Production and Systemic Absorption of Toxic Byproducts of Tissue Combustion During Laparoscopic Cholecystectomy

Justin S Wu, M D, Terri Monk, M D, Donna R Luttmann, R.N, Thomas A Meininger, Nathaniel J Soper, M D

Among the potential hazards of laparoscopic surgery using electrocautery is the release of chemical byproducts of incomplete tissue combustion into the pneumoperitoneum with subsequent transperitoneal absorption into the bloodstream and/or release into the operating room. The purpose of this study of patients undergoing laparoscopic cholecystectomy (LC) was twofold (1) to assess the relationship between intraperitoneal concentration of carbon monoxide (CO) and blood levels of carboxyhemoglobin (COHb) and methemoglobin (MetHb), and (2) to assess the surgeon's inhalation of CO resulting from ambient smoke exposure During LC with monopolar electrocautery, 21 patients were evaluated intraoperatively for intraperitoneal [CO] by sampling gas from a trocar, whereas arterial [COHb] and [MetHb] were determined perioperatively The surgeon's venous blood was drawn pre- and postoperatively to assay [COHb] and [MetHb] Patients completed visual analogue questionnaires 6 hours and 24 hours postoperatively to assess for adverse symptoms Mean (± SEM) patient age and weight were 45 ± 3 years and 84 ± 4 kg, respectively Mean duration of the operation was 69 ± 5 minutes, and electrocautery was used for 3 0 ± 0 3 minutes Intraperitoneal [CO] rose to peak levels of 209 ± 19 ppm at 50 minutes, whereas systemic [COHb] and [MetHb] were unchanged The surgeon's systemic [COHb] and [MetHb] did not increase postoperatively Nausea, abdominal pain, and fatigue scores decreased significantly between 6 and 24 hours postoperatively, however, there were no correlations between these symptoms and peak intraperitoneal [CO] Although LC using electrocautery increases intraperitoneal [CO] to "hazardous" levels, systemic [COHb] and [MetHb] are not elevated by generation of intraperitoneal smoke The surgeon's exposure to CO by the evacuation of smoke through laparoscopic ports is negligible Production of smoke during LC using monopolar electrocautery, therefore, does not appear to pose a threat to either the patient or the surgeon (J GASTROINTEST SURG 1998, 2 399-405)

Since its introduction nearly a decade ago, laparoscopic cholecystectomy (LC) has become the new "gold standard" therapy for uncomplicated cholelithiasis, replacing the traditional open operation in most patients [1] Other laparoscopic abdominal operations are also increasing in popularity because of their advantages in terms of minimal abdominal wall trauma, decreased postoperative pain, shorter hospital stay, and earlier return to normal physical activities when compared to their open counterparts [2] However, among the real and potential disadvantages of laparoscopic surgery are the detrimental effects from the "closed abdomen" and CO_2 pneumoperitoneum [3-5]

One theoretical disadvantage that has not been thoroughly investigated is that of smoke generated by electrocautery in the CO_2 pneumoperitoneum. The gaseous products of incomplete tissue combustion could be dangerous to the patient because of transperitoneal absorption into the systemic circulation or to the operating room personnel because of smoke evacuated through trocar valves Three studies have documented elevated intraperitoneal [CO] in patients undergoing laparoscopic operations using electrocautery. Two of those studies also found elevated systemic carboxyhemoglobin (COHb) levels[6] (Ott DE, personal communication), whereas one

From the Departments of Surgery (J S W, D R L, T A M, and N J S) and Anesthesiology (T M), Washington University School of Medicine, St Louis, Mo
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Reprint requests Nathaniel J Soper, M D, Department of Surgery, Washington University School of Medicine, Box 8109, Ste 6108, One Barnes Hospital Plaza, St Louis, MO 63110

study did not [7] In addition, one study found elevated systemic methemoglobin (MetHb) levels as well as the presence in the pneumoperitoneum of 26 additional toxic chemical byproducts resulting from pyrolysis of protein and lipids during laparoscopic surgery.[8] The concentrations of these compounds were not measured, and the significance of these findings and their risks are as yet unknown. Therefore the goals of this study were (1) to ascertain the relationship between intraperitoneal concentration of CO and systemic [COHb] and [MetHb] in patients undergoing LC and (2) to assess the surgeon's exposure to the evacuated smoke through the trocars.

MATERIAL AND METHODS

After approval of the experimental protocol by the Washington University School of Medicine Human Subjects Committee, 21 patients scheduled to undergo LC for cholelithiasis were enrolled in the study A detailed preoperative history recorded pertinent factors that might affect COHb and MetHb levels; these included cigarette or cigar use, exposure to other smokers, automobile use for more than 2 hours a day, and work exposure to automobile exhaust Patients with a history of severe chronic obstructive pulmonary disease, those on home oxygen therapy, and those with hereditary methemoglobinemia were excluded from the study. All patients were informed of the purpose and risks of the study and signed consent forms

Patient Preparation

The patients were anesthetized with intravenous thiopental (3 to 5 mg/kg), vecuronium (0.1 mg/kg), and fentanyl (3-5 μg/kg). Anesthesia was maintained with isoflurane, vecuronium, and fentanyl Ventilation was mechanically controlled with an inspired oxygen concentration of 35%, at a rate and a tidal volume adjusted to maintain end-tidal CO_2 tension between 30 and 40 mm Hg as measured by capnography. An arterial line was placed in the radial artery following induction of anesthesia to allow frequent arterial blood samplings and was removed before the patient awoke

Blood Sampling

After induction of general anesthesia, the abdomen of each patient was insufflated with 100% CO_2 until the intra-abdominal pressure reached 12 to 15 mm Hg This pressure was maintained throughout the procedure Arterial blood samples (3 ml each) were drawn after the induction of anesthesia and 1 minute prior to insufflation as a baseline, during the surgical procedure at 1 minute after insufflation of pneumoperitoneum (before cautery use), and at 15, 30, 45, 60, 75, and 90 minutes (or until the procedure was completed) intraoperatively Arterial blood samples were analyzed for total hemoglobin, oxyhemoglobin, COHb, and MetHb by the OSM3 Hemoximeter (Radiometer Copenhagen, Copenhagen, Denmark). The manufacturer listed the accuracy of this instrument as ±1% Venous samples were drawn from the surgeon preoperatively and immediately postoperatively for analysis of total hemoglobin, COHb, and MetHb concentrations

Gas Sampