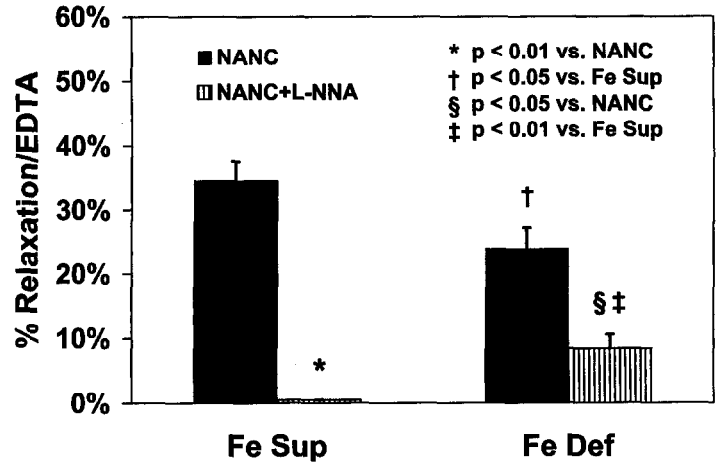

Fig. 2. Electrical field stimulation under NANC conditions (black bars) and NANC + L-NNA (vertical line) for iron-supplemented *(Fe Sup)* and iron-deficient *(Fe Def)* prairie dogs. The data correspond to mean ± SEM (n = 6) and are expressed as percentage of optimal relaxation from EDTA.

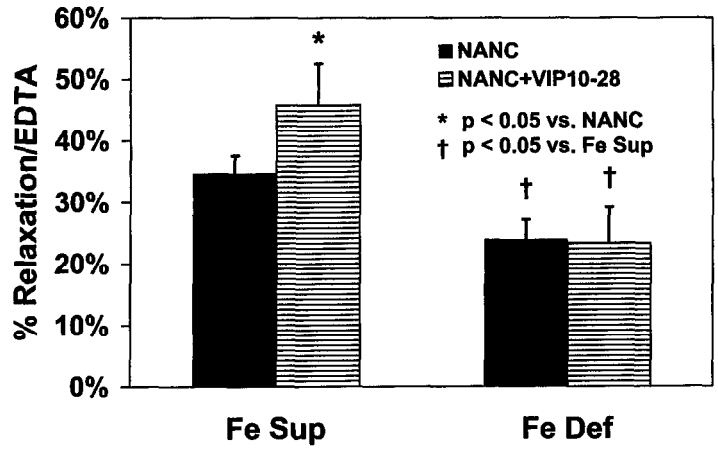

Fig. 3. Electrical field stimulation under NANC conditions (black bars) and NANC + VIP_{10-28} (horizontal line) for iron-supplemented *(Fe Sup)* and iron-deficient *(Fe Def)* prairie dogs. The data correspond to mean ± SEM (n = 6) and are expressed as percentage of optimal relaxation from EDTA.

unchanged compared to NANC alone (23.4 ± 5.8% vs. 23.9 ± 3.2%; $P = 0.86$) (Table I and Fig. 3). When both L-NNA and VIP_{10-28} were added, iron-supplemented ileum relaxation was again completely abolished, whereas iron-deficient ileum still had some residual relaxation (Table I and Fig. 4). Finally, optimal relaxation was measured in each strip with EDTA (20 mmol/L), a calcium chelator. The optimal relaxation between the iron-supplemented and iron-deficient animals was not significantly different (0.28 ± 0.03 N/cm^2 vs. 0.27 ± 0.05 N/cm^2; $P = 0.86$).

Western Blot Analysis

Western blot analyses of prairie dog ileal homogenates were performed to determine whether nNOS protein levels were influenced by iron deficiency. The iron-supplemented animals (n = 6) had a strong immunoreactive band at 155 kDa, whereas the iron-deficient animals (n = 6) had a weaker band. When loading errors were corrected by comparing these protein levels to β-actin and then comparing them to brain nNOS levels, the iron-supplemented and iron-deficient protein levels were not significantly different (69 ± 17% vs. 40 ± 8% brain nNOS; $P = 0.17$).

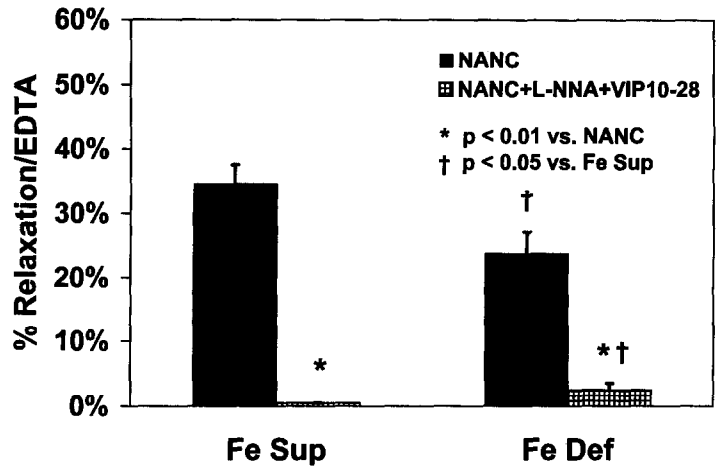

Fig. 4. Electrical field stimulation under NANC conditions (black bars) and NANC + L-NNA + VIP_{10-28} (crosshatched bars) for iron supplemented *(Fe Sup)* and iron-deficient *(Fe Def)* prairie dogs. The data correspond to mean ± SEM (n = 6) and are expressed as percentage of optimal relaxation from EDTA.

DISCUSSION

These studies demonstrate that an iron-deficient diet not only has an effect on hemoglobin levels, but also decreases the EFS-induced inhibition of the ileum from NANC neurons. In iron-supplemented animals, ileal NANC inhibition is caused by NOS; however, in iron-deficient animals, NANC inhibition is only partially caused by NOS. With iron deficiency, a compensatory mechanism caused by VIP as well as a non-VIP, non-NOS mechanism is observed. On the other hand, iron deficiency does not affect ACh-induced excitation.

Intestinal motility disorders may affect the entire gastrointestinal tract. Irritable bowel syndrome is the most common intestinal motility disorder. A primary component of irritable bowel syndrome is thought to be a motor disturbance within the ileum. A correlation has been shown to exist between small bowel motor disturbances and symptoms of irritable bowel syndrome.[2] Irritable bowel syndrome is a common disorder with an incidence of up to 20% of the general population.[1] As a result, irritable bowel syndrome represents a significant primary and tertiary health care cost. Irritable bowel syndrome is twice as prevalent in women of childbearing age compared to men. In addition, the ratio of women who seek medical care for irritable bowel syndrome is 3:1 compared to men.[1] Women of childbearing age who are likely to suffer from irritable bowel syndrome also have a high incidence of iron deficiency.[5]

The same population of women who are iron deficient and prone to irritable bowel syndrome also have a high incidence of gallstone disease.[6] Iron deficiency has been shown recently to be implicated in gallstone formation. Transferrin, a serum and bile transporter of iron, is increased in iron deficiency. Transferrin has been shown to be a potent cholesterol crystal pronucleator.[7] In addition, prairie dogs fed a combination iron-deficient, high-cholesterol diet will develop more cholesterol crystals than similar animals on either an iron-deficient or a high-cholesterol diet alone.[8] Both gallbladder and sphincter of Oddi resting tone and response to cholecystokinin are altered in iron-deficient prairie dogs.[9,10] Finally, nNOS levels within the gallbladder wall are decreased in iron deficiency, potentially affecting gallbladder resting compliance and therefore influencing biliary stasis.[4]

nNOS has been shown to be present throughout the entire gastrointestinal tract and has been implicated as the enzyme responsible for NANC relaxation.[11,12] Although nNOS is the likely isoform of the NOS family of enzymes to be involved in this model, potential interactions with other NOS enzymes, especially endothelial (e)NOS, have been proposed.[13] We examined both the eNOS and inhibitory (i)NOS levels in the ileal specimens using Western blot analysis and found no difference between the iron-supplemented and iron-deficient animals. Thus iron deficiency does not alter the quantity of these enzymes in this model. Moreover, to further strengthen nNOS as the enzyme acting in this system, a number of studies have shown that L-NNA, the arginine analog used in this experiment to inhibit NANC relaxation, is a 300-fold more potent inhibitor of nNOS compared to iNOS.[14,15] Unfortunately, many of the inhibitors of nNOS also block eNOS so pharmacologic determi-

nation of the role of these respective enzymes would not be possible with this model.

The enzyme nNOS is a homodimer that requires a number of cofactors to function properly.[16] One of the cofactors necessary for nNOS function is iron-containing heme.[3] The heme moiety is required for electron transport. Studies have shown that intact nNOS without sufficient heme is nonfunctional.[16] In the gallbladder, iron deficiency has been shown to alter motility and decrease nNOS levels.[4,9] In the ileum, the present study demonstrated that iron deficiency decreased nNOS function. Western blot analysis demonstrated lower ileal nNOS levels in iron deficiency, but this difference was not statistically significant ($P = 0.17$), perhaps because of a type II statistical error as the power of the test was 0.16. One potential criticism of this experiment is that despite the decreased NANC relaxation, we were unable to show a decrease in nNOS levels within the ileal tissue. In addition to the possibility of a type II error, the reason for the decreased NANC relaxation may be due to the nNOS enzyme and its resulting signaling cascade not functioning properly in iron deficiency. Further studies to examine NO donors such as nitroprusside, nNOS function directly, or NO byproducts such as nitrates would help elucidate this finding.

A number of neurotransmitters have been shown to be present in NANC neurons throughout the gastrointestinal tract. Adenosine triphosphate and NO have been implicated in rats to be NANC neurotransmitters in the stomach and duodenum, whereas VIP and NO have been demonstrated to be NANC neurotransmitters in the stomach and colon of guinea pigs.[17,18] In the rat ileum, NO has been shown to be central in relaxation.[19] Despite the central role of NO, VIP cannot be excluded as a neurotransmitter in the ileum. In fact, before the acceptance of NO as a neurotransmitter, VIP has been shown to induce relaxation in the rat ileum.[20] Studies done with NOS knockout mice have demonstrated that the NANC neuron/gastrointestinal smooth muscle interaction is a complicated interaction of multiple neurotransmitters. The use of nNOS knockout mice could be a potential follow-up to this experiment in this muscle bath model. Evidence exists for a direct action of NO on guanylate cyclase in gastrointestinal smooth muscle. In addition, VIP has been shown to cause relaxation of intestinal smooth muscle, as well as indirectly influencing the production of NO from nNOS.[13]

In nNOS knockout mice, the small bowel is able to relax because other NANC neurotransmitters compensate in the absence of NO production.[13] In this study, the function of NOS was diminished in the presence of iron deficiency. In iron-deficient ileum, the NANC neurotransmitter VIP and potentially a third neurotransmitter compensate for the relative absence of NO. An interesting finding in this study is that despite the compensation of other NANC neurotransmitters, they are unable to achieve the degree of relaxation observed with NO alone in iron-supplemented animals. Future studies will need to be performed to determine the mechanisms of this compensation and which intracellular messengers communicate the response.

Another potential criticism of this study is that VIP_{10-28}, a VIP antagonist, may not be a complete antagonist. Various VIP antagonists have residual intrinsic activity similar to that of VIP.[21,22] If VIP_{10-28} were a partial agonist/antagonist in this experiment, the finding of increased EFS-induced relaxation with NANC and VIP_{10-28} in the iron-supplemented animals would be explained (Table I and Fig. 3). Evidence exists in knockout mice that VIP not only has a direct effect on gastrointestinal smooth muscle but also has a feedback mechanism on NANC neurons stimulating nNOS to release NO.[22] Therefore, if VIP_{10-28} has a partial agonist effect, it could actually lead to increased NO release and explain the enhanced relaxation observed in this study. If VIP did not affect either smooth muscle directly or through the release of NO, no difference should have been observed when both NOS and VIP were blocked. However, the EFS response when NOS and VIP were blocked in the iron-deficient ileum was less than that seen when only NOS was blocked. Thus this experiment suggests that VIP is one of the NANC neurotransmitters upregulated in iron deficiency.

This study suggests that NO is the primary NANC neurotransmitter in the ileum. However, with iron deficiency, NOS production of NO is reduced. In this situation, other inhibitory neurotransmitters such as VIP and a non-NOS, non-VIP neurotransmitter are upregulated. In this manner, iron deficiency may potentially contribute to the symptoms of intestinal motility disorders, and a clinical correlation should be further investigated.

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Discussion

Dr. S.W. Ashley (Boston, Mass.). Can you tell whether this is an effect on synthesis of the NOS, or is it just that the iron is not present to act as a cofactor?

Dr. M. Goldblatt. The decrease in hemoglobin that we observed was clearly not severe anemia, so we believe that there should still be a sufficient quantity of iron and hemoglobin available as a cofactor. It does appear that this is, at least in part, a problem in synthesis, and some preliminary studies have shown that there seems to be a decrease in the quantity of NOS available.

Dr. J.A. Bastidas (Stanford, Calif.). My first question relates to synthesis of the nNOS protein. You have previously shown that in the gallbladder there was decreased protein, and in these studies apparently that was not the case. So I would like to ask what your explanation might be. In your methods you suggest that you normalize your NOS protein, not only to beta actin, but then to brain nNOS. Why do you normalize to brain nNOS? Do you know whether brain nNOS is unchanged in the iron deficiency state?

My second question has to do with how you determined your doses for the various inhibitors. Your NOS inhibitor was used at a concentration of 10^{-4} mol/L, whereas everything else was used at much lower concentrations. Did you use dose-response curves or are these well-established doses?

Last, there are several NOS isoforms and I was curious to know whether you have looked at various isoforms in this model, and whether you have looked at any immunohistochemical values.

Dr. Goldblatt. We are not exactly sure why a decrease in NOS is found in the gallbladder and not in the ileum. It may be due to the fact that there is no decrease in the quantity of protein available, but a decrease in the function of the protein. An enzyme assay would help clarify this. The second possibility is that we actually committed a type II error and there was a statistical difference. Although we showed a trend toward that difference, we were unable to reach statistical significance.

The reason for using brain nNOS as a control was to load a known quantity of brain nNOS onto each gel. That was used to normalize the values from one gel to another to adjust for differences in developing strengths and densities between gels.

As for your question concerning the strengths of inhibitors, results achieved with L-NNA at a concentration of 10^{-4} mol/L are well published. So we did not calculate concentration response curves in our sample, but these have

been calculated by others. This is an accepted concentration that produces complete inhibition. Finally, other isoforms of NOS have not yet been investigated. We have only looked at nNOS. This isoform is most likely to be decreased in this model due to the fact that we are stimulating neurons. However, when VIP is involved as an additional neurotransmitter, other isoforms including excitatory NOS may act directly on the smooth muscle, and this is something we have yet to examine.

Dr. H.J. Sugerman (Richmond, Va.). The gastric bypass operation is one of the greatest producers of iron deficiency, but we do not see motility disorders after this operation. Therefore I wonder about your fundamental hypothesis.

Dr. Goldblatt. We need to confirm the fact that iron deficiency is really seen in intestinal motility disorders. We know that women who are menstruating have a higher incidence of iron deficiency anemia, but we have yet to confirm that there is a direct correlation between the two groups. In your population with iron deficiency after gastric bypass, the effects of intestinal motility after small bowel anastomoses may confound the issue.

Dr. V.H. Finch (Chicago, Ill.). Did you compare the anemia of iron deficiency to other types of anemia in regard to their effect on motility?

Dr. Goldblatt. In this study we did not investigate other forms of anemia. In previous studies done in our laboratory, using prairie dogs in a gallbladder model, there were two groups of anemic animals. One was fed an iron-deficient diet, and the other was actually phlebotomized to simulate anemia due to blood loss. The results in terms of gallbladder motility and the effects of iron deficiency were very similar. We have not studied other forms of anemia.

Dr. K.A. Kelly (Scottsdale, Ariz.). In patients who have intestinal motility disorders and who are also iron deficient, does the motility disorder improve if these patients are treated with iron?

Dr. Goldblatt. The next obvious step in this study would be to replace the iron and examine the long-term effects. In this animal model, we have not yet examined what would happen to ileal motility if we placed these animals on an iron-deficient diet and then replaced the iron.

Quality of Life Following Laparoscopic Gastric Banding in Patients With Morbid Obesity

Stephan M. Freys, M.D., Harald Tigges, M.D., Johannes Heimbucher, M.D., Karl-H. Fuchs, M.D., Martin Fein, M.D., Ph.D., Arnulf Thiede, M.D.

In a prospective study of 188 patients with morbid obesity, the time-dependent changes in the quality of life of individual patients were analyzed following laparoscopic gastric banding (LGB). These 188 patients (148 females and 40 males; age 19 to 59 years; body mass index 33 to 72 kg/m^2) underwent evaluation of the LGB according to a strict protocol that included psychological testing using standardized instruments, detailed medical evaluation, upper gastrointestinal function studies, and evaluation of quality of life using the Gastrointestinal Quality of Life Index (GIQLI). Following this evaluation, 73 patients (57 females and 16 males; age 37 years [range 19 to 59 years]; body mass index 48 kg/m^2 [range 37 to 72 kg/m^2]) underwent LGB and were followed up for 2 years focusing on weight loss, postoperative morbidity, weight-related comorbidity, and quality of life. The results demonstrate that LGB is well able to allow for a significant loss of excess weight and a significant improvement in patients' quality of life, both after a rather short period of time after surgery and at a continuous rate throughout the follow-up. The price for this success that was found in approximately 90% of patients is a complication rate of 38%; 85% of these patients, almost one third of all patients, must undergo some type of revision surgery. However, once the complications are resolved, these patients achieve the same level of weight loss and improvement in quality of life as patients with an uncomplicated postoperative course. (J GASTROINTEST SURG 2001;5:401-407.)

KEY WORDS: Laparoscopic gastric banding, quality of life, morbid obesity

The aims of surgical treatment in patients with morbid obesity are reduction of body weight, a positive influence on weight-related comorbid conditions, and an improvement in the concomitant psychological and social limitations of these patients. With the advent of minimally invasive procedures allowing limited objective and subjective trauma in the obese patient, there has been renewed interest in bariatric surgery during the past few years. A large number of clinical studies were well able to prove the applicability, safety, and efficiency of the laparoscopic approach in morbidly obese patients.[1-12] However, following the initial positive reports, a more widespread application produced more critical reports that mainly focused on the problems and complications inherent in the new technique.[13-19] In light of these recent publications, it seems appropriate to define the success and failure of laparoscopic gastric banding not just in terms of data reflecting weight loss, postoperative morbidity, complication rates, and the development of weight-related comorbidity but also on the basis of an assessment of patients' quality of life. At present, there are only a few reports that focus on changes in quality of life following bariatric surgery. Most of these reports date back to the period of conventional surgery for morbid obesity[20-28]; these reports employed individually designed, nonvalidated instruments for assessing quality of life and/or evaluated several surgical techniques in comparison to conservative treatment options. To date, there are only two studies reporting on the quality-of-life outcome following laparoscopic surgery for morbid obesity,[29,30] both of which used nonvalidated instruments. It was therefore the aim of this prospective clinical study to analyze changes in the quality of life of patients undergoing laparoscopic gastric banding (LGB) for morbid obesity by use of a val-

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idated clinical instrument[31,32] drawing comparisons to weight loss and postoperative complications.

MATERIAL AND METHODS

From January 1997 to November 1999, a total of 188 patients (148 females and 40 males; age 19 to 59 years; body mass index 33 to 72 kg/m^2) underwent evaluation for LGB according to a strict protocol[33] that included psychological testing using standardized instruments, a detailed medical evaluation, upper gastrointestinal function studies, and evaluation of quality of life. Following this evaluation, 73 patients underwent LGB; this study population consisted of 57 female and 16 male patients who had a mean age of 37 years (range 19 to 59 years). In 62 patients a Lap-Band (BioEnterics Corp., Carpinteria, Calif.) was used and in 11 patients a Swedish Adjustable Gastric Band (Obtech Medical AG, Zug, Switzerland) was implanted.

The laparoscopic approach was standardized in all patients. Five ports were inserted in a semicircular fashion above the umbilicus parallel to the subcostal margin; a limited dissection was then performed to mobilize the greater curvature at the angle of His. For implantation of the Lap-Band, a careful retrogastric dissection along the posterior wall of the stomach was performed in order to create a narrow tunnel for passage of the band. The Swedish Adjustable Gastric Band required a slightly different dissection technique. The retrogastric tunnel was dissected in the layer between the right crus of the diaphragm, the arcuate ligament, and the left crus of the diaphragm leaving fatty tissue with branches of the left gastric artery and the vagal branches within the band (Fig. 1). The position of the individual band and the retrogastric tunnel is determined by inflation of a 30 ml calibration balloon inserted transorally into wedge position in the cardia. Following antegastric closure of the band, its position is secured by a rather limited plication of the anterior gastric wall, which is sutured to the anterior aspect of the gastric pouch above the band. The connecting tube between the gastric band and the port system is brought out through the left subcostal trocar incision where it is connected to the port chamber, which is then affixed with sutures to the costal fascia.

Postoperatively, enteral nutrition in the form of semisolid food was started on day 2 and the patients were discharged following a radiographic examination for control of band position, pouch size, and port chamber position once a normal diet had been resumed for 2 days without any complications. Four to six weeks after the patients were discharged, the port chamber was filled with saline solution according to each individual's subjective feeling of postprandial

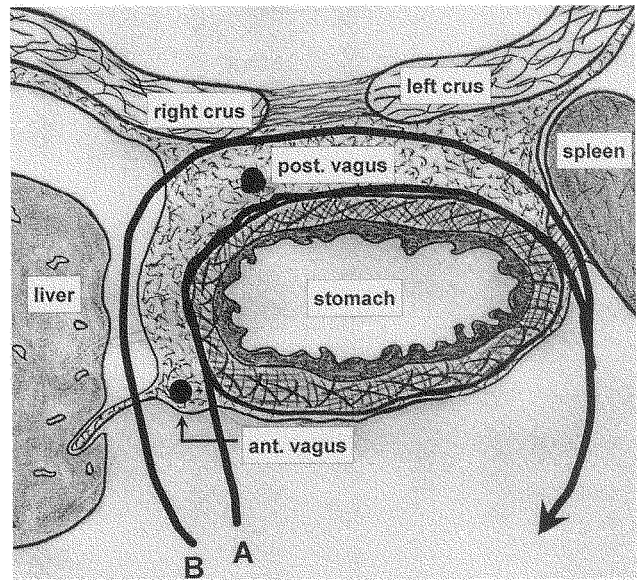

Fig. 1. Mode of dissection for implantation of the Lap-Band **(A)** and the Swedish Adjustable Gastric Band **(B).**

fullness. All patients were then followed up on an outpatient basis with visits to our hospital at 3-month intervals with documentation of weight loss, postoperative complications, course of weight-related comorbid conditions, and quality of life. Quality of life was measured by means of the Gastrointestinal Quality of Life Index (GIQLI),[31,32] a validated instrument developed specifically for patients with gastrointestinal disease. It consists of a one-page questionnaire containing 36 questions, each with five response categories focusing on the following five dimensions of quality of life: symptoms, emotions, physical function, social function, and medical treatment; responses to the questions are totaled to give a numerical score. Statistical comparisons between pre- and postoperative data on body weight and quality of life were performed by use of the Wilcoxon test for paired samples.

RESULTS

All laparoscopic operations were completed without the need for conversion to an open procedure. The mean operative time was 95 minutes (range 55 to 185 minutes), and the median length of hospitalization was 8 days (range 6 to 56 days). The overall rate of follow-up during the 2-year study period was 72%. The 73 patients would have had to present themselves for a total of 188 outpatient visits during the follow-up period; however, only 135 of these outpatient visits were performed as scheduled. Eighteen patients did not comply with the recommended follow-up outpatient visits; thus no objective data are

Table I. Weight loss following laparoscopic gastric banding (n = 73)

	Preoperative (n = 73)	6 months postoperative (n = 42)	12 months postoperative (n = 23)	18 months postoperative (n = 13)
Body weight (kg)	138 ± 22*	109 ± 22	106 ± 28	107 ± 24
Body mass index (kg/m^2)	48 ± 6*	38 ± 6	36 ± 7	39 ± 7
Loss of excess weight (%)	0	38.2 ± 19.2	47.9 ± 25.8	46.5 ± 17.7

Values are mean ± standard deviation
*P <0.0002 vs. 6, 12, and 18 months.

Table II. Complications following laparoscopic gastric banding (n = 73)

Complications	Conservative treatment	Operative treatment	Total
Pouch dilatation	2	11	18%
Port dislocation	0	4	5%
Port site infection	0	5	7%
Gastric perforation	0	2	3%
Port leakage	0	1	1%
Recurrent vomiting	3	0	4%
Trocar site hernia	0	0	0
Trocar site infection	0	0	0
Bleeding	0	0	0
Deep venous thrombosis	0	0	0
TOTAL	6%	32%	38%

available for these patients. On telephone interviews these patients reported no complications and refused to participate in follow-up investigations because of their general well-being. Three patients were lost to follow-up.

Before the operation, the study population was characterized by a mean body weight of 138 kg (range 98 to 204 kg), a mean excess body weight of 68 kg (range 38 to 130 kg), and a mean body mass index of 48 kg/m^2 (range 37 to 72 kg/m^2). Following surgery, the mean body weight was 109 kg at 6 months, 106 kg at 12 months, and 107 kg at 18 months. These results represent an excess weight loss of 38%, 48%, and 47%, respectively, leading to a decrease in the body mass index from a preoperative mean value of 48 kg/m^2 to postoperative values of 38 kg/m^2 after 6 months, 36 kg/m^2 after 12 months, and 39 kg/m^2 after 18 months. There was a significant reduction in body weight according to both the actual body weight and the body mass index if the individual preoperative values were compared to all follow-up measurements (Table I).

Postoperative complications occurred in 28 of the 73 patients (Table II). The most frequent problem was dilatation of the gastric pouch above the level of the inserted band; this dilatation was restricted to the pouch itself with no extension into the esophagus in any of the patients. This complication was managed conservatively in two patients by restriction of food and temporary drainage of the dilated pouch via a nasogastric tube, which led to reversal of the dilated pouch. In 11 patients, conservative measures did not produce the desired effect and a laparoscopic reintervention was necessary in seven patients to reposition the band across the dilated pouch. During this reoperation, special care was taken to envelop the gastric band securely with plication of the anterior gastric wall at approximately 240 degrees of its circumference, thus attempting to ensure that no slippage of the band might provoke another pouch dilatation. In all seven patients who underwent successful repositioning of the band, the revision surgery allowed for a further course that was uneventful. In four patients the gastric band had to be explanted because the dilatation of the fundus was too severe causing it to slip upward underneath the band. This explantation was performed laparoscopically in all patients, and none of these patients had any other type of concomitant bariatric procedure. A port dislocation was observed in four patients necessitating operative refixation of the chamber to the fascia; following reoperation these patients all experienced a subsequently uneventful course. The complication leading to the longest and most problematic reinterventions was port site infection. This complication occurred in five patients, each time within the first 3 months following the initial implantation. A long-term successful operative revision with implantation of a new port chamber was observed in only one of these patients; in all other patients repeated operative interventions (two reoperations in two patients, three reoperations in one, and five reoperations in one) finally led to explantation of the port chamber. In addition, the gastric band had to be explanted in one of these patients because of an intra-abdominal infection. A gastric perforation during implantation of the band occurred in two patients; in both of them, this complication was not detected until postoperative day 2 during the radiographic contrast study. The gastric band was explanted in both

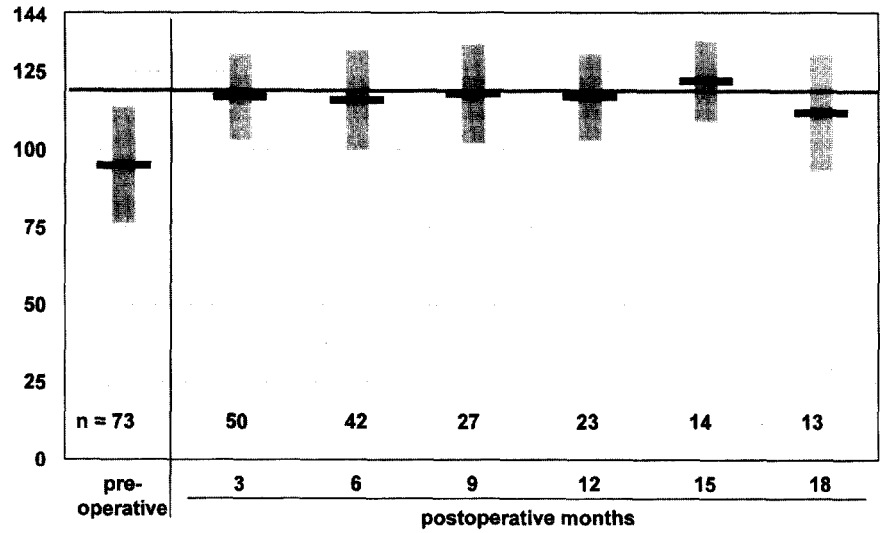

Fig. 2. Gastrointestinal quality-of-life index following laparoscopic gastric banding (mean scores) (n = 73).

Table III. Gastrointestinal quality-of-life index (GIQLI) following laparoscopic gastric banding: Total score and constituting dimensions (n = 73)

	Preoperative (n = 73)	6 months postoperative (n = 42)	12 months postoperative (n = 23)	18 months postoperative (n = 13)
GIQLI total score	95 ± 19*	116 ± 16	117 ± 14	112 ± 19
Symptoms	60 ± 7	63 ± 9	66 ± 7	64 ± 7
Emotions	10 ± 5	15 ± 5	15 ± 4	15 ± 5
Physical function	13 ± 7	20 ± 6	20 ± 7	19 ± 7
Social function	9 ± 4	13 ± 4	13 ± 2	12 ± 4
Medical treatment	3 ± 1	4 ± 0.5	3 ± 1	3 ± 1

Mean ± standard deviation.
*P <0.0003 vs. 6, 12, and 18 months.

patients. Minor complications were port chamber leakage in one patient, which could only be corrected by insertion of a new chamber, and recurrent vomiting in three patients, which was managed conservatively in all three. No other perioperative or postoperative complications were observed, and there were no trocar site problems, bleeding episodes, or occurrences of thrombosis. In summary, 38% of patients had postoperative complications, 32% of patients required reoperation because of their individual complications, the port chamber was successfully exchanged in two patients, and in 10% of patients the entire gastric banding system had to be explanted.

Weight-related comorbid conditions, either alone or in combination, requiring medical and/or behavioral and/or physical treatment were found in 66 (90%) of the 73 patients and included arterial hypertension in 69%, diabetes mellitus in 25%, arthrosis in 89%, and sleep apnea in 14%. Throughout the follow-up period, an improvement in symptoms and/or a reduction or discontinuation of treatment measures was found in 50% of patients with arterial hypertension, 56% with diabetes, 30% with arthrosis, and 33% with sleep apnea.

Quality of life was assessed by means of GIQLI preoperatively and during all follow-up outpatient visits. The responses to the 36 questions were totaled to provide one numerical score; at the same time this instrument is designed to subanalyze five dimensions of quality of life including symptoms, emotions, physical and social functions, as well as information on the impact of medical treatment. The results of the GIQLI score and the inherent five dimensions before and after primary and secondary surgical intervention are shown in Fig. 2 and Table III. The postoperatively collected data demonstrate an increase in the GIQLI score from a preoperative mean value of 95 points to a postoperative mean value of 116 points at 3 months, 117 points at 12 months, and 112 points at 18 months. The range of postoperative

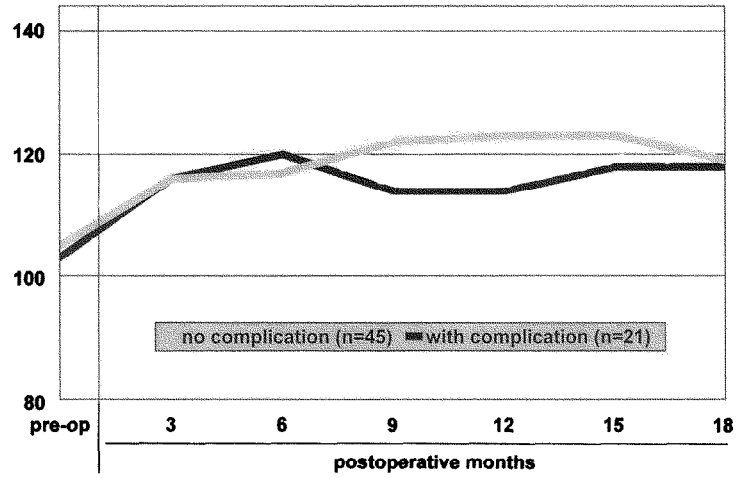

Fig. 3. Gastrointestinal quality-of-life index following laparoscopic gastric banding (mean scores). Comparison of patients without postoperative complications (n = 45) and patients with postoperative complications that were successfully managed (no band explantation) (n = 21).

scores was close to the given mean normal scores (mean score ± standard deviation for 150 healthy volunteers serving as normal subjects: 120 ± 15 points[31]). All postoperative scores remained at constant levels during the period of follow-up and were higher than the equivalent preoperative values, reaching a high level of significance ($P < 0.0003$) already at the time of primary follow-up 3 months after surgery. The scores of the five subanalyzed dimensions show a similar temporal course; following an initial rise at 3 months, the scores remained constant throughout the period of follow-up. An additional analysis was performed in those patients who had an uneventful postoperative course (n = 45) as compared to those patients who had postoperative complications that were resolved either by conservative or operative treatment (n = 21); the GIQLI scores for these two subgroups of patients (Fig. 3) do not show significant differences throughout the period of investigation.

DISCUSSION

The advent of minimally invasive techniques has led to renewed interest in weight reduction surgery within the past few years. This development can be attributed to the following three factors: (1) a continuous improvement in surgical techniques, which allows the adoption of well-established procedures from the conventional to the laparoscopic approach; (2) sound data on the long-term success of conventional bariatric surgery, which are available and reproducible; and (3) reports of low complication rates with laparoscopic surgery, especially in high-risk and obese patients, which obviously lowers the anxiety threshold for patients considering operative intervention.

In light of these developments, it appears necessary to evaluate success and failure during the introduction of an innovative treatment option such as LGB, not only according to traditional analyses of weight loss, complication rates, and weight-related comorbid conditions but also to consider facets of patients' quality of life and/or combined aspects of these parameters.

The preoperative workup of all patients who presented to our department for potential bariatric surgery led to a selection of only 39% of patients who were considered appropriate candidates.[33] Patients were excluded for the following reasons: (1) because they considered surgery as the treatment of first choice not having undertaken any conservative trial of weight reduction (25%); (2) because they did not want to comply with the necessary postoperative changes in life-style (14%); (3) because of a negative recommendation following psychological evaluation (20%); or (4) because of medical contraindications such as cardiopulmonary, gastroesophageal, or peptic ulcer disease (3%).

The operative technique strictly followed the published experiences and recommendations set forth by several groups with long-standing expertise.[1-5] The actual technique of LGB was chosen because of personal team experience with more than 250 laparoscopic antireflux procedures.[34] All operations were performed by four experienced laparoscopic surgeons.

The results of the loss of body weight lie within the experience of most groups reporting on this type of surgery with median values for body mass index between 30 and 35 kg/m^2 or median values for excess weight loss between 45% and 56% 1 year after surgery.[9,10,16,17,19] As in other publications,[7,35] we observed an initial rather rapid decrease in body weight within

the first 6 months, which was then followed by a lesser decrease over the next 6 months, and finally reaching a plateau at 18 to 24 months postoperatively.

The complication rate of 38% is at the upper limit of reported complication rates in the literature. Most recent larger series report a decrease in complication rates with ongoing experience; however, there are still large discrepancies with individual results ranging from 3% to 39%.* There was a rather small number of general surgical complications not directly related to the procedure performed. On the other hand, procedure-related complications (pouch dilatation, port dislocation, port site infection, port leakage) were present in every third patient.

The overall rate of reoperation in this study amounted to 32%, placing it at the upper limit of reported reoperation rates with a range from 7% to 35%.[9,10,17,19,38] In fact, there are two reports documenting reoperation rates of 80% and even 87%.[39,40] However, in the first report 50% of reoperations were due to problems with the reservoir, which were resolved by using an improved reservoir, whereas in the second report a material defect of a new band type led to this unacceptably high rate of reoperation. A striking finding in our study is the fact that if postoperative complications occur, they necessitate a surgical reintervention in quite a large percentage of patients; 23 (82%) of 28 patients with postoperative complications underwent revision surgery, half of these patients because of pouch dilatation. On the other hand, if a surgical repair was performed, this had a long-lasting effect with a further uneventful course in the majority of patients (19 [83%] of 23 patients). Port site infection represented the most problematic complication: four of the five affected patients underwent a total of nine revision interventions.

The decrease in the number of patients with weight-related comorbidity appears to be a promising development at first sight. Half of the patients suffering from hypertension and/or diabetes and approximately one third of the patients suffering from arthrosis and/or sleep apnea report an improvement. However, it must be taken into consideration that these improvements entail rather subjective components, since the criteria marking the "improvement," that is, the necessity for treatment, the decrease, and/or the discontinuation of therapeutic measures, are no substitute for hard data for objective evaluation. Nevertheless, if taken into consideration, these data at least allow for the recognition of a trend toward an improvement in weight-related comorbidity in 40% of patients following LGB.

*References 4, 7, 8, 14, 17-19, and 35-37.

The introduction of instruments for assessing quality of life has caused quite a bit of skepticism among clinicians, especially surgeons, about the reliability of such "soft" data. However, in the past few years several instruments have been developed to allow for an objective measurement of quality of life. The GIQLI applied in this study is an instrument that was designed in the early 1990s by Eypasch et al.[31,32] to assess health-related quality of life in clinical studies of patients with gastrointestinal disease and in daily clinical practice. The GIQLI was chosen for our study because it is the only existing validated instrument for assessing quality of life with regard to the gastrointestinal tract in health and disease that is available in German (since 1993) and in English (since 1995). It was validated with 168 normal individuals, reproducibility was tested in 50 patients with stable gastrointestinal disease, and responsiveness was tested in 194 patients undergoing laparoscopic cholecystectomy.[32] The analysis of quality of life by means of the GIQLI demonstrates that LGB is well able to improve patients' quality of life in a significant manner. This effect can be proved as early as 3 months after surgery, and it persists throughout the period of follow-up. All patients had a subnormal GIQLI score before operative treatment and had already improved their scores after only 3 months to the level of healthy volunteers serving as normal control subjects.[31] The subanalysis of the five dimensions constituting the GIQLI reveals that this positive effect is reflected in all aspects of health-related quality of life—that is, the patients' subjective perception of disease-related symptoms, their emotional status, and their physical and social functions improve and persist to the same extent in a parallel fashion. The perspective of possible or previously experienced loss of excess weight seems to outweigh potential concomitant gastrointestinal side effects and the "negative" experience of early satiety and postprandial fullness in individuals who quite often have centered their entire daily agenda around their nutritional activities. The experience of postoperative complications including conservative treatment in five patients and operative treatment in 16 patients who kept their band system did not change the degree of subjective perception of quality of life. The comparison between patients with and without complications revealed that quality of life is improved and maintained before, during, and after therapeutic reintervention to correct for side effects caused by the initial surgery. Again, the prospect of losing weight seems to be such a strong incentive that these patients are well able to tolerate any new or unpredictable complications to the extent that their quality of life is equal to that in patients with an uneventful postoperative course.

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Functional Outcome After Heller Myotomy and Fundoplication for Achalasia

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This study aims to provide longitudinal prospective data on symptomatic outcome following Heller myotomy with fundoplication and to examine variables that might predict a poor outcome. Patients were prospectively followed by means of a biannual mailed questionnaire that assessed symptoms, satisfaction with the procedure, medication, and need for further intervention. Patients were classified as achieving a good or poor outcome based on predetermined criteria. Duration of clinical remission was determined using Kaplan-Meier curves. Between 1992 and 1999, 62 patients with at least 12 months' follow-up were categorized as having either a good outcome (41 patients) or a poor outcome (21 patients). The cumulative probability of a good outcome at 7 years was 37%. Dysphagia significantly increased over the follow-up period despite initial resolution. Patient variables (age, sex, symptom duration, esophageal dilatation, manometric findings) and operative factors (myotomy length, wrap type, case number, mucosal perforation, primary therapy) were not demonstrated to influence outcome at 3 years. A comparison of Nissen fundoplication with partial fundoplication suggested increased dysphagia and chest pain in the Nissen group. Despite initial symptomatic relief, patients with achalasia suffer a progressive decline with recurrent dysphagia and regurgitation. The type of fundoplication used may contribute to these poor results. (J GASTROINTEST SURG 2001;5:408-413.)

KEY WORDS: Achalasia, esophageal surgery, fundoplication, myotomy, laparoscopy

Achalasia is a rare esophageal motility disorder characterized by a nonrelaxing lower esophageal sphincter and disordered esophageal body motility. Disruption of the lower esophageal sphincter by pneumatic balloon dilatation or by surgical myotomy provides significant symptomatic relief. Recent reports of follow-up after Heller myotomy via minimally invasive surgery have suggested that good or excellent results are achievable in more than 90% of patients.[1-7] However, follow-up for these patients is limited. Achalasia is a progressive disease[8] and therefore treatment should be considered palliative. Follow-up after surgical myotomy suggests that only 50% of patients maintain a favorable result at 15 years.[9,10] This study aims to assess the functional outcome of laparoscopic Heller myotomy with fundoplication in patients followed up to 7 years postoperatively and examines factors that may contribute to a poor result.

PATIENTS AND METHODS

Patients

From 1992 to 1999, a total of 70 consecutive patients with achalasia were seen by a single specialist upper gastrointestinal surgeon for laparoscopic Heller myotomy and fundoplication. Of these, 62 patients had a potential postoperative follow-up period of 12 months or more. Prospective data were recorded (Q & A, Symantec) with entry fields including age, sex, duration of symptoms, presence of a dilated esophagus, previous therapy, and manometric and endoscopic findings. Recorded operative details included length of myotomy, type of fundoplication, mucosal perforation, and need for conversion. Postoperative complications and need for reoperation were also prospectively recorded. Experience in laparoscopic Heller myotomy commenced at the same time as laparoscopic antireflux surgery and accounted for 18 of the first 100 laparoscopic esophageal cases.

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Table I. Clinical data

Clinical criteria	Value (range)
No. of patients	62
Mean age (yr)	47.4 (12-87)
Males:females	29:33
Duration of symptoms (mo)	75 (4-240)
Mean preoperative dilatations	1.8 (0-4)
Indications for surgery	
Primary	15
Failed pneumatic dilatation	39
Failed Botox	1
Perforation after pneumatic dilatation	5
Previous hiatal surgery	2
Type of surgery	
Myotomy plus 360-degree fundoplication	49
Myotomy plus partial fundoplication	13
Conversion to open surgery	7
Elective open surgery	4

The diagnosis of achalasia was determined preoperatively by esophageal manometry in all patients. This was classified as vigorous if there were high-amplitude, prolonged synchronous contractions. The esophagus was classified as dilated if comment on this was made in preoperative barium swallow reports or at preoperative endoscopy. However, only three patients had an esophageal diameter greater than 6 cm.

Follow-Up

Patients were followed prospectively at 1 month, 3 months, 1 year, 3 years, 5 years, and 7 years postoperatively. This was accomplished at 1 and 3 months by means of a structured interview, and at later times using a symptom questionnaire that was mailed to each patient. A repeat gastroscopy was done at 3 months and subsequently if patients were symptomatic. Symptoms of dysphagia, heartburn, chest pain, and regurgitation were scored from 0 to 3 for both severity and frequency. These scores were then multiplied to obtain a score ranging from 0 to 9. A score of 0 indicates an asymptomatic patient. A score of 9 indicates severe symptoms occurring daily.[11] Any medication the patient was taking was also recorded, and patients satisfaction was graded using a modified Visick score: 1 = patient regards the procedure a complete success and now is asymptomatic; 2 = only minor problems remain; 3 = patient shows improvement but has major residual problems; and 4 = patient is no better or is worse than preoperatively. Patients were contacted by a research assistant independent from the routine surgical follow-up in an attempt to reduce bias.

Operative Technique

All patients were considered for a laparoscopic procedure, although in several patients myotomy plus fundoplication was done as an open procedure (Table I). A five-port laparoscopic approach was used with full esophageal mobilization, division of short gastric vessels, and loose hiatal repair. The myotomy was performed anteriorly and extended from 1 to 1.5 cm on the stomach to the level of the diaphragmatic hiatus with the esophagus pulled down into the abdomen. The mean length of the myotomy was 6.7 cm. It was extended more proximally for patients with predominant chest pain or vigorous achalasia. A fundoplication, most commonly a 360-degree floppy Nissen, was then performed. This was fixed to the cut edge of the myotomy and the median arcuate ligament. An anterior 120-degree fundoplication was also used early in the series.

Classification of Outcome

For the purposes of this study, patients were regarded as achieving either a good outcome or a poor outcome. Patients were allocated to the poor outcome category if they had a Visick score of 3 or 4, or if they required reoperation or pneumatic dilatation for symptoms more than 1 month after their original surgery. Reoperation or endoscopy required within 1 month of surgery was regarded as resulting from technical error. A poor outcome was also considered to have occurred if the patient had a dysphagia or regurgitation score greater than 5 or a heartburn score, despite medication, greater than 5.

Statistical Analysis

Because of differing lengths of follow-up, the Kaplan-Meier method[12] was used to assess outcome; a good outcome was regarded as "remission." A univariate analysis of possible prognostic factors and outcome was carried out at 3 years postoperatively using the log-rank test. Ninety-five percent confidence intervals were calculated. Symptom scores were compared by means of the Mann-Whitney U test.

RESULTS

Short-term outcomes, intraoperative and postoperative complications, and the effect of the learning curve for laparoscopic Heller myotomy have been previously reported.[13] The current study examines the 62 patients with a potential postoperative follow-up of at least 1 year. Patient information and operative details are summarized in Table I. In seven cases conversion to an open procedure was required. The indi-

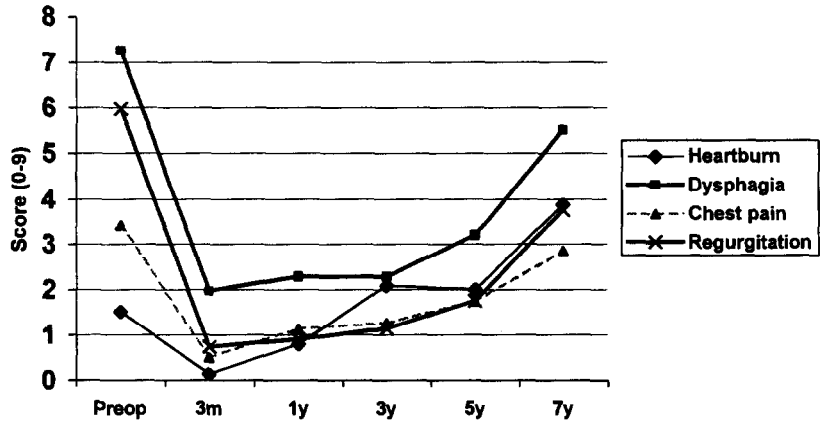

Fig. 1. Effect of time on symptom scores.

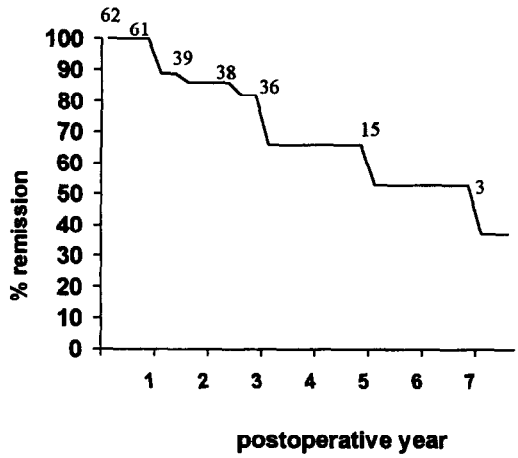

Fig. 2. Cumulative probability of a good outcome after Heller myotomy (numbers indicate patients at risk).

Table II. Comparison of symptom scores*

Symptom	Preoperative score	Postoperative score	*P* value
Dysphagia	7.3 (3.03)	2.8 (2.68)	<0.001
Heartburn	1.4 (2.63)	1.8 (2.27)	0.31
Chest pain	3.4 (3.58)	1.4 (2.21)	<0.001
Regurgitation	6.0 (3.42)	1.2 (1.82)	<0.001

*Scores are mean with standard deviation in parentheses.

cation for conversion was previous hiatal surgery in two cases, severe periesophagitis in two cases, and posterolateral perforation after pneumatic dilatation in three cases.[14] All 62 patients had participated in follow-up, although in five cases follow-up data were not available for the most recent time interval. The mean available follow-up was 38 months with a median of 3 years (range 0.4 to 7 years).

Preoperative symptom scores are shown in Table II and are compared to the most recent postoperative symptom scores, demonstrating a significant improvement. However, an alteration in the mean symptom score over time demonstrates deterioration during postoperative follow-up (Fig. 1). Using the predetermined criteria, 41 patients were classified as having a good postoperative outcome and 21 as having a poor outcome. The reasons for classification as a poor outcome included dysphagia in 13, heartburn in two, reoperation in two, redilatation in three, and a Visick score of 3 or 4 in nine. Several patients had more than one reason for classification as a poor outcome. The cumulative probability of a good outcome after Heller myotomy and fundoplication for achalasia at 7 years is 0.37, as shown in Fig. 2. A univariate analysis was used to compare the influence of patient variables and operative factors on the probability of a good outcome at 3 years postoperatively. Patient variables are presented in Table III and operative factors in Table IV. No factor was demonstrated to be significant at 3 years.

At 5 years postoperatively, only 15 patients remained in clinical "remission." This small number was insufficient to compare most variables. Comparison of outcome for total or partial fundoplication was possible with the probability of a good outcome for Nissen fundoplication of 0.32 and for a partial fundoplication of 0.75 ($P = 0.29$, chi-square 1.12). Comparison of myotomy length was also possible with the probability for a good outcome being 0.37 if the myotomy was 7 cm or less and 0.72 for a myotomy greater than 7 cm ($P = 0.11$, chi-square 2.55).

A comparison of dysphagia scores for total and partial fundoplication showed no statistical difference at 3 years ($P = 0.36$) or at 5 years ($P = 0.08$) (Fig. 3). There was also no difference when comparing total and partial fundoplication scores at 5 years for regur-

Table III. Preoperative patient variables

Variable	No. of patients	Poor outcome	3 yr remission (95% CI)	*P* value
Age				
<41 yr	26	9	0.53 (0.34-0.72)	0.40
41+ yr	36	12	0.68 (0.51-0.84)	
Sex				
M	29	8	0.70 (0.50-0.90)	0.88
F	33	13	0.63 (0.45-0.81)	
Duration of symptoms				
<25 mo	17	7	0.56 (0.31-0.81)	0.41
25 mo+	45	14	0.73 (0.57-0.85)	
Dilated esophagus				
Yes	23	8	0.55 (0.30-0.80)	0.18
No	39	13	0.73 (0.57-0.85)	
Manometry				
Vigorous	7	4	0.57 (0.21-0.93)	0.54
Nonvigorous	55	17	0.66 (0.51-0.81)	

CI = confidence interval.

Table IV. Operative factors

Factor	No. of patients	Poor outcome	3 yr remission (95% CI)	*P* value
No. of cases*				
<100	18	9	0.82 (0.57-1)	0.46
100+	44	12	0.76 (0.56-0.96)	
Myotomy length				
<7 cm	36	13	0.60 (0.45-0.75)	0.34
7 cm+	26	8	0.72 (0.49-0.95)	
Wrap type				
Nissen	49	18	0.56 (0.39-0.73)	0.44
Anterior	13	3	0.75 (0.51-0.99)	
Mucosal perforation†				
Yes	11	5	0.41 (0.06-0.76)	0.12
No	51	16	0.71 (0.57-0.85)	
Prior endoscopic treatment				
Yes	47	16	0.59 (0.3-0.88)	0.20
No	15	5	0.67 (0.52-0.82)	

*Laparoscopic esophageal cases.
†Intraoperative perforation.

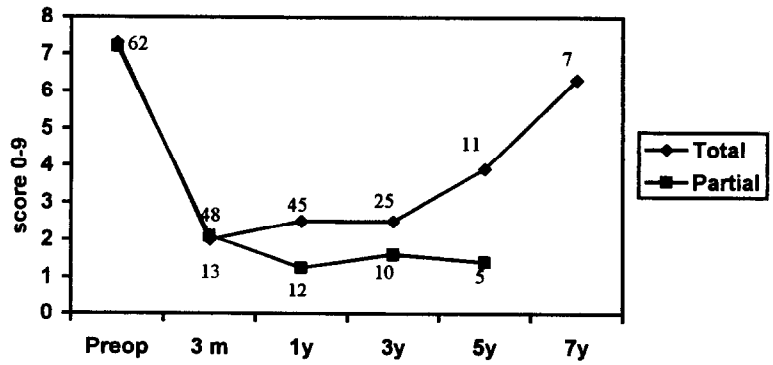

Fig. 3. Effect of type of fundoplication: Change in dysphagia score over time (numbers indicate patients at risk).

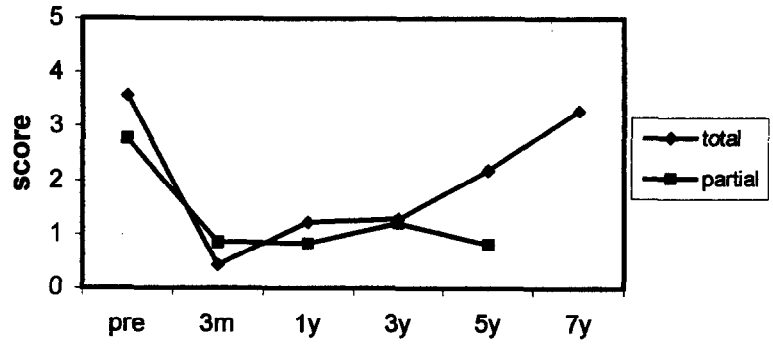

Fig. 4. Effect of type of fundoplication: Change in chest pain score over time (numbers at risk as for Fig. 3).

gitation (2.0 vs. 1.1) or heartburn (1.8 vs. 2.7). Only one patient has documented esophageal stricture as a result of gastroesophageal reflux. This patient had originally had an anterior fundoplication that was converted to a Toupet fundoplication because of dysphagia. The scores for chest pain were significantly higher for total fundoplication (2.2 vs. 0.8; $P = 0.002$) (Fig. 4).

DISCUSSION

Although deterioration in esophageal function with time is well documented after Heller myotomy[9,10] or esophageal dilatation,[15] the results of this study demonstrate more rapid and greater deterioration postoperatively than is generally reported. According to the criteria used in this study, the long-term functional outcome after Heller myotomy and fundoplication would appear unsatisfactory. This study demonstrates a worsening of symptoms postoperatively after initial resolution and a progressive decrease in the number of patients achieving a good outcome.

An earlier point estimation of outcome of the same population of patients showed that more than 80% of patients had a good or excellent result.[13] This demonstrates the usefulness of survival rate methodology over point estimation for analysis of outcome. The greater number of new patients having a good early result can skew long-term outcome. Similarly, mean postoperative symptom scores show a significant reduction from preoperative levels, whereas when monitored over time, a steady deterioration in the score can be seen.

Retrospective studies using survival analysis to measure outcome after Heller myotomy for achalasia demonstrate a similar deterioration in outcome with only about 50% of patients achieving a good result at 10 years.[9,10] However, this deterioration is not universally reported with some investigators maintaining a 90% success rate at 5 years.[16,17] There are several reasons that may explain this disparity in results. First, the definition of a "poor" outcome differs from one series to another. For example, Bonavina et al.[16] classified failure due to dysphagia as only those patients requiring subsequent dilatation or reoperation, whereas in the present study, patients may have indicated satisfaction with the procedure but could still be classified as having a poor outcome because of moderate dysphagia, although they may not consider this troublesome. Second, this study includes patients who underwent the procedure during the "learning curve" period. As for laparoscopic fundoplication,[18] a learning curve has been demonstrated for laparoscopic Heller myotomy.[7,13] Although it was demonstrated that this influences the need for early reintervention as a result of technical errors such as hiatal stenosis or paraesophageal herniation,[13] these factors were excluded from the present study and analysis suggests that case number does not influence late outcome. Third, there is the possibility that the surgery performed was inadequate. Reasons for failure suggested in the literature include inadequate myotomy, fused myotomy, periesophageal fibrosis, reflux, sigmoid esophagus, or mucosal herniation.[2,9,10,19] Inasmuch as most patients had an excellent result from 3 months to 1 year postoperatively and then deteriorated, an incomplete or inadequate myotomy is unlikely to be the cause of the problem. Fourth, the type of fundoplication used may influence postoperative outcome. Most patients in this series had a total fundoplication. Although there was no statistically significant difference in overall outcome between patients with a total or partial fundoplication, there was a trend favoring partial fundoplication with patients experiencing less postoperative dysphagia and chest pain. Total fundoplication after Heller myotomy is preferred in some centers as an antireflux procedure,[20,21] although it is argued that total fundoplication provides too great a barrier for swallowing in the adynamic esophagus.[22] A similar late deterioration after total fundoplication has been reported by Topart et al.[22] However, without a control group, the contribution of the wrap to

deterioration versus a natural progression of disease is difficult to determine. Without a randomized trial, there is no reliable evidence to definitively show that total fundoplication results in a worse outcome after myotomy, but there are few available long-term data after laparoscopic Heller myotomy.[1] The demonstrated trend in the present study is of some concern.

Although no factors were found to be significant at 3 years in the present study, findings are limited by the small numbers at the longer follow-up intervals, and in some of the subgroups of patients. This may have prevented demonstration of significant differences. Patients having a longer myotomy and a partial wrap had a trend toward an improved outcome, both overall and for dysphagia. Thus this study demonstrates deterioration in outcome after an initially successful Heller myotomy. The reasons for this are not fully explained. They can be partly attributed to careful follow-up and the use of survival methodology, but they could also be explained by a deleterious effect of total fundoplication. We would encourage the use of survival analysis techniques to aid in the accurate assessment of outcome after both Heller myotomy and pneumatic dilatation and caution against the use of total fundoplication after Heller myotomy for achalasia.

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Esophageal Carcinosarcoma

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Carcinosarcoma is an uncommon malignancy of the esophagus that presents as a bulky intraluminal polypoid lesion of the esophagus. Histologically, both carcinomatous and sarcomatous components are seen. Because of accelerated intraluminal growth, esophageal carcinosarcoma often presents relatively early. This report describes a 64-year-old man with carcinosarcoma who was successfully treated with an esophagectomy. As in typical squamous cell carcinoma, early detection and treatment by surgical resection are needed to produce significant long-term survival. (J GASTROINTEST SURG 2001;5:414-417.)

KEY WORDS: Digestive system neoplasms, esophageal neoplasms, esophagus, carcinosarcoma

Carcinosarcoma is an uncommon malignancy of the esophagus. It represents only 0.5% to 2.8% of all esophageal neoplasms.[1-8] Carcinosarcoma often presents as a bulky intraluminal polypoid esophageal lesion that harbors both carcinomatous and sarcomatous components. Because of its accelerated intraluminal growth, esophageal carcinosarcoma often presents relatively early. Ultimately the treatment is similar to that of esophageal carcinoma requiring esophagectomy for resectable lesions. This report describes a patient with esophageal carcinosarcoma who was successfully treated with an esophagectomy.

CASE REPORT

A 64-year-old man presented with a 3-month history of progressive dysphagia and odynophagia. He denied having any reflux symptoms or significant weight loss. The patient had smoked one pack of cigarettes per day for 45 years, and admitted to heavy alcohol intake until 15 years ago. His physical examination findings and laboratory values were all within normal limits.

A barium swallow outlined a bulky lesion in the esophagus (Fig. 1). An esophagogastroduodenoscopy was performed demonstrating a mass (Fig. 2), and a biopsy of this mass revealed carcinosarcoma. With a normal abdominal CT scan and no extraluminal extension on a CT scan of the chest, the patient underwent an Ivor Lewis esophagectomy and esophagogastrostomy via abdominal and right thoracotomy incisions. A feeding jejunostomy and pyloroplasty were also performed. Pathologic specimens confirmed the diagnosis of stage IIA (T2N0M0) esophageal carcinosarcoma (Fig. 3). The postoperative course was benign, and the patient is doing well 18 months later with no evidence of any recurrence.

DISCUSSION

In 1865 Virchow[9] described carcinosarcoma as a rare malignant neoplasm composed of both epithelial (carcinomatous) and mesodermal (sarcomatous) elements. Although esophageal carcinosarcoma was first described by Hansemann[10] in 1904, the first case of esophageal carcinosarcoma treated by resection was reported by Stout et al.[11] in 1949. Since then the literature has been quite confusing regarding the terminology for carcinosarcoma. Some examples of the many various terms previously used to describe this unusual tumor are as follows: pseudosarcoma, polypoid squamous carcinoma, spindle cell squamous carcinoma, polypoid carcinoma with pseudosarcomatous features, spindle cell carcinoma, carcinoma with prominent spindle cells, carcinoma with sarcomatoid changes, polypoid carcinoma, metaplastic carcinosarcoma, and polypoid spindle cell carcinoma.

Pseudosarcoma was a term initially used by Lane[12] in 1957 to describe neoplasms of the upper areodigestive tract, which consisted of discrete epithelial and mesenchymal components. This is to be compared with carcinosarcoma where the two components intermingle.[13] Lane suggested that the sarcomatous elements were only a reactive fibroblastic proliferation stimulated by the adjacent epidermoid malignancy.

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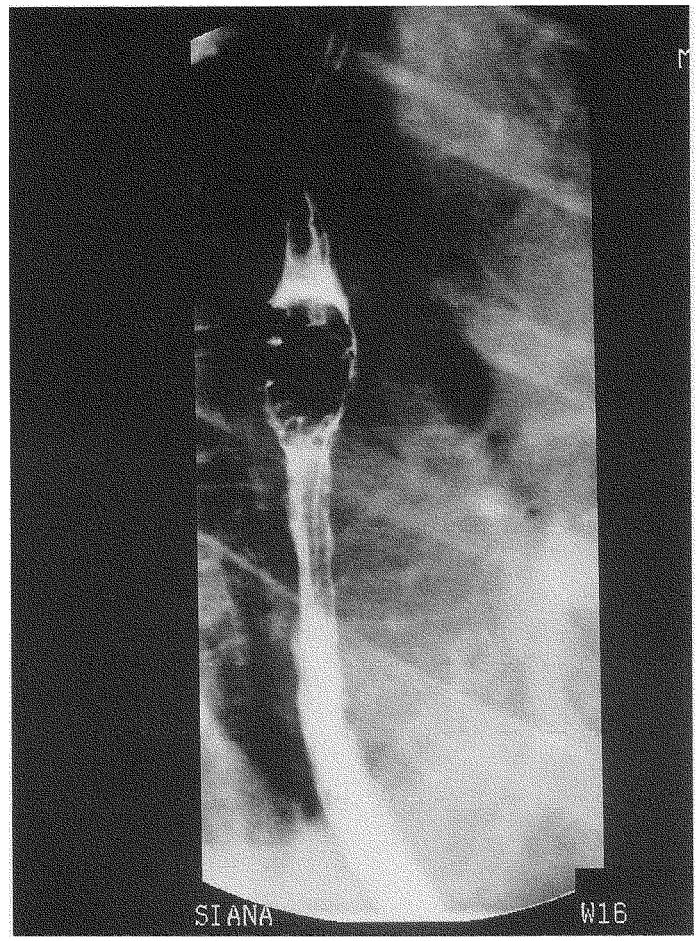

Fig. 1. Barium swallow esophagogram showing dilation of the esophagus with a polypoid lesion in midesophagus.

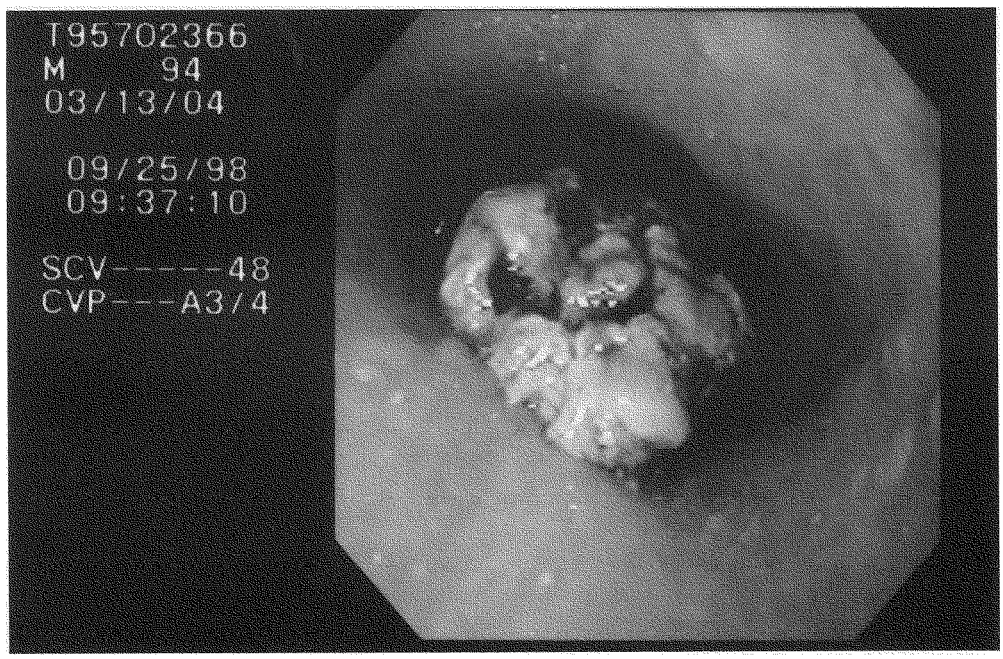

Fig. 2. Endoscopic view of the lesion. Note its polypoid and friable nature.

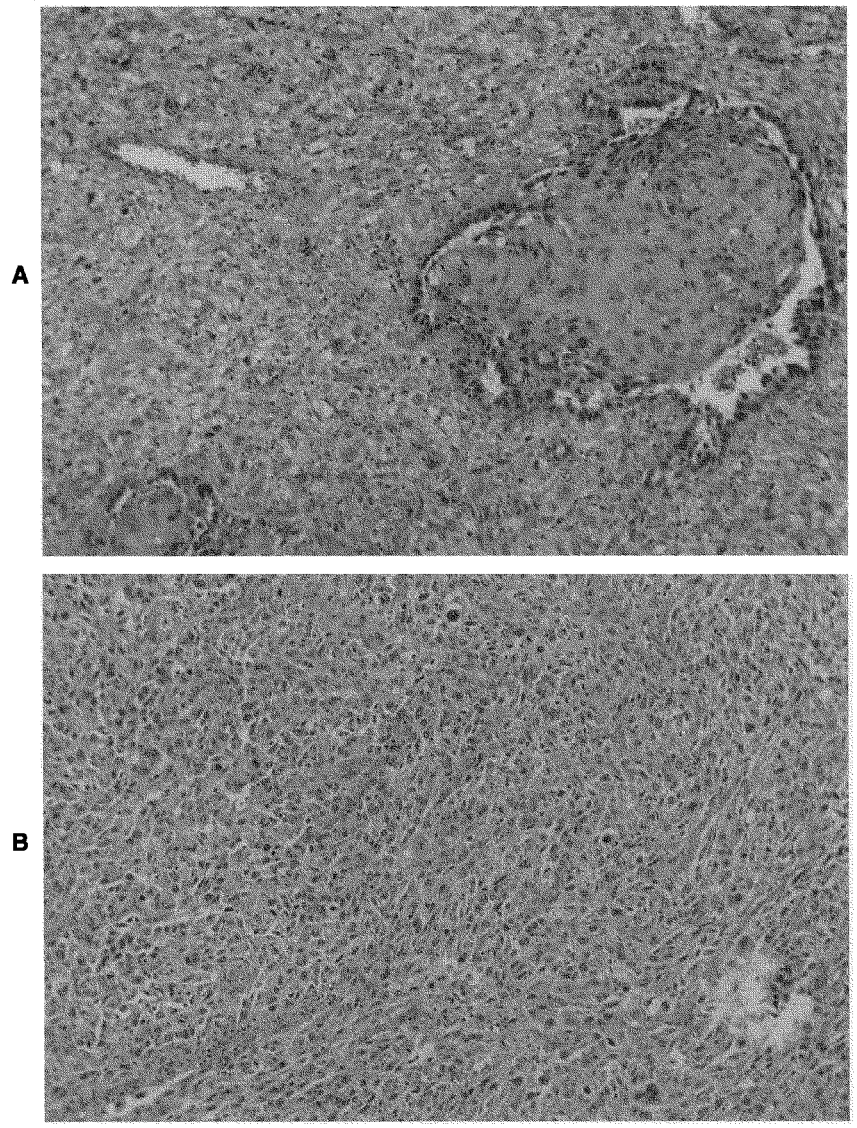

Fig. 3. Histology of the resected lesion (original magnification ×10). **A,** The specimen contains a mixture of epithelial and stromal elements. To the right is a nest of differentiated squamous carcinoma, whereas the remainder of the field contains the stromal component of pleomorphic spindle cells and giant cells with irregularly shaped nuclei and bizarre mitoses. **B,** The stromal portion of the tumor contains bizarre spindle and giant cells. A tripolar mitotic cell is seen centrally.

Since this sarcomatous component was not a neoplastic process, he proposed that it did not metastasize. However, metastases of the sarcomatous element have been reported.[13-15] As early as 1978, Osamura et al.[13] hypothesized that carcinosarcoma and pseudosarcoma were, in fact, the same pathologic and clinical entity. Recently Iascone and Barreca[16] reviewed the records of 127 cases of carcinosarcoma and 56 cases of pseudosarcoma from the literature to establish demographic data, symptoms, location, frequency of lymph node metastasis, invasiveness, and recurrence rates. They found no clinical or behavioral differences between carcinosarcoma and pseudosarcoma. They thus concluded that these two pathologic diagnoses were actually the same disease process.

Three predominant theories have been postulated regarding the histogenesis of esophageal carcinosarcoma. As previously mentioned, the first is that the spindle cell component is a reaction to the carcinoma.[12,17,18] The second theory, known as the collision theory, proposes that the two components are actually separate tumors that have collided. The final theory suggests that the sarcomatous cells are just metaplastic epithelial cells. Recent immunohisto-

chemical and electron microscopic examinations of these tumors support this theory.[19-23]

Treatment of esophageal carcinosarcoma does not differ from that of other malignant esophageal lesions. Resection should be considered for all lesions in operable patients. The indications for resectability are the same for esophageal adenocarcinoma or squamous cell carcinoma.

Most esophageal carcinosarcomas present as large bulky polypoid lesions. Because they are uncommon neoplasms, and their treatment has been resection, the assumption of rapid growth of this tumor remains to be conclusively proved. However, Sasajima et al.[24] described a patient who was followed by means of serial esophagograms because the patient initially refused treatment. They estimated the doubling time to be 2.2 months, whereas other investigators have reported that esophageal carcinomas have doubling times at least twice as long (5 months). This rapid growth may account for the earlier diagnosis of carcinosarcomas and therefore the potential for better outcomes. Because the intraluminal component of these tumors is often larger than that of typical carcinomas at the same stage, symptoms occur much earlier in its course. Although this allows for earlier diagnosis and treatment, esophageal carcinosarcomas do not necessarily carry a better prognosis.

Because of the relative rarity of esophageal carcinosarcoma, the relative prognosis of this lesion compared to that of typical esophageal squamous cell carcinoma has been difficult to ascertain. Previous investigators have suggested a better prognosis with carcinosarcoma.[6,26,27] However, Iyomasa et al.[5] compared 20 cases of esophageal carcinosarcoma with 773 cases of esophageal squamous cell carcinoma. Although the 3-year survival rate for carcinosarcoma was better than that for squamous cell carcinoma (63% vs. 28%), there was no significant difference in the 5-year survival rates (27% vs. 22%). Carcinosarcoma may have become symptomatic before squamous cell carcinoma, but the earlier diagnosis did not translate to a better long-term prognosis.

In summary, esophageal carcinosarcoma is a rare disease entity. As in typical squamous cell carcinoma, early detection and treatment by surgical resection are needed to produce significant long-term survival.

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Selective Role of Vagal and Nonvagal Innervation in Initiation and Coordination of Gastric and Small Bowel Patterns of Interdigestive and Postprandial Motility

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Our previous studies suggested that extrinsic innervation modulates upper gut motility but is not requisite for cyclic interdigestive and postprandial motility of the stomach. However, the specific role of vagal and nonvagal extrinsic innervation in the initiation, coordination, and pattern of gastric motility in dogs after denervation of the entire upper gastrointestinal tract remains unclear. The aim of this study was to determine the role of vagal and nonvagal extrinsic innervation in control of gastric motility patterns. Mongrel dogs were subjected first to extrinsic denervation (in situ neural isolation) of the stomach, small bowel, proximal colon, liver, and pancreas but specifically maintaining vagal innervation to the stomach alone. After fasting and fed motility patterns were measured with indwelling gastric and small bowel manometry catheters, the dogs underwent transthoracic truncal vagotomy (completion of total extrinsic denervation of stomach), and motility studies were repeated. Vagal integrity to the stomach and pancreas was confirmed by means of a modified Hollander test and serum pancreatic polypeptide concentrations after the injection of exogenous insulin, respectively. We found that a cyclic motility pattern (migrating motor complex) persisted during fasting in both the stomach and the small bowel and that the patterns of the stomach and the duodenum remained temporally coordinated before and after vagotomy. However, although a cyclic phase III activity persisted in the stomach after vagotomy, the number of contractions and the motility index during phase III were decreased, and the duration between groupings of contractions was increased. No differences were noted in the duration of postprandial inhibition after feeding meals before and after vagotomy. These observations support our hypothesis that the vagal nerves are not necessary for the initiation or temporal coordination of global fasting or postprandial gastroduodenal motility patterns but are involved in modulating the pattern of contractions during gastric phase III. (J GASTROINTEST SURG 2001;5:418-433.)

KEY WORDS: Vagus nerves, motility, migrating motor complex, vagotomy, extrinsic denervation

Szurszewski[1] first described a cyclic pattern of migrating myoelectric activity in the fasted state in dogs in the duodenum and small intestine. Code and Marlett[2] later characterized this global interdigestive fasting motility pattern by dividing it into four phases of contractions called the interdigestive myoelectric (motor) complex (MMC). Phase I is a quiescent period with virtually no contractions. Phase II consists of intermittent low-amplitude contractions. Phase III, also called the activity front, consists of a short burst of regular high-amplitude contractions that migrate down the small intestine in a very orderly manner. Phase IV represents a short transition period back to the quiescence of phase I. The period of this global cyclic pattern of contractile activity is approximately 2 hours.

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Numerous studies have addressed neurohormonal mechanisms of control of interdigestive gastrointestinal motor activity. Brown et al.[3] demonstrated that motor activity of an autotransplanted pouch of gastric fundus (sympathetically and vagally denervated) increased markedly after alkalinization of the duodenal lumen. They isolated a peptide, later termed "motilin,"[4-6] which they hypothesized to be the cause of this phenomenon; this peptide hormone motilin produced high-amplitude contractions in the denervated gastric pouch when administered intravenously in dogs.[4] Itoh et al.[7,8] showed that intravenous motilin appeared to induce gastric phase III contractions in conscious dogs. Currently we and other investigators support the concept that initiation of the gastric MMC is mediated by motilin,[9-11] whereas others maintain that the intrinsic nervous system and/or extrinsic innervation mediate initiation of fasting motility patterns. For instance, Hall et al.[12] and Chung and Diamant[13] showed that the MMC of the stomach, but not the jejunoileum, was disrupted by acute, reversible vagal blockade; these investigators maintain that vagal innervation is necessary for initiation of the gastric MMC. Our laboratory has proposed the hypothesis that vagal nerves neither initiate the gastric MMC nor regulate temporal coordination of the gastric and duodenal MMCs. Our aim in this study was to determine the role of vagal and nonvagal extrinsic innervation in control of gastric motility patterns during fasting, especially during phase III, and after feeding.

MATERIAL AND METHODS

Preparation of Animal Model

Surgical procedures and subsequent care and conduct of experiments were performed after approval from and according to criteria set forth by the Institutional Animal Care and Use Committee at Mayo Foundation in accordance with the guidelines of the National Institutes of Health and Public Health Service Policy on the Humane Use and Care of Laboratory Animals.

Three healthy female mongrel dogs weighing 15 to 20 kg were used in this study. They were anesthetized with 12.5 mg/kg of intravenous methohexital sodium (Brevital; Eli Lilly and Co., Indianapolis, Ind.) and maintained with a mixed inhalation of halothane and oxygen. Postoperatively the dogs were given butorphanol tartrate (Fort Dodge Animal Health, Fort Dodge, Iowa), 0.2 to 0.4 mg/kg intramuscularly, and buprenorphine hydrochloride (Buprenex; Reckitt & Colman Products, Hill, England), 0.01 to 0.02 mg/kg subcutaneously, for 2 days to control pain after each operation.

The preparation was carried out in three steps (Fig. 1). In step A (pre-stage 1) the colonic mesenteric arcade was doubly ligated in the mid-descending colon 50 cm distal to the ileocecal junction but proximal to the inferior mesenteric artery via a 10-minute minilaparotomy. The dogs were allowed a 1-week recovery period. Because the venous drainage of the descending colon is largely proximal via the middle colic

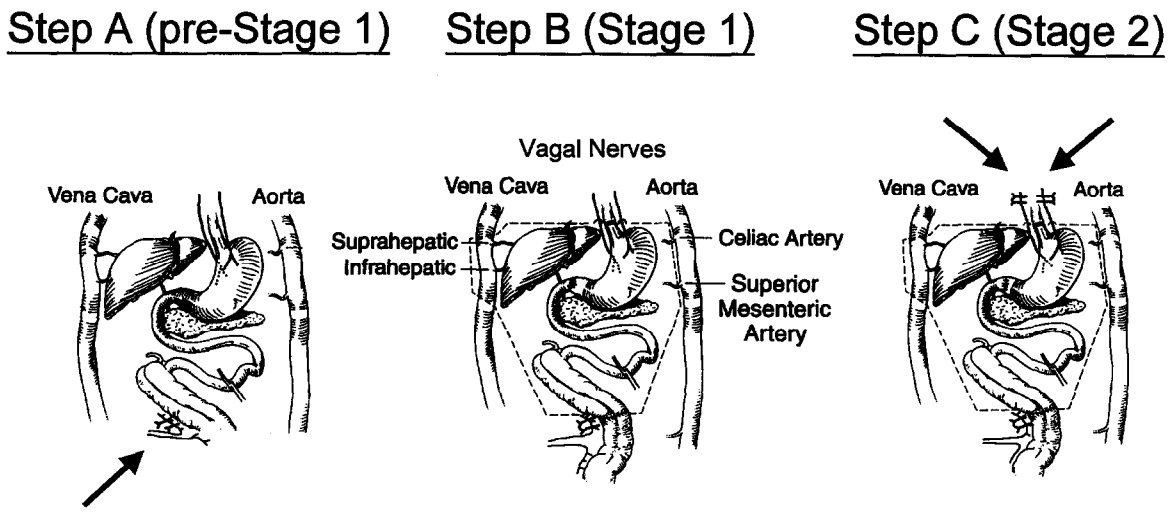

Fig. 1. Three-step operation for in situ neural isolation of the upper gut. *Step A*, Ligation of the colonic mesenteric arcade (arrow). *Step B*, In situ multivisceral neural isolation of the stomach, duodenum, small intestine, proximal colon, liver, and pancreas with preservation of the vagal nerves to the stomach, duodenal transection/reanastomosis, and pyloromyotomy. All tissue connections were transected (dotted lines) except for the walls of the vessels shown. *Step C*, Transthoracic supradiaphragmatic truncal vagotomy (arrows).

vein, this ligation allowed time for collateral pathways of venous drainage of the distal descending colon to develop. Step B (stage 1) involved a modification of multivisceral in situ neural isolation. All tissue continuity (neural, lymphatic, and all other connective tissue) between the upper gut visceral complex consisting of the stomach, small intestine, proximal colon, liver, and pancreas was transected except for the walls of the superior mesenteric artery, the celiac artery, and the suprahepatic and infrahepatic venae cavae under two times optical magnification for a distance of 2 cm according to our previous study[14]; however, the vagal nerves to the stomach were carefully preserved intact at the esophagogastric junction. The esophagus and distal colon were transected and reanastomosed. Esophagoesophageal continuity was restored using a 33 mm end-to-end autostapler (Endopath; Ethicon Endo-Surgery, Inc., Somerville, N.J.) introduced through an anterior gastrotomy, while the colonic transection was resutured with a standard two-layer, hand-sewn anastomosis. Duodenal transection and end-to-end reanastomosis were also performed 1 cm distal to the pylorus to neurally isolate the stomach from the duodenum. In addition, the superior pancreaticoduodenal artery and vein containing the presumed vagal innervation to the pancreas were transected and ligated adjacent to the site of the duodenal transection/reanastomosis in an attempt to vagally isolate the stomach from the pancreas. A pyloromyotomy was performed to prevent potential gastric stasis after the later transthoracic vagotomy of step C (stage 2). The anterior gastrotomy was used to place a modified Thomas cannula to allow direct access to the gastric lumen. Three polyethylene manometry catheters (outside diameter = 1.8 mm; inside diameter = 1.0 mm) were chronically implanted into the gastric antrum 2, 3, and 4 cm proximal to the pylorus to record motor activity. Six other manometry catheters were implanted into the duodenum and jejunum approximately 15, 30, 45, 60, 75, and 90 cm distally from the pylorus to record duodenojejunal motor activities. Each manometry catheter was cemented within stainless steel cannulas embedded in both lateral abdominal walls. The obligate pneumothoraces of each side were evacuated postoperatively using chest tubes.

After completing the first set of experiments (stage 1), the dogs underwent step C (stage 2), a transthoracic, supradiaphragmatic truncal vagotomy to complete extrinsic denervation of the stomach (see Fig. 1). A 1 cm portion of each vagal trunk was excised 4 cm above the diaphragm. This three-stage operation carried a very high perioperative technical mortality, especially after step B, thus explaining why the total number of dogs used in this study was only three.

Conduct of Experiments

The dogs were fasted and hydrated with an intravenous infusion of electrolyte solution containing prophylactic antibiotics for the first 5 days postoperatively (steps B and C). The dogs were housed in individual cages and fed once daily at 9:00 AM; drinking water was supplied ad libitum. However, it was often necessary to give additional electrolyte solution or additional meals as supplements because of the loss of body weight due to a watery diarrhea that persisted for 4 to 6 weeks after step B (stage 1).

Two weeks were allowed for the dogs to recover from the latter two surgical procedures (steps B and C), during which they were trained to stand in a Pavlov sling for 8 to 10 hours per day. Experiments were started in the morning after more than a 12-hour fast. Only one study was performed each day, and no dog was studied more than four times weekly. Dogs were studied over a 3- to 5-month period after stage 1 and a 1- to 2-month period after stage 2.

Experiments for Vagal Integrity

Vagal integrity was determined using a modified Hollander test[15,16] as previously.[14] In brief, 15 units of regular insulin (Regular Iletin I; Eli Lilly and Co.) were administered intravenously, while plasma glucose concentrations were monitored using blood glucose testing tapes (Glucostix; Bayer Co., Elkhart, Ind.).

Measurement of pH of Gastric Juice. Gastric juice was collected by means of intermittent aspiration using an orogastric (pre-stage 1) or Thomas cannula (stages 1 and 2). Samples were taken at 15-minute intervals for measurement of pH beginning 15 minutes before and for 60 minutes after intravenous injection of insulin. A decrease in gastric pH to <1.5 during documented hypoglycemia (less than 40 mg/dl) suggests vagal integrity to the stomach.[15,16]

Plasma Concentration of Pancreatic Polypeptide. Plasma concentrations of pancreatic polypeptide (PP) were measured by a well-established immunoassay.[17,18] Blood samples were collected at 15-minute intervals beginning 15 minutes before and for 60 minutes after intravenous insulin. Blood was collected on ice and immediately centrifuged. The supernate was stored at −70° C for later batch assay. The lack of an increase during insulin-induced hypoglycemia suggests loss of vagal innervation to the pancreas.

Experiments of Motor Activity

Interdigestive State. Manometry catheters were perfused with deionized water (0.1 ml/min) by means of a low-compliance perfusion system (using a nitrogen pressure of 10 psi) connected to strain gauge

transducers (PX-MK099; Baxter Healthcare Corp., Irvine, Calif.), which transmitted intraluminal pressures to an eight-channel Grass recorder (Grass model 7D polygraph; Grass Instrument Co., Quincy, Mass.) using time constants of 1 second. Manometry data were simultaneously collected on an IBM XT computer at a sample rate of 10 Hz for later analysis. We recorded three to four cycles of the spontaneous MMC in the interdigestive state. At the end of each day's experiment, 0.1 μg/kg or 0.3 μg/kg of exogenous canine motilin (Peninsula Laboratories, Belmont, Calif.) or 15 units of regular insulin was infused intravenously over 30 seconds during phase I approximately 30 minutes after a spontaneous gastric phase III; motor activity was recorded for 30 to 60 minutes.

Postprandial State. The dogs were given oral meals of 50 g or 200 g of a pork liver (128 kcal/100 g liver) blended with 50 ml of tap water 30 minutes after a spontaneous gastric phase III. Some dogs needed to be given the test meals via the Thomas cannula because they would not eat the liver meal. Motor activity was recorded until the next spontaneous gastric MMC occurred.

Analysis of Data

All manometric recordings were analyzed by visual inspection. Criteria of the four phases of gastric, duodenal, and jejunal MMCs were used as in previous reports.[2,19] The duration of MMCs was assessed as the time between the start of successive phase III contractions at each channel (stomach, duodenum, and jejunum). The durations of the individual phases of the MMC (I, II, III, and IV) at each of three channels (stomach, duodenum, and jejunum) were also calculated. The timing between the onset of related gastric and duodenal MMCs was measured. Positive values signify that the gastric phase III started before the duodenal phase III, whereas negative values represent a duodenal phase III beginning before the gastric phase III. Similar analyses of induction of premature phase III activity after injection of motilin or insulin were calculated.

To quantitate gastric phase III activity before and after truncal vagotomy, the following parameters were determined before and after vagotomy as shown in Fig. 2: (1) duration of gastric phase III; (2) maximum amplitude of contractions during gastric phase III; (3) total number of contractions per gastric phase III; (4) number of groupings of contractions per gastric phase III; (5) number of contractions per grouping during gastric phase III; (6) duration of groupings of contractions; (7) duration between groupings of contractions; and (8) motility index (MI) during phase III (calculated by computer analysis as MI = $\log_e$ [sum of amplitudes × frequency of pressure waves + 1], which is a function both of frequency and amplitude of individual contractions). Premature gastric phase III activity induced by administration of motilin or insulin was quantitated similarly.

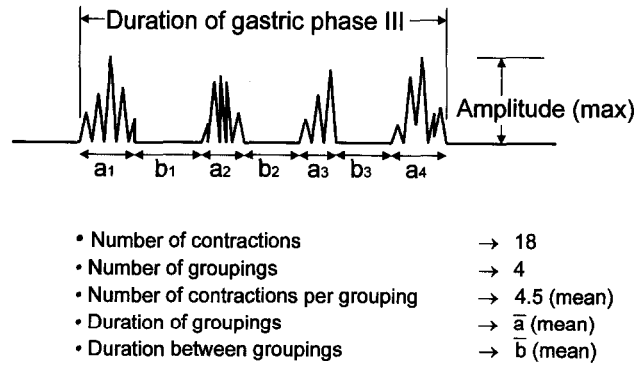

Fig. 2. Schematic diagram explaining quantification of gastric phase III.

In the digestive state, the duration between the start of feeding and the start of the first gastric MMC after feeding was measured.

Statistical Methods

More than four experiments were performed in the interdigestive state, and two experiments each were performed in the postprandial state after feeding a small (50 g) or large (200 g) meal of pork liver in both stages to each dog. Mean values were calculated on each experimental day, then across experiments in each dog, and finally a grand mean was calculated across all dogs. Differences before and after vagotomy were compared by means of Student's t test for paired data, with $P < 0.05$ considered statistically significant. All values within the text are expressed as mean ± standard error of the mean (SEM).

RESULTS

Health of Animals

All experiments were performed only on healthy dogs. The mortality of step B was very high (only 3 of 15 dogs survived). Causes of death included pneumothorax in two, hypovolemic shock in two, bleeding from the diaphragm in one, bleeding from colocolostomy in one, peritonitis in one, and no obvious findings in two. No dogs died after step C (vagotomy), and all dogs thereafter remained healthy. However, after step B (stage 1), all dogs developed severe, watery diarrhea that persisted for 4 to 8 weeks, after which the stool became more formed. The three surviving dogs lost 22%, 8%, and 5% of their body

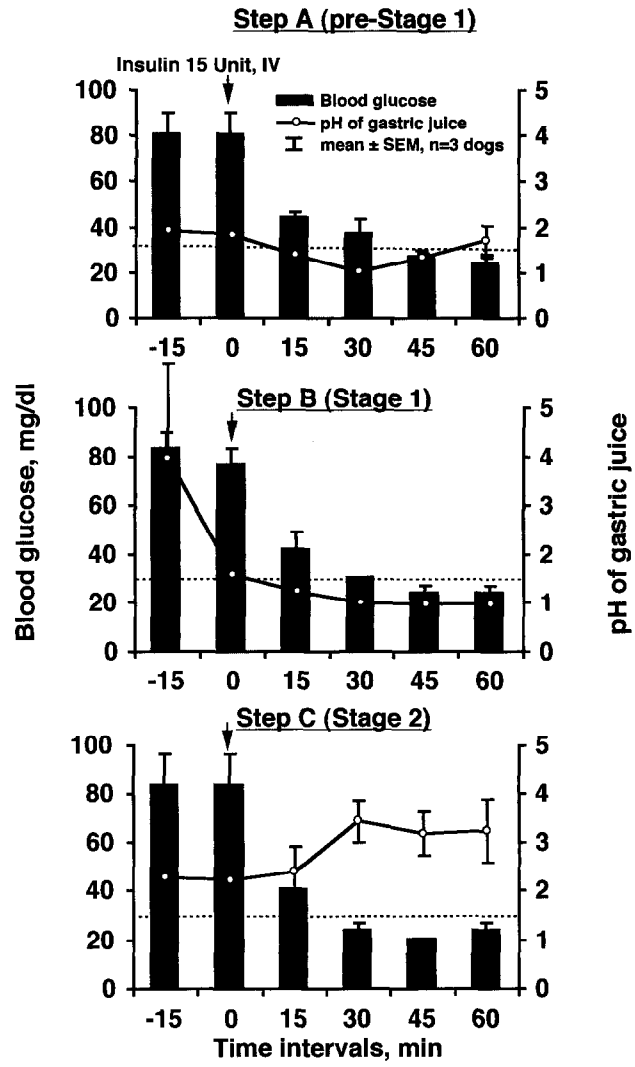

Fig. 3. Effect of exogenous insulin on blood glucose concentration and pH of gastric juice **(A)** after step A, **(B)** after stage 1 (vagal nerves to stomach intact), and **(C)** after stage 2 (truncal vagotomy).

weight, respectively, 1 month after completion of stage 1. One dog lost more than 20% of its preoperative body weight after stage 1 because of severe, watery diarrhea; we did not perform experiments until the body weight increased to only 10% loss of preoperative body weight. After stage 2, body weight remained stable.

Vagal Integrity

After stage 1 (in situ neural isolation with vagal preservation), the modified Hollander test showed that, similar to control values (Fig. 3, *A*), gastric pH decreased to less than 1.5 (Fig. 3, *B*). After stage 2 (vagotomy) (Fig. 3, *C*), pH did not decrease during insulin-induced hypoglycemia. Under control conditions, hypoglycemia induced an increase in plasma PP after injection of insulin (74 ± 10 pg/ml before insulin vs. 215 ± 9 pg/ml at 60 minutes after insulin; $P < 0.01$). After stage 1, PP still increased during the hypoglycemia, but PP at 60 minutes after injection of insulin in stage 1 was lower than that in pre-stage 1 (215 ± 9 vs. 169 ± 4 pg/ml; $P < 0.05$). After stage 2, PP no longer increased during the hypoglycemia, confirming a complete abdominal (and pancreatic) vagotomy.

Spontaneous Interdigestive Motor Patterns

After stage 1, a cyclic pattern of contractile activity occurred in the stomach and small intestine in all dogs. This global motor pattern was closely characteristic of the typical MMC with four phases of activity (Fig. 4). Phase III activity in the stomach remained temporally coordinated with phase III activity in the duodenum. Every gastric phase III was closely associated with a duodenal phase III that began simultaneously or just after the start of the gastric phase III. In contrast, on occasion (2% ± 1% of the time) a duodenal phase III was not preceded by a gastric phase III.

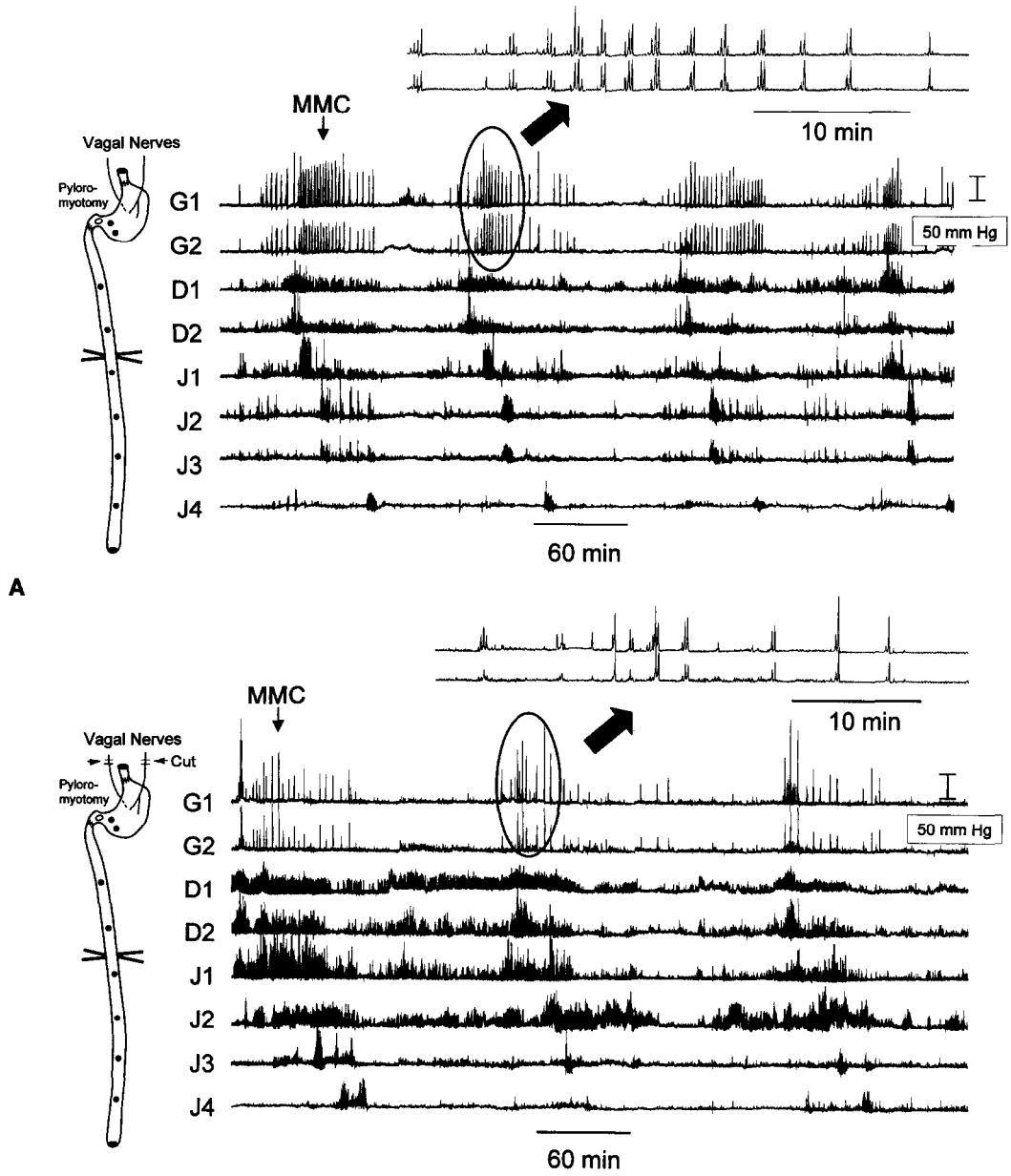

Fig. 4. Cyclic gastrointestinal motor activity in the interdigestive state after stage 1 *(top)* and after stage 2 *(bottom)* in three dogs (**A, B,** and **C**). In both stages, the cyclic gastric myoelectric motor complex *(MMC)* pattern persisted and migrated aborad in all dogs. *Continued.*

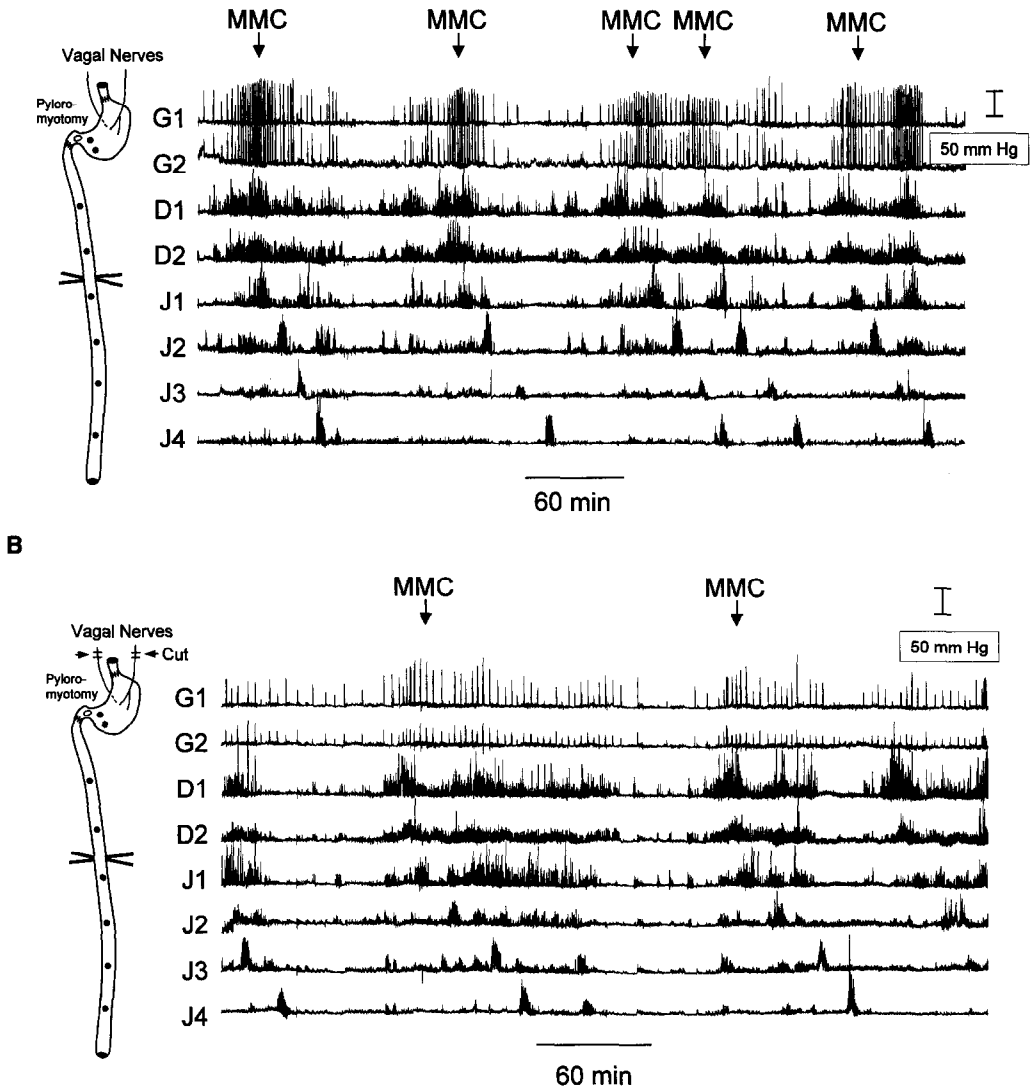

Fig. 4, cont'd. For legend see p. 423.

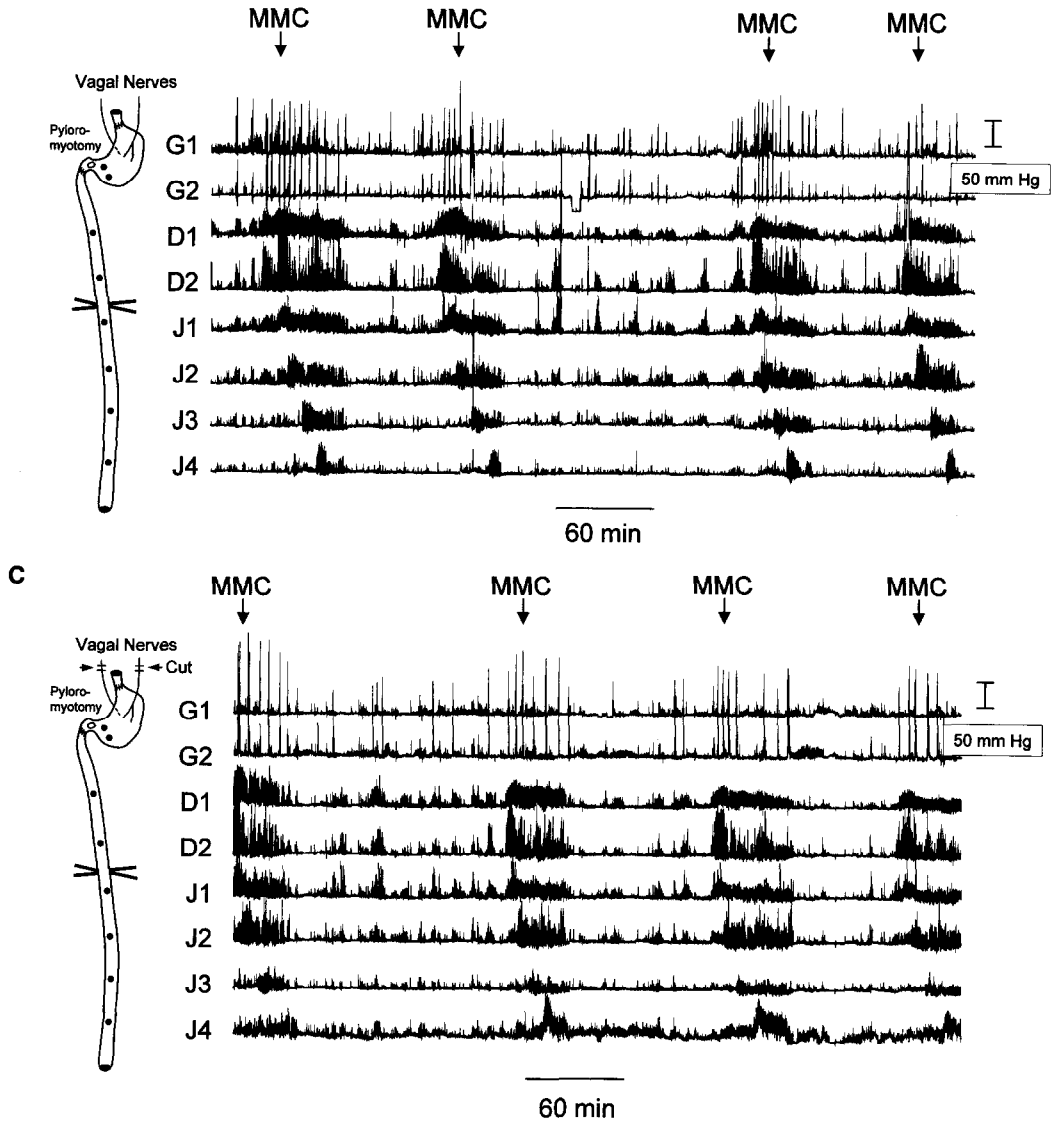

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Table I. Spontaneous Interdigestive Motility Patterns

	Stage 1* (min)			Stage 2† (min)		
	Stomach	Duodenum	Jejunum	Stomach	Duodenum	Jejunum
Duration of MMC	128 ± 18	127 ± 18	127 ± 17	137 ± 7	132 ± 11	131 ± 11
Duration of each phase of MMC						
I	25 ± 3	33 ± 6	38 ± 9	39 ± 12	36 ± 8	37 ± 8
II	40 ± 11	43 ± 11	47 ± 12	35 ± 11	40 ± 6	44 ± 6
III	25 ± 2	10 ± 1	7 ± 0	22 ± 4	9 ± 0	7 ± 0
IV	47 ± 12	47 ± 8	40 ± 8	36 ± 4	43 ± 3	38 ± 3

Values are mean ± SEM; n = 3 dogs. No statistical differences were noted.
*Before vagotomy.
†After vagotomy.

Table II. Quantification of gastric phase III

	Stage 1*			Stage 2†		
	Spontaneous	Motilin-induced‡	Insulin-induced	Spontaneous	Motilin-induced	Insulin-induced‡
Duration (min)	25 ± 2	7 ± 1	9 ± 1§	22 ± 4	12 ± 4§	7 ± 5
Maximum amplitude (mm Hg)	111 ± 24	93 ± 17	86 ± 23	105 ± 20	104 ± 9	70 ± 40
Number of contractions	48 ± 7	19 ± 2	27 ± 4§	17 ± 2‖	14 ± 2§	7 ± 6
Number of groupings	13 ± 2	5 ± 1	6 ± 1	8 ± 2	5 ± 1§	5 ± 3
Number of contractions per grouping	4 ± 1	4 ± 1	6 ± 3	2 ± 1	4 ± 1	1 ± 1
Duration of groupings (min)	1 ± 1	1 ± 1	1 ± 1	1 ± 1	1 ± 1	0 ± 1
Duration between groupings (min)	1 ± 1	1 ± 1	1 ± 1	3 ± 1‖	2 ± 1	1 ± 1
Motility index	2 ± 1	10 ± 1	11 ± 1	10 ± 1‖	10 ± 1	7 ± 4
Maximum amplitude of DIII (mm Hg)	82 ± 21	81 ± 27	47 ± 9	78 ± 14	67 ± 18	42 ± 12
Maximum amplitude of JIII (mm Hg)	75 ± 8	47 ± 17	40 ± 6§	79 ± 6	63 ± 13	49 ± 14

DIII = duodenal phase III; JIII = jejunal phase III.
Values are mean ± SEM; n = 3 dogs.
*Before vagotomy.
†After vagotomy.
‡n = 2 dogs only.
§$P < 0.05$ compared to spontaneous phase III in same stage.
‖$P < 0.05$ compared to parameter in stage 1.

After stage 2, this cyclic global pattern continued with very few changes. Gastric and duodenal phase III activity remained temporally coordinated. All gastric phase IIIs were associated with a duodenal phase III, but 7% ± 4% of all duodenal phase IIIs were not preceded by a gastric phase III.

Table I quantitates certain parameters of this cyclic activity. The period of the MMC and the duration of each phase of the MMC in the stomach, duodenum, and jejunum did not differ between stages 1 and 2. Similarly the timing between the onset of phase III in the stomach and duodenum varied between −2 and +3 minutes and did not differ between stages 1 and 2. There were, however, some differences in the regularity of the MMC in these dogs. On at least one of the four days of fasting experiments, there were intervals that followed a characteristic MMC during which the typical cyclic pattern disappeared (Fig. 5), and a persistent noncyclic pattern of intermittent contractions occurred for 2 to 6 hours, after which the typical MMC returned. Over a total fasting recording period of 33, 73, and 48 hours in stage 1 in the three dogs, and 36, 48, and 44 hours in stage 2, this noncyclic activity comprised approximately 26% ± 13% of the interdigestive motor pattern in stage 1 and 32% ± 11% in stage 2. Such disruption of established interdigestive motility would be distinctly uncommon in a neurally intact dog.

Exogenous Motilin and Insulin

Exogenous motilin at a dose of 0.1 μg/kg and 0.3 μg/kg induced within 10 minutes a premature gastric phase III 28% ± 15% and 67% ± 33% of the time, respectively, after stage 1 and 33% ± 17% and 43% ± 7% after stage 2 (Fig. 6). Phase III activity occurred in the stomach and then migrated aborad along the small bowel manometry catheters. Table II shows the

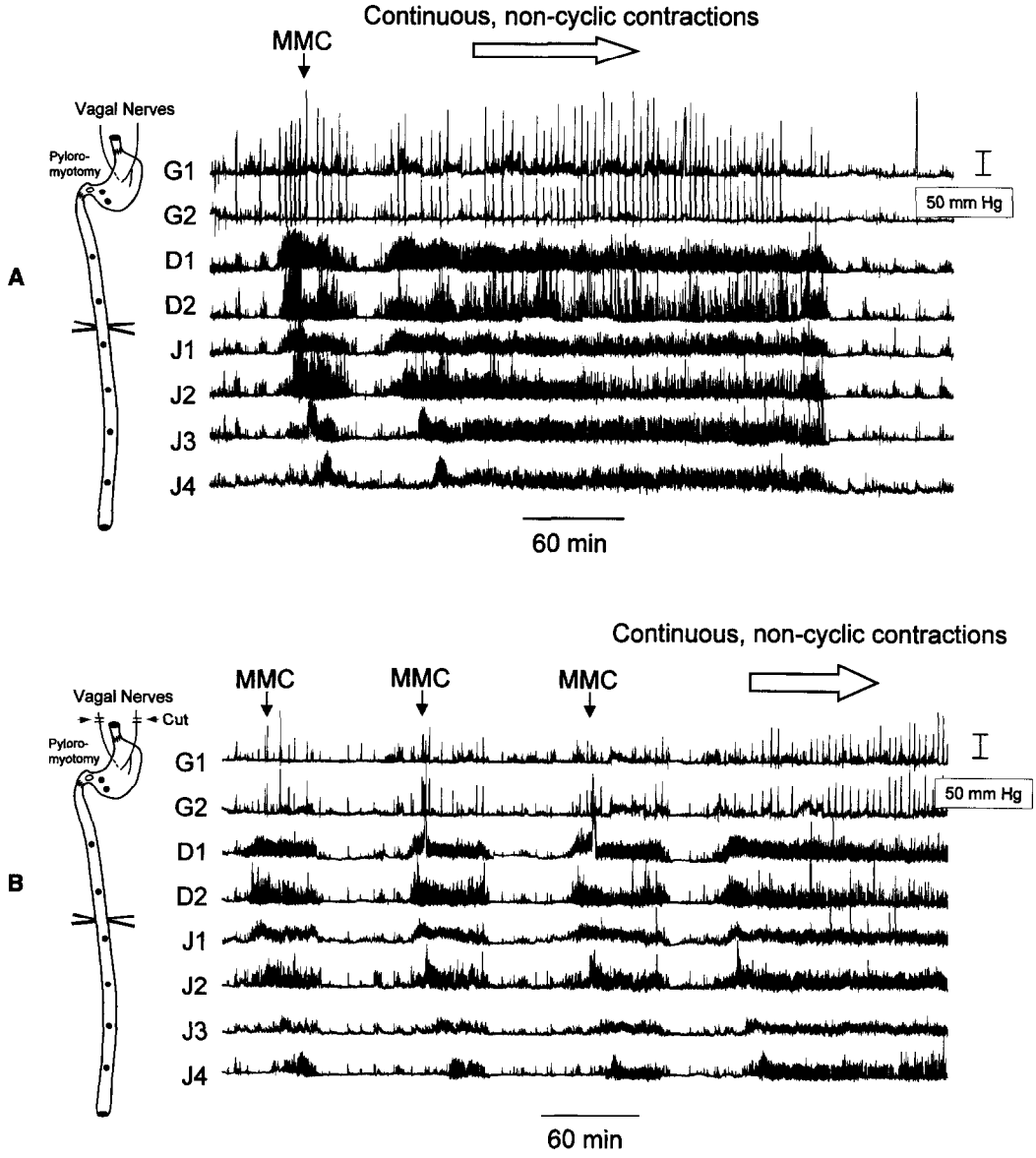

Fig. 5. Disruption of cyclic interdigestive gastrointestinal motor activity of one dog **(A)** after stage 1 and **(B)** after stage 2. This motility pattern was seen approximately 26% ± 13% in stage 1 and 32% ± 11% in stage 2 of the time of recording of fasting motility.

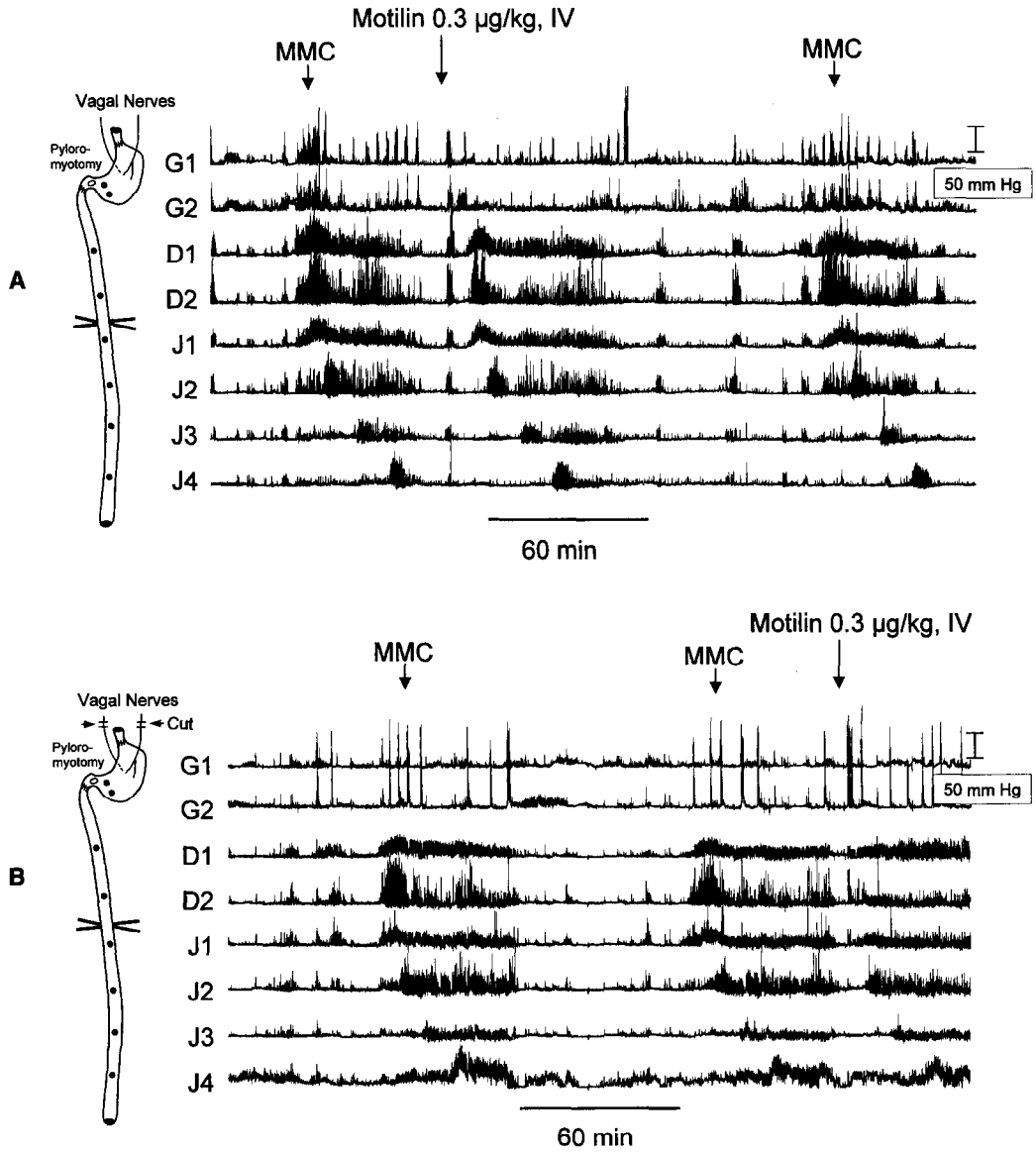

Fig. 6. Gastrointestinal motor activity after injection of exogenous motilin **(A)** after stage 1 and **(B)** after stage 2.

characteristics of the premature motilin-induced gastric phase III. The duration of motilin-induced phase III activity was shorter in the stomach than spontaneous phase III.

After exogenous intravenous insulin (15 U), a premature gastric phase III was followed by a duodenal phase III 43% ± 10% of the time after stage 1; the phase III was followed by approximately 60 minutes of continuous, noncyclic, antral contractions (Fig. 7). After stage 2, insulin was similarly successful (43% ± 23%) in inducing a premature gastric and/or duodenal phase III, but the prolonged antral contractions no longer occurred. However, the characteristics of the premature gastric phase III in stage 2 tended to be different from those in stage 1 (see Table II).

Quantification of Phase III Motor Pattern

Table II compares the characteristics of gastric phase III activity after stage 1 and stage 2 in an attempt to quantitate the motor pattern (see Fig. 2). Phase III activity as measured by the antral manometry catheters occurred as a typical 10- to 30-minute burst of high-amplitude contractions; the contrac-

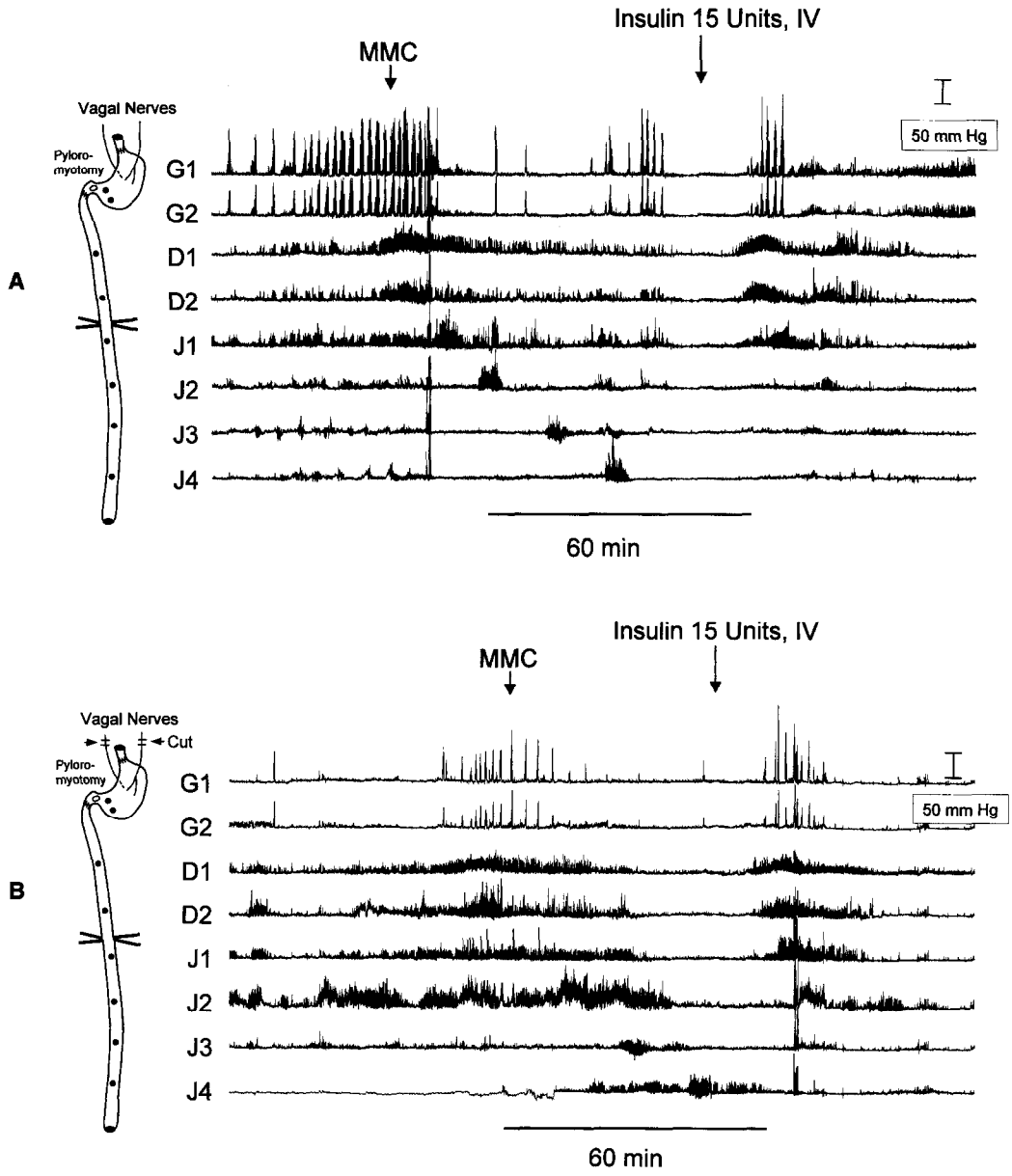

Fig. 7. Gastrointestinal motor activity after injection of exogenous insulin **(A)** after stage 1 and **(B)** after stage 2. Note the continuous contractions seen in A but not in B.

tions within phase III occurred as multiple groups of three to six contractions separated by intervals of 30 seconds to 1 minute as occurs in neurally intact dogs. The duration and the maximum amplitude of contractions during phase III did not differ before and after vagotomy. In contrast, the total number of contractions and the MI decreased after stage 2, whereas the duration between groupings of contractions increased (each $P < 0.05$). The number of groupings of contractions was greater in stage 1 than in stage 2 ($P = 0.058$).

Postprandial Motor Patterns

Ingestion of the liver meal rapidly disrupted the cyclic interdigestive motor pattern and induced a typical pattern of intermittent contractions. Subjectively this pattern did not appear to be different between stages 1 and 2. The duration of postprandial inhibition was similar between stages 1 and 2 with both the 50 g meal (157 ± 9 minutes vs. 130 ± 26 minutes; $P > 0.05$) and the 200 g meal (298 ± 42 minutes vs. 314 ± 46 minutes; $P > 0.05$). The MI in the gastric antrum also did not differ for the first hour after feed-

ing of 50 g (9 ± 1 vs. 11 ± 0; $P = 0.08$) or 200 g (11 ± 1 vs. 12 ± 1; $P = 0.2$).

DISCUSSION

In this study we investigated the role of vagal and nonvagal extrinsic innervation after a model of in situ neural isolation of the stomach and upper gut in the initiation and coordination of gastric and small bowel patterns of interdigestive and digestive motor activities. We demonstrated that the extrinsic nerves are not required for initiation of a cyclic gastric and small bowel MMC or for temporal coordination of gastroduodenojejunal motor activity in the interdigestive state. A novel, detailed quantitative analysis helped us to demonstrate the differences in the pattern of contractile activity of gastric phase III before and after total abdominal vagotomy in the otherwise neurally isolated upper gut. Exogenous insulin as well as exogenous canine motilin induced a premature gastric MMC despite lack of nonvagal and vagal innervation to the stomach. After feeding meals of two different caloric densities, inhibitory durations of the MMC did not differ before and after vagotomy.

Many previous studies have addressed the factors that might control the initiation, migration, and temporal coordination of the gastrointestinal MMC.[20] Most all of this work has been done in dog models. In the small intestine, it is well accepted that initiation of the MMC and its orderly coordinated migration aborad is under the control of the intrinsic nerves of the bowel wall (enteric nervous system).[21-23] However, the control of the gastric MMC remains controversial. Many studies support a hormonal basis for initiation of the gastric MMC based on many dog studies. These studies have clearly shown that as serum concentrations of the regulatory peptide motilin cycle in temporal coordination with gastric phase III,[24] exogenous intravenous motilin will induce a premature gastric (and small bowel) MMC[7,8]; duodenectomy to remove the source of endogenous motilin abolishes the gastric MMC[11] at least for the first few months postoperatively,[25] and immunoneutralization of circulating endogenous motilin by intravenous infusion of antimotilin antibodies inhibits the presence of a gastric MMC for the duration of the effective immunoneutralization.[26] In addition to these studies on initiation of the gastric MMC, the close temporal coordination of gastric and duodenal phase III activity also may be controlled by hormonal mechanisms. Intrinsic (enteric) neural continuity between the stomach and duodenum is not necessary to maintain this close temporal coordination,[19,27-29] and exogenous intravenous motilin induces a premature but temporally coordinated MMC in the stomach and the duodenum despite disruption of intrinsic neural continuity between the stomach and the duodenum.

Our current study approached this topic via selected neurotomies, specifically concentrating on the role of vagal innervation in the control of fasting and fed motor patterns in a dog model. Many previous studies have addressed the role of the vagus in this control. Aeberhard and Bedi[30] studied the effects of proximal gastric vagotomy followed by total abdominal vagotomy on fasting motility patterns. They found that the MMC persisted in the stomach, suggesting that vagal innervation was not necessary for interdigestive motor patterns in the stomach and small bowel. Others arrived at similar findings with different models of gastric vagotomy.[31] Our previous work[14,19,27,28,32] investigated this topic and arrived at similar conclusions by selected different models of staged or total gastric vagotomy and complete extrinsic denervation of the stomach alone or combined with extrinsic denervation of the small bowel as well. Spencer et al.[27] showed that a cyclic MMC activity persisted in the stomach and duodenum after both a staged initial complete nonvagal extrinsic denervation of the stomach as well as after subsequent completion of vagal denervation of the stomach. Van Lier Ribbink et al.[19] developed a canine model of complete neural isolation of the entire stomach and showed not only a clear persistence of a cyclic motor pattern in the stomach that remained temporally coordinated with the duodenal MMC, but also that endogenous motilin cycled in temporal concert with this gastric cycle and exogenous intravenous motilin induced a premature gastric (and intestinal) MMC.[33] We extended this work by developing a model of upper gut complete neural isolation and again showed persistence of a cyclic motor pattern in stomach and duodenum that maintained temporal coordination with plasma motilin concentrations.[14,32] This combined work strongly suggested that vagal innervation is not necessary for initiation or temporal coordination of the gastric MMC.

In contrast, Hall et al.[12] and Chung and Diamant[13] showed that the MMC in the stomach and duodenum but not in the upper small bowel was disrupted by a technique of acute reversible vagal blockade (cervical vagal cooling to 4° C). This important work questioned previous studies on the role of vagal innervation and suggested that vagal innervation was essential for initiation of the gastric MMC. A study by Gleysteen et al.,[34] however, showed that cooling of the supradiaphragmatic intrathoracic vagal nerves had no effect on the gastric MMC, again questioning the role of vagal extrinsic nerves in control of the gastric MMC. The findings of Gleysteen et al.[34] contrasted with the work of Hall et al.[12] and Chung and Dia-

mant,[13] possibly related to differing and confounding effects of cervical vagal cooling versus supradiaphragmatic vagal blockade. One possibility is that in the dog, the distal thoracic vagal nerves also contain sympathetic fibers, the latter of which may function as "inhibitory" nerves if unimpeded by vagal input.[35] Chung et al.[36] addresses this topic with another study that showed the persistent absence of the gastric MMC during combined adrenergic pharmacologic blockade and vagal cooling. They have maintained that the MMC is not solely mediated by sympathetic fibers entering the vagus in the thorax, again proposing that vagal innervation is a critical pathway for initiation of the gastric MMC. To address this controversial topic, our current study was designed to extend our previous work[14,32] and to determine the role of specific extrinsic and intrinsic nerves to the stomach using selective neurotomies. We created a canine model of controlled staged "neural isolation" of the stomach both from the central nervous system (vagal, sympathetic) but also from the small bowel (intrinsic neural continuity).

Our experimental preparation interrupted the continuity of the enteric nervous system from the esophagus, duodenum, and distal colon, and completely interrupted input of all neural information to the stomach from extrinsic and intrinsic nerves. Our recordings of global motor activity clearly show a persistence of a cyclic motor pattern in the stomach that always remained temporally coordinated with the duodenal MMC, despite nonvagal and vagal denervation and lack of intrinsic neural continuity with the duodenum (proximal duodenal transection). We did, however, note that the motor pattern after vagotomy appeared different during phase III with fewer contractions and an altered overall grouping of individual contractions. We had noted similar changes in our previous work[14,32] but were not able to quantitate the differences.

Because of these changes in motor "pattern" during phase III, we developed a novel means of quantitating both the amount and pattern of contractile activity (see Fig. 2). Quantitative analysis showed that during gastric phase III, the number of contractions, the number of groupings of contractions, and the overall total contractile activity as measured by MI decreased; in addition, the duration between groupings of contractions increased after vagotomy, whereas the duration and maximum amplitude of contractions during gastric phase III did not differ before and after vagotomy. This quantification confirmed our subjective observations. These data suggest that although vagal nerves are not needed for initiation of the MMC or for temporal coordination of gastric phase III with phase III in the duodenum, central neural input via the vagal nerves does appear to modulate the contractile patterns during gastric phase III. Specific contractile patterns that were not seen in fasting intact dogs were discovered in 26% and 32% of the studies during the interdigestive state in stages 1 and 2, respectively. These patterns involved individual, nongrouped, high-amplitude contractions, similar in amplitude to those during gastric phase III that continued for 2 to 6 hours without any overall global cyclic nature, either in the stomach or the small bowel. We had noted a similar pattern previously[14,32] and also determined that plasma motilin concentrations did not cycle during this aberrant motor pattern despite persistence of the fasting state. We did not measure plasma motilin concentrations in this current study. These observations suggest that the normal cyclic motor patterns in the interdigestive state may be disrupted intermittently by these noncyclic motor patterns after multivisceral upper gut transplantation and may have some clinical relevance.

We also investigated the role of exogenous motilin and insulin in this model of staged nonvagal and vagal denervation of the upper gut. As seen with our other canine preparations of extrinsically denervated stomach,[19] motilin induced a temporally coordinated premature MMC in both the stomach and the small bowel, despite extrinsic denervation and lack of intrinsic neural continuity of the stomach and duodenum. This observation further supports a role for plasma motilin in the initiation of the MMC and may explain why the stomach that is neurally isolated from the remainder of the gut[19] still undergoes a cyclic motility that remains in temporal coordination with the remainder of the upper gut.

We also studied exogenous insulin because of the known effect of hypoglycemia on gut function as mediated by vagal innervation. Prior to vagotomy, insulin-induced hypoglycemia increased gastric acid production and serum PP concentrations and induced about half the time both a premature gastric and a duodenal MMC in the nonvagally denervated upper gut; in addition, a prolonged contractile activity occurred in the antrum after the phase III activity. In contrast, after completion of neural isolation by total abdominal vagotomy, gastric acid secretion and release of endogenous PP no longer occurred nor did the prolonged antral contractile activity; induction of a premature MMC, however, did still occur about half the time, suggesting that the ability of exogenous insulin to induce a premature MMC[37] is not dependent on vagal integrity.

Finally, we studied the effects of nonvagal and vagal innervation to the upper gut on postprandial motility. Some previous work suggested that vagotomy abolished or shortened postprandial inhibition of interdigestive motor patterns.[38] We found no evidence that

vagotomy, per se, had any effect on the duration of the postprandial inhibition of the MMC after either a small (64 kcal) or a large (256 kcal) liver meal. Because we did not study the dogs before nonvagal neural isolation, we cannot comment on the role of nonvagal extrinsic innervation; however, the duration of inhibition with these meals was somewhat shorter than was shown in our previous studies in neurally intact dogs.[39] However, our previous studies[14,19] showed that the primary factor(s) leading to inhibition of the MMC postprandially is not neural in origin.

In summary, this study shows clearly that although vagal innervation to the stomach modulates the pattern of contractions in the stomach during phase III of the MMC, vagal innervation *is not necessary for the initiation* of the gastric (or small bowel) MMC and *does not mediate the temporal coordination* of the gastric and small bowel MMC in the canine model. In addition, vagal innervation does not mediate postprandial inhibition of the MMC after in situ neural isolation. One unique noncyclic motor pattern was noted in this study of upper gut neural isolation that had not been described previously. These motor patterns may have relevance to clinical upper gut multivisceral transplantation.[40]

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A Simple Scoring System for Predicting Bile Duct Stones in Patients With Cholelithiasis

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A means of accurately predicting the presence of stones in the bile duct in patients undergoing laparoscopic cholecystectomy for gallbladder stones is lacking. With the use of a three-stage analysis, a predictive score was developed from seven common parameters. Initially the score was formulated by using data from a retrospective series of patients undergoing laparoscopic cholecystectomy; the system was then tested prospectively over a 1-year period in patients undergoing laparoscopic cholecystectomy for gallbladder stones. This simple scoring system demonstrated an ability to predict bile duct stones with a sensitivity in excess of 70%. The use of such a score may allow the development of preoperative strategies for treating patients undergoing laparoscopic cholecystectomy. (J GASTROINTEST SURG 2001;5:434-437.)

KEY WORDS: Bile duct stones, laparoscopic cholecystectomy, predictive score

Several strategies exist for management of patients with a high risk of stones in the bile duct who are undergoing laparoscopic cholecystectomy. One strategy is to have these patients undergo preoperative investigations such as endoscopic retrograde cholangiopancreatography (ERCP) or intravenous cholangiography and then treat any stones demonstrated in the bile duct by endoscopic sphincterotomy.[1] Another is to proceed directly to laparoscopic cholecystectomy and investigate the bile duct by means of intraoperative cholangiography, treating any stones detected in the bile duct either during the same procedure or at subsequent ERCP.[2] The latter strategy has gained support as expertise with laparoscopic management of bile duct stones has improved. Furthermore, a recent multicenter study has demonstrated the efficacy of this approach.[3] However, one of the reasons why the preoperative investigation and treatment strategy has shown low efficacy is the inaccuracy of clinical and laboratory signs for predicting the presence of stones in the bile duct. Consequently we undertook the following study with the aim of developing a simple scoring system using readily available clinical and laboratory parameters for predicting bile duct stones in patients undergoing laparoscopic cholecystectomy for cholelithiasis.

METHODS

The study was conducted in three progressive stages. First, simple clinical and laboratory parameters for predicting bile duct stones were selected and their limit of abnormality arbitrarily defined. Second, using these parameters, a correlation and predictive value were calculated from a retrospective review of patient records. A score was developed and, in the third stage, prospectively tested against findings in patients with cholelithiasis undergoing laparoscopic cholecystectomy.

Preoperative signs and laboratory investigations that may predict bile duct stones are shown in Table I. We arbitrarily chose values greater than 10% above the upper limit of normal for each investigation as abnormal and allocated a score of 1 for each abnormality to each patient studied. Because there were seven parameters chosen, any one patient could only achieve a maximum score of 7. For the retrospective stage of the study, patient records and relevant x-ray findings (i.e., operative cholangiography and/or ERCP) were reviewed for evidence of stones in the bile duct. All patients presenting between January 1993 and June 1997 were included in this review. Patients who did not have all seven parameters measured or who did not have good-quality cholangiograms, via

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Table I. Preoperative parameters for predicting bile duct stones

History of jaundice within 6 mo
History of pancreatitis within 6 mo
Bilirubin more than 10% above the upper limit of normal
One or more liver function tests more than 10% above the upper limit of normal (AP, ALT, or AST)
Amylase more than 10% above the upper limit of normal
Dilated CBD on ultrasound ≥6 mm
Stone in CBD on ultrasound

AP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBD = common bile duct.

either ERCP or operative cholangiography, were excluded from the retrospective analysis. For each of the seven parameters, the positive predictive value for bile duct stones was calculated. The seven parameters were then ranked, and the score was reallocated according to the positive predictive value so that the total sum would be 10.

Thus the parameter with the highest positive predictive value acquired a score of 3 and the parameter with the lowest predictive value a score of 0.5. Any one patient having all seven parameters positive would score a maximum of 10. The new score was then tested against the retrospective data to determine the correlation between it and the positive predictive value for bile duct stones. Finally, the new score was tested prospectively in new patients undergoing laparoscopic cholecystectomy between July 1997 and September 1998. The presence of stones in the bile duct was determined by either operative cholangiography or preoperative ERCP.

RESULTS

Retrospective Evaluation of Parameters

Between January 1993 and June 1997, a total of 1013 patients underwent laparoscopic cholecystectomy. Of these patients, 865 met all the criteria for inclusion in the study. The remaining patients were excluded, and the reasons are shown in Table II. The demographics of these patients and the incidence of bile duct stones are presented in Table III.

Correlation between one or more of the seven parameters in predicting bile duct stones is shown in Table IV. Four hundred eighty-four patients had no positive parameters; however, in nine of them (2%), stones were detected in the bile duct. The highest number of positive parameters in any one patient was six out of seven in two patients. However, only one of these patients had stones in the bile duct.

Table II. Patients excluded from study

Reason for exclusion	No. of patients
No IOC	109
No IOC or preoperative investigations	10
No preoperative investigations	29
TOTAL	148

IOC = intraoperative cholangiography.

Table III. Patients

	Total	Median age (yr)	Bile duct stones (%)
Total	865	52 (range 15-92)	13.5
Male	244 (28%)	59 (range 22-87)	13.5
Female	621 (72%)	49 (range 15-92)	13.5

Table IV. Correlation between predictive parameters and bile duct stones

Total score	No. of patients	No. with bile duct stones
0	484	9 (2%)
1	198	22 (11%)
2	58	18 (32%)
3	66	36 (54%)
4	45	22 (49%)
5	12	9 (75%)
6	2	1 (50%)

The positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity for each of the seven parameters were calculated and are shown in Table V. The presence of a stone in the bile duct demonstrated via ultrasonography had the highest PPV.

Using the PPV, a score based on a maximum of 10 was developed by rounding off a PPV score of 32.5% as equivalent to one unit (Table VI). Consequently the finding of a stone in the bile duct by ultrasonography was given a score of 3, whereas a history of recent pancreatitis was given a score of 0.5. Any one patient having all seven parameters positive would be assigned a score of 10.

This new score was applied to the retrospective data and the results are shown in Table VII. It was noted that a score of 4 or higher predicted the presence of bile duct stones in more than 70% of patients. Interestingly, all patients with a positive score for stones in the bile duct on ultrasonography also registered one or more other scores, hence totaling 4 or more.

Table V. Predictive values for the seven parameters

Risk factors	Positive predictive value	Negative predictive value	Sensitivity	Specificity
History of jaundice	65% 44/68	90% 721/797	37% 44/117	97% 724/748
History of pancreatitis	18% 11/62	86% 697/803	9% 11/117	93% 697/748
Bilirubin	50% 57/115	92% 690/750	48% 57/117	92% 690/748
Liver function tests	31% 93/298	95% 543/567	79% 93/117	73% 543/748
Amylase	22% 15/68	87% 695/797	12% 15/117	93% 695/748
Diameter of CBD on ultrasound	49% 66/135	95% 679/730	56% 66/117	91% 679/748
Stones in CBD on ultrasound	90% 19/21	88% 746/844	16% 19/117	99% 746/748

Table VI. Predictive score calculated using a scoring system based on a total value of 10

Preoperative risk factors	Positive predictive value	Allocated score
CBD stones on ultrasound	90%	3
Recent jaundice	65%	2
Abnormal bilirubin	50%	1.5
Dilated CBD on ultrasound	49%	1.5
Abnormal liver function tests	31%	1
Abnormal amylase	22%	0.5
Recent pancreatitis	18%	0.5

Table VII. Score applied to retrospective data

Score	No. of patients	No. with bile duct stones
0	484	9 (2%)
0.5 to 3.5	293	43 (14.5%)
≥4	88	65 (73%)
≥5	51	38 (74%)
≥6	36	26 (72%)
≥7	17	13 (76%)
≥8	11	11 (100%)

Table VIII. Bile duct stones in patients undergoing laparoscopic cholecystectomy

	Total	No. with bile duct stones
Both sexes	207	30 (14.5%)
Female	149	20 (13.5%)
Male	58	10 (17%)

Prospective Evaluation of the Predictive Score

The predictive score was applied prospectively to 216 patients presenting for laparoscopic cholecystectomy. Nine patients were excluded because of failure to visualize the bile duct by means of cholangiography. Patient demographics and the presence of bile duct stones are shown in Table VIII. Applying the predictive score using the seven previously defined parameters showed that a score of 4 or above predicted the presence of bile duct stones in 21 (84%) of 25 patients undergoing laparoscopic cholecystectomy for bile duct stones (Table IX).

Table IX. Prospective use of predictive score for bile duct stones in patients undergoing laparoscopic cholecystectomy

Score	Total	No. with bile duct stones
0	110	3 (3%)
0.5 to 3.5	72	6 (8.5%)
≥4	25	21 (84%)

DISCUSSION

The results of this study demonstrate the efficacy of a simple predictive score[4,5] for determining the presence of bile duct stones in patients undergoing laparoscopic cholecystectomy. A score of 4 or higher using seven simple and readily available predictive parameters indicates a probability above 70% for stones in the bile duct. In this study we used seven signs that are readily available for patients undergoing laparoscopic cholecystectomy for gallstones. For the serologic investigations a value of 10% above the upper limit of normal has been used for a positive score. Other studies[4,5] have used values 25% or 50% above normal and might reflect one of the reasons for their reduced sensitivity when compared to the current study. The positive finding of a stone in the bile duct on ultrasonography contributed most to the total of the score, but inevitably one of the serologic markers was also elevated.

The clinical relevance of a score that could help predict the presence of stones in the bile duct allows for a decision to be made as to whether to treat bile duct stones before laparoscopic cholecystectomy via ERCP or proceed directly to surgery and treat the bile duct stones laparoscopically. Such a decision

would depend on local expertise and the efficacy of one approach over another.

Previous studies evaluating the role of preoperative ERCP (two-stage approach) in the treatment of bile duct stones[3] have shown low efficacy with this approach because of the large number of patients who did not have stones in the bile duct at the time of ERCP. This occurred despite one or more clinical or laboratory signs suggestive of a stone in the bile duct. Using a predictive score, as has been developed in this study for the selection of patients who may have stones in the bile duct, may enhance the efficacy of preoperative ERCP in these patients.

For any predictive score to be useful, it needs to make use of findings that are readily available from investigations that are simple to perform and used routinely. The scoring system reported in this study fulfils these criteria and can be readily used to predict the presence of stones in patients with cholelithiasis. This scoring system could be used in future studies, possibly to address strategies for investigating and treating bile duct stones, as it would identify those patients most likely to have stones. Consequently the risks and costs of laparoscopic management of bile duct stones could be weighed against the cost of preoperative ERCP in these patients.

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Operations for Peptic Ulcer Disease: Paradigm Lost

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Over the past several decades, the pharmacologic and endoscopic treatment of peptic ulcer disease (PUD) has dramatically improved. To determine the effects of these and other changes on the operative management of PUD, we reviewed our surgical experience with gastroduodenal ulcers over the past 20 years. A computerized surgical database was used to analyze the frequencies of all operations for PUD performed in two training hospitals during four consecutive 5-year intervals beginning in 1980. Operative rates for both intractable and complicated PUD were compared with those for other general surgical procedures and operations for gastric malignancy. In the first 5-year period (1980 to 1984), a yearly average of 70 upper gastrointestinal operations were performed. This experience included 36 operations for intractability, 15 for hemorrhage, 12 for perforation, and seven for obstruction. During the same time span, 13 resections were performed annually for gastric malignancy. By the most recent 5-year interval (1994 to 1999), the total number of upper gastrointestinal operations had declined by 80% (14 cases), although the number of operations for gastric cancer had changed only slightly. Operations decreased most markedly for patients with intractability, but the prevalence of operations for bleeding, obstruction, and perforation was also decreased. We conclude that improved pharmacologic and endoscopic approaches have progressively curtailed the use of operative therapy for PUD. Elective surgery is now rarely indicated, and emergency operations are much less common. This changed paradigm poses new challenges for training and suggests different approaches for practice. (J GASTROINTEST SURG 2001;5:438-443.)

KEY WORDS: Peptic ulcer disease, gastroduodenal ulcers, *Helicobacter pylori*, endoscopic hemostasis, ulcer operations

For many decades the operative management of peptic ulcer disease (PUD) was one of the cornerstones of alimentary tract surgery. Landmark investigations by a number of investigators served as the pathophysiologic foundation on which new surgical strategies for the management of PUD were developed.[1] Subsequently a variety of basic and clinical studies documented that operative therapy could be extremely effective in controlling either intractable or complicated peptic diseases. Used appropriately, various surgical approaches reliably assured a low risk of morbidity and an acceptable rate of recurrence.[2]

In parallel with these remarkable surgical advances, significant progress was also being made with nonoperative methods. In 1977, antisecretory treatment with H_2 receptor inhibitors was introduced and quickly accepted as the primary therapy for gastric and duodenal ulcers. Within 5 years, more than 1.5 billion cimetidine tablets were being purchased in the United States annually (Benz GC, personal communication). A decade later the first proton pump inhibitor was marketed, primarily as a means of managing otherwise intractable peptic disorders. Finally, in 1983, an etiologic role for intragastric infection with *Helicobacter pylori* was suggested and later confirmed.[3] For the first time a durable cure for active PUD could be achieved by the short-term administration of a combination of antibacterial agents.[4]

These newer pharmacologic strategies, as well as evolving endoscopic approaches and other less precise epidemiologic factors, have drastically altered the natural history of PUD. Recently this has led several prominent authors to publish editorials concerning this decrease in operative volume.[5-7] Still, few objective data concerning this effect have been published during the past decade. To delineate the current impact of these

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changes on surgical training and surgical practice, we report the time trends of operations for PUD in two major training hospitals over the past 20 years and compare them with the time trends of other general surgical procedures.

METHODS

All patients undergoing operations at our two training hospitals (University Hospital, Bexar County Hospital District, and the Audie L. Murphy Memorial Division of the South Texas Veterans Health Systems) are prospectively enrolled in a continuously verified computerized surgical database. Collated data include demographic information, specific diagnoses, anesthetic and wound classifications, operative details, and outcomes. Using this database, a retrospective review of all operations for PUD was performed for the 20-year period from January 1, 1980 to December 31,1999. The operations were further separated into "indication for operation" subsets that included intractability, bleeding, perforation, and obstruction. The frequencies of all such operations were determined for four consecutive 5-year intervals. The findings were compared with the total number of general surgical operations performed during the same time intervals and the number of operations performed specifically for gastric malignancy.

RESULTS

During the two decades studied, a total of 771 operations for PUD and 247 for gastric cancer were performed. Overall, duodenal ulcers were responsible for 76% of the total operative cohort, whereas gastric ulcers accounted for another 24%. All operations were supervised by a general surgery faculty that changed little during the 20-year duration of the study. Moreover, the definitions used to classify the various presentations and/or complications of PUD remained constant throughout all time periods studied.

The specific time trends of operations for PUD are graphically depicted in Fig. 1. An 80% decrease was noted in the total number of PUD operations as measured from the inception of the study in 1980 to its termination in 1999. Thus, during the first time period (1980 to 1984) a yearly average of 70 operations for PUD were performed, whereas during the last time period (1995 to 1999) the yearly average of operations for PUD decreased to 14. In contrast, during the same 20-year period, the total number of general surgery procedures continued to increase (30%) and the number of operations performed for gastric malignancy remained relatively stable.

The distribution of operations into the major subcategories of PUD is plotted in Fig. 2. Over the duration of the study, surgery for intractability decreased by 95% with gastric and duodenal ulcers affected equally. In fact, not a single operation was performed for intractability at this center during the last 3 years of the study. During the same two-decade interval, operations for uncontrolled hemorrhage decreased by 86%, whereas operations for perforation decreased by 31%. Most of the changes in these categories were attributable to a reduction in the frequency of operations for complicated duodenal ulcers; operations for complicated gastric ulcers showed less of a decrease.

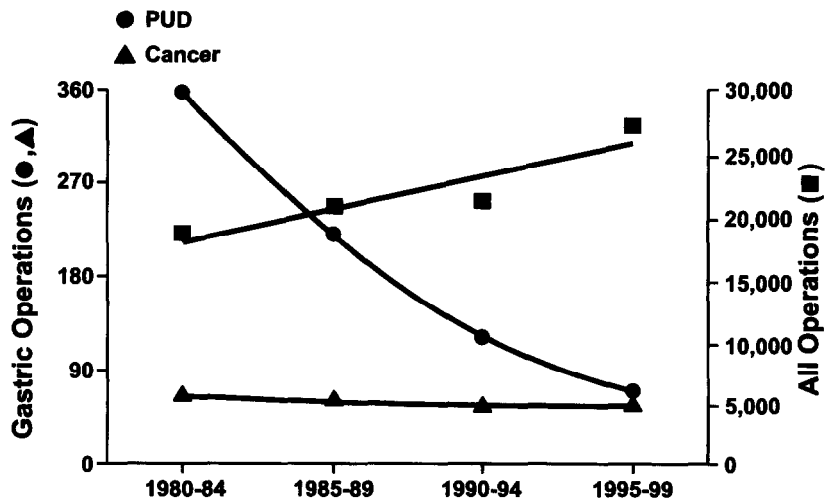

Fig. 1. Time trends of operations for peptic ulcer disease (PUD) compared with all general surgical procedures and all operations for gastric carcinoma for the 20-year period, 1980 to 1999.

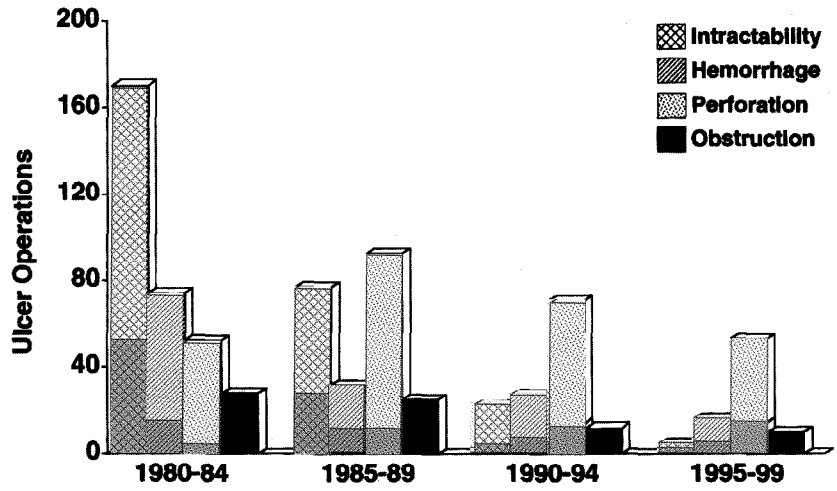

Fig. 2. Time trends of operations for peptic ulcer disease by specific indications (1980 to 1999). The lower, shaded area in each column represents the gastric ulcer component; the remainder of the column depicts patients with duodenal ulcers.

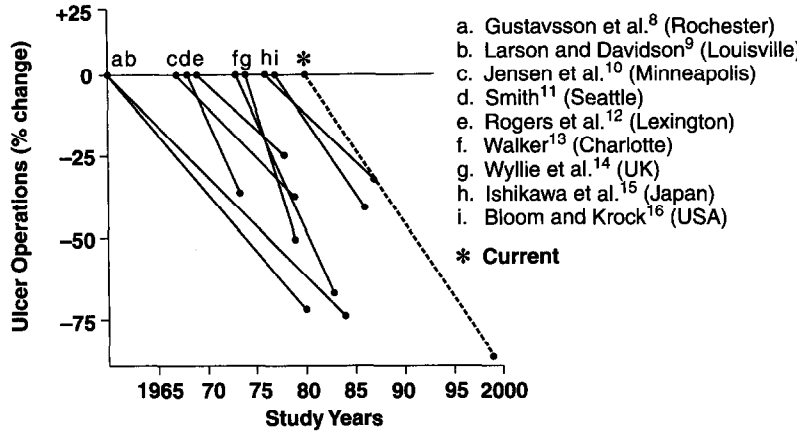

Fig. 3. Summary of published reports from various geographic regions documenting changes in the frequency of all operations for peptic ulcer disease since 1960.

Gastric outlet obstruction was also affected, exhibiting a 46% decrease in associated operative frequency over the past 20 years.

DISCUSSION

The results of this study confirm and extend data previously reported concerning the changing prevalence of ulcer surgery. Beginning more than 20 years ago, a diverse group of surgical investigators documented a steep decline in the frequency of operations for all indications in patients with PUD (Fig. 3).[8-16] However, relevant contemporaneous information on this subject is sparse. Our data clearly demonstrate that the decline in ulcer-related operative procedures is continuing in spite of increases in many other operative categories. Thus, during the last 5 years of our study, the total number of procedures performed for PUD decreased by more than 80%, whereas the number of general surgical procedures increased by nearly 30%. This change appears to reflect a persistent, international trend in which there are fewer ulcer-related hospitalizations and less frequent ulcer-related office visits.[17] As expected, a parallel decrease in the total disability and mortality rates associated with PUD has also been observed.[18]

It seems certain that the overall reduction in the number of operations for PUD can be attributed to multiple causes. Importantly, epidemiologic studies have regularly demonstrated that the actual incidence of ulcer disease has been steadily declining over the past 20 to 30 years, especially in men and in patients

who are less than 65 years of age.[19] Although our study did not look specifically at the issue of total admissions for PUD, there is no reason to expect that our local experience differs significantly from national trends. The specific reasons for the well-documented and continuing decrease in incidence are not well understood, although a so-called "cohort effect" and such societal factors as a decline in smoking and an increased awareness of the risks of nonsteroidal anti-inflammatory agents have been implicated.[20] In addition, the widespread availability of antacids and potent antisecretory agents, such as H_2 receptor antagonists and proton pump inhibitors, has undoubtedly contributed to the more recent changes observed in the prevalence of ulcer-related problems. For example, an abrupt 39% decrease was observed in the number of operations performed for PUD in six European centers immediately following the introduction of cimetidine in 1975.[21] The subsequent confirmation of *H. pylori* as a key pathogenic factor in gastroduodenal ulceration has had an even greater effect. Eradication of the organism in infected patients with PUD has now become the standard of care and is regarded as the most cost-effective way to alter the natural history of symptomatic ulcer disease.[22-24] In fact, these new treatment paradigms have rendered the category of medically intractable PUD nearly obsolete.[25] In the present study, surgical intervention has been necessary for intractability in only three patients during the past 5 years, and no patient in either of our hospitals has required an operation for this indication since 1997.

In contrast, patients with complicated ulcer disease still occasionally require surgical intervention, albeit on a highly selective basis. Much like intractability, the management of perforated, stenotic, and bleeding ulcers is being transformed by the ongoing evolution in pharmacotherapy. Moreover, endoscopic interventions have also been shown to be remarkably effective in controlling many of the acute manifestations of complicated ulcers.

Before 1985, hemorrhage was the most common reason for emergency ulcer surgery; now operative control of bleeding is only infrequently necessary. In our cohort the number of emergency operations performed for hemorrhage dropped by 95% after 1980. This experience is similar to other historical comparisons[26] but differs from reports from the Mayo Clinic and Switzerland, where operative rates for ulcer hemorrhage remained relatively stable until at least 1990.[27,28] Such heterogeneity is not easily explained but may relate partly to differences in the local protocols governing the management of peptic ulceration.

Regardless, the advent of therapeutic endoscopy in the late 1970s was responsible for at least modest changes in clinical practice. Hemostatic methods such as injection therapy, heater probe application, bipolar electrocautery, and laser photocoagulation have since been repeatedly documented as effective in the initial control of the primary bleeding site.[29] A recent meta-analysis assessing the pooled results from 25 randomized trials concluded that endoscopic hemostasis can reduce operation rates by nearly two thirds and can trim the associated mortality by one third.[30] Nonetheless, bleeding may persist or immediately recur in 2% to 40% of patients after therapy, depending on the endoscopic appearance of the ulcer; in such cases either repeat therapeutic endoscopy or urgent operation is usually warranted.[31] In addition, approximately one third of patients will have episodes of rebleeding during long-term follow-up if further treatment is not instituted. Pharmacotherapy with proton pump inhibitors may help to limit these recurrences,[32] but the use of anti-*Helicobacter* therapy appears to have an even more favorable and durable effect.[33] Already two prospective, randomized studies have documented nearly complete protection against rebleeding 1 year after therapeutic endoscopy and eradication of *H. pylori* infection.[34,35] Recently other investigators have noted that the protection from rebleeding persists for at least 2 years after *H. pylori* eradication.[36]

As operations for hemorrhage have declined, perforation has become the most common indication for surgery in patients with PUD. As observed in some earlier reports, we found only a modest decrease in the prevalence of perforated ulcers following the introduction of antisecretory medications (31%).[37-39] This limited change is presumably explained by the abrupt onset of symptoms that typifies perforation, since the lack of a prodrome precludes the timely use of preemptive medical therapy. Once diagnosed, most gastroduodenal ulcer perforations can be successfully managed with urgent operative closure, either open or laparoscopic. In addition, perioperative testing for *H. pylori* is now recommended since recurrent ulceration is much more likely to develop in the presence of persistent infection.[40,41] Recently this combined approach has been validated by a prospective study in which 99 *H. pylori*–positive patients with perforated ulcers were randomized to receive either omeprazole alone (control) or anti-*Helicobacter* therapy.[42] After 1 year, the ulcer relapse rate was nearly eightfold higher in the control group than in the anti-*Helicobacter* group (38.1% vs. 4.8%). Understandably such findings have prompted renewed interest in the use of nonoperative therapy in patients presenting with sealed perforations.[43] A more selective approach has been proposed wherein infected patients who present with sealed ulcers are treated conservatively using an appropriate antibiotic-based regimen.[44] Definitive ul-

cer operations are reserved for patients who are found to be *H. pylori* negative or, alternatively, for patients who develop recurrent ulcers following documented eradication of *H. pylori* infection.

Gastric outlet obstruction is the least common complication of PUD, accounting for only 13% of all ulcer operations in our hospitals. Over the past 20 years, the total number of operations performed in our hospitals for gastric outlet obstruction has decreased by 59%. In contrast, earlier studies from both the United States and Finland described little change in the prevalence of gastric outlet obstruction.[45,46] Currently, nonoperative strategies are being advocated with increasing frequency even though supportive data remain scanty. In preliminary reports, medical therapy with antisecretory agents and anti-*Helicobacter* therapy appears to promote a relatively rapid resolution of reversible pyloric edema and spasm but fails to relieve the fibrotic component of stenosis.[47] The resultant improvement in luminal diameter, albeit small, is sufficient in some patients to allow gradual resumption of a normal dietary intake.[48-49] In other patients, endoscopic balloon dilatation has been shown to achieve nearly immediate relief of obstructive symptoms. However, the reported technical success rate of 70% to 80% is somewhat offset by an associated risk of perforation of approximately 7% and a long-term relapse rate of 30% to 50%.[50,51] Such results suggest that dilatation should continue to be used only selectively.

In contrast to our experience with PUD, the annual number of operations performed for gastric malignancy in this series has not changed significantly over the past 20 years. This pattern differs from that of other reports that describe a continuing nationwide decrease in the incidence of gastric neoplasms. The unique stability of our oncologic experience may be related to the large proportion of Hispanic Americans involved, since the incidence of gastric cancer in this ethnic group appears to be at least twice that of other western control populations.[52]

Based on the results of this survey, it is obvious that various epidemiologic factors coupled with continuing improvements in pharmacologic and endoscopic therapy have irrevocably changed the profile of gastrointestinal ulcer surgery. The need for operative interventions for PUD is no longer common and is continuing its dramatic two-decade decline. Few patients now require surgery for intractability, and the proportion of patients requiring an operation to control such complications as perforation, hemorrhage, or obstruction also continues to decrease. Taken together, these changes are creating new paradigms for surgical practice and are mandating new approaches to surgical education.

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Update: Surgery for the Morbidly Obese Patient
M. Deitel and G.S.M. Cowan, Jr., eds.
Toronto, Canada: FD-Communications, Inc., 2000. Pages: 529. Price: $195.

This book serves as an update of bariatric surgery in the new era of minimally invasive approaches, gastric banding, and a review of the current state of the art addressing currently accepted procedures. The two editors are fairly well known in this field and have recruited most, albeit not all, of the well-known and expert bariatric surgeons around the world.

The chapters of the book address selected topics relevant to morbid obesity in terms of etiology ("Etiology and Genetics of Massive Obesity" by Perusse, Chagnon, and Bouchard), weight-related morbidity ("Diseases and Problems Secondary to Massive Obesity" by Herrera, Lozano-Salazar, Gonzales-Barranco, and Russ), and appropriate patient selection ("Criteria for Selection of Patients for Bariatric Surgery" by Cowan, Hiler, and Buffington). Many other chapters address important topics such as obesity in children, anesthetic considerations, and both preoperative and postoperative metabolic considerations. Most of the book concentrates on the many and diverse bariatric procedures currently available discussing technique and outcomes. The book ends with a discussion of a very relevant consideration ("The Medico-Legal Aspect of Bariatric Surgery" by O'Leary) and discussions addressing quality of life and plastic surgery. The last chapter remains a very controversial topic—"National and International Liaison and Training in Bariatric Surgery" by Alverez-Cordero. This chapter (in my opinion) seems inappropriate and self-aggrandizing; the author speaks for and claims a "national and international" consensus that currently does not exist for or represent the broad community of bariatric surgeons at large—this is unfortunate. Overall the book is designed for the multidisciplinary team caring for the bariatric patient. Figures are used liberally to illustrate operations, outcomes, and other key points; details of the operative procedures are simple enough for all disciplines involved.

In summary, this book serves as a nice update on bariatric surgery in the year 2000.

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Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice, 16th edition
Courtney M. Townsend, Jr., R. Daniel Beauchamp, B. Mark Evers, Kenneth L. Mattox, editors.
Philadelphia: WB Saunders, 2001. Pages: 1782. Price: $125.

This classic surgical textbook dates back more than 65 years under the previous direction of Frederick Christopher, Loyal E. Davis and, most recently, David C. Sabiston, Jr. The current edition, published in the first year of the twenty-first century, does indeed provide "cutting edge" information for surgeons in training and surgical practitioners. Because of the complexities of modern-day surgery and the ever so important alliance between basic science and surgery, three associate editors have joined in on this treatise. The text begins with an excellent overview of the history of surgery, which is a must for all students, young and old. This edition includes entirely new chapters on the role of cytokines as mediators of the inflammatory response, molecular and cell biology, surgical and critical care, respiratory failure, endocrine pancreas, pain management and conscious sedation, surgery in geriatric patients, surgery in obese patients, and principles of minimally invasive surgery, in addition to 114 new contributors considered leaders in their field. There is a strong emphasis that pervades the chapters with regard to outcome-based surgery and medicine. The important concepts of clinical trials are emphasized throughout with detailed discussions regarding the advantages and disadvantages of different types of trials. In years past, the emphasis on surgery was to avoid death while trying to help the patient. Once this was accomplished, this concept was followed by a need to reduce complications. Today the emphasis is on safety, efficacy, comfort, and cost-effectiveness. As the reader moves from the history of surgery to the landmark operations of the twentieth century, and now this era of minimally invasive surgery, one clearly senses these changes and their importance as one embarks upon this text. The book is extremely well illustrated in black and white with useful tables, radiographs, pathologic specimens, and technical drawings. This treatise is organized into 13 sections that include basic principles of surgery, perioperative management, trauma and critical care, transplantation and immunology, surgical oncology, organ-specific topics, and specialties in general surgery. It is extremely well referenced and up-to-date. My only criticism, which is minor, has to do with the font size used. Clearly the overall size of the textbook has been reduced, making it somewhat more challenging to read. Fortunately enough visual adjuncts are available to make it readable for middle-aged and older practitioners. This surgical reference is a must for any serious student of surgery. Even though more up-to-date information may be available online, this highly regarded reference will continue to serve as a valuable guide for the more common questions and as an excellent starting point for more detailed research.

Geoffrey B. Thompson, M.D.

Outcome of Laparoscopic Anterior 180-Degree Partial Fundoplication for Gastroesophageal Reflux Disease

To the Editors:

I read with great interest the article by Watson et al.[1] (J GASTROINTEST SURG 2000;4:486-492.) concerning results after anterior 180-degree partial fundoplication, and I have several comments and questions. First, how many patients had Barrett's esophagus (with intestinal metaplasia) before surgery and what were the results in this particular group? I noticed that one patient developed adenocarcinoma and one patient had high-grade dysplasia. (This was out of how many preoperative cases?) Second, why were 24-hour pH studies performed in only half of the patients? I believe it is important to study all patients who are potential candidates for surgery in order to properly select those who are the most suitable. I also noticed that 94% of the patients who were referred for surgery had not been adequately controlled with medication. What does this mean? In my experience, the best candidates for surgery are those who respond very well to medical treatment and have a recurrence of their symptoms very soon after stopping their medication. The high rate of postoperative complications in this report is surprising; 4% of patients had to be reoperated, which is very unusual for the laparoscopic procedure. The follow-up was too short for definitive results. Only 30% of the patients had 3 years of follow-up, with 16% having recurrent reflux symptoms. This recurrence rate was 11% at 1 year. Therefore we can postulate that 8 to 10 years later, the recurrence rate will probably be much higher.

In addition, some of the objective control data from 2 or 3 years of follow-up is missing. For example, how many patients had repeated postoperative endoscopy, how many had 24-hour pH studies 3 years after surgery, and how many had manometric evaluation? These are all very important aspects to consider if we are to establish *true objective late results* in patients undergoing antireflux surgery. I must emphasize this point because I have read articles in many surgical journals and the vast majority do not report results of late objective evaluations.

It is difficult to understand the 91% rate of excellent and good results, when 16% had recurrent reflux symptoms, which for me represent failures, because surgery is performed in order to stop reflux symptoms. With this kind of discussion, we will be able to improve and better understand the pathophysiology of surgical treatment in patients with reflux esophagitis.

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Santiago, Chile

Reply

We thank Dr. Csendes for his interest in our article and appreciate the opportunity to respond. Dr. Csendes has raised many pertinent issues, and this enables us to expand on the information provided in our original report.

In the cohort of 107 patients, 17 (16%) had Barrett's esophagus identified before surgery. Thus the incidence of high-grade dysplasia or carcinoma in this group was 12% at short-term follow-up. The subgroup with Barrett's esophagus had a higher incidence of recurrent reflux (3 patients were reoperated for reflux and one patient required a proton pump inhibitor). However, no statistically significant difference was demonstrated between the patients who had Barrett's esophagus and those who did not.

Our routine practice is to offer antireflux surgery to patients with objectively demonstrable gastroesophagal reflux. We are cognizant of the fact that there is no "gold standard" investigation for reflux, and results of endoscopy or pH monitoring can be normal in patients with gastroesophageal reflux, who would benefit from surgical management. Hence, like many other investigators, we operate on patients with typical reflux symptoms who have endoscopic evidence of ulcerative esophagitis, but we do not routinely perform 24-hour pH monitoring in this group. We reserve pH monitoring for those patients who have no endoscopic evidence of esophagitis or for those whose symptoms are atypical. For this reason only half of the patients in our study underwent preoperative pH monitoring.

In the majority of the patients in our study, symptoms could not be adequately controlled with medication. This means that at the time of surgery, these patients had ongoing symptoms of reflux, despite treatment with antisecretory medication. Nevertheless, most of these patients had had at least partial relief of their symptoms at some stage when using antisecretory medication. Only 6% of patients had achieved complete control of their reflux symptoms at the time of surgery, and these patients underwent surgery so they could stop taking medication.

We reported four early reoperative procedures in our patient group. We have previously described our indications and experience with early laparoscopic intervention following laparoscopic fundoplication, and it is likely that our use of routine postoperative contrast x-rays and the low threshold for early laparoscopic reexploration have contributed to this. We would prefer early laparoscopic reintervention, so that longer term morbidity and late surgical revision could be prevented. Details of this approach have been described elsewhere.[1]

We agree that long-term follow-up was not reported in our paper, and ultimately the success of the partial fundoplication procedure will be decided by long-term follow-up. These findings will be reported when they become available. Furthermore, we agree that the incidence of re-

Outcome of Laparoscopic Anterior 180-Degree Partial Fundoplication for Gastroesophageal Reflux Disease

To the Editors:

I read with great interest the article by Watson et al.[1] (J GASTROINTEST SURG 2000;4:486-492.) concerning results after anterior 180-degree partial fundoplication, and I have several comments and questions. First, how many patients had Barrett's esophagus (with intestinal metaplasia) before surgery and what were the results in this particular group? I noticed that one patient developed adenocarcinoma and one patient had high-grade dysplasia. (This was out of how many preoperative cases?) Second, why were 24-hour pH studies performed in only half of the patients? I believe it is important to study all patients who are potential candidates for surgery in order to properly select those who are the most suitable. I also noticed that 94% of the patients who were referred for surgery had not been adequately controlled with medication. What does this mean? In my experience, the best candidates for surgery are those who respond very well to medical treatment and have a recurrence of their symptoms very soon after stopping their medication. The high rate of postoperative complications in this report is surprising; 4% of patients had to be reoperated, which is very unusual for the laparoscopic procedure. The follow-up was too short for definitive results. Only 30% of the patients had 3 years of follow-up, with 16% having recurrent reflux symptoms. This recurrence rate was 11% at 1 year. Therefore we can postulate that 8 to 10 years later, the recurrence rate will probably be much higher.

In addition, some of the objective control data from 2 or 3 years of follow-up is missing. For example, how many patients had repeated postoperative endoscopy, how many had 24-hour pH studies 3 years after surgery, and how many had manometric evaluation? These are all very important aspects to consider if we are to establish *true objective late results* in patients undergoing antireflux surgery. I must emphasize this point because I have read articles in many surgical journals and the vast majority do not report results of late objective evaluations.

It is difficult to understand the 91% rate of excellent and good results, when 16% had recurrent reflux symptoms, which for me represent failures, because surgery is performed in order to stop reflux symptoms. With this kind of discussion, we will be able to improve and better understand the pathophysiology of surgical treatment in patients with reflux esophagitis.

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We agree that long-term follow-up was not reported in our paper, and ultimately the success of the partial fundoplication procedure will be decided by long-term follow-up. These findings will be reported when they become available. Furthermore, we agree that the incidence of re-

current reflux will increase to some extent as follow-up progresses. However, this is a problem with all antireflux procedures including Nissen fundoplication. The incidence of recurrent reflux can be difficult to define. The 16% recurrence rate quoted by Dr. Csendes includes some patients with minimal reflux symptoms. Some of these patients had occasional episodes of reflux but did not require specific treatment, a situation that occurs in many "normal" people. With further follow-up, 50 patients have now been followed for at least 3 years, and 45 of them (90%) have had no reflux symptoms at all. Of the other patients, some are quite satisfied with the overall outcome of their surgery, as they require no treatment for reflux and experience only minimal symptoms.

We have not yet performed objective investigations at later follow-up. It is often difficult to convince asymptomatic patients to undergo endoscopy, pH studies, and manometry, and we plan to repeat these tests once the follow-up has exceeded 5 years. However, despite this, the ultimate success of an antireflux procedure is determined by its clinical success, that is, whether the symptoms are relieved and whether any side effects ensue? For this reason, clinical results are useful in assessing the likely outcome of any procedure in routine clinical practice.

The apparent discrepancy between overall success (91%) and reflux symptoms is explained above. Not all patients who had some symptoms of reflux (e.g., occasional minor episodes of heartburn) had symptoms that were troublesome or required treatment. The overall outcome was determined in each patient by weighing the benefits of the procedure performed against the potential for side effects following surgery.

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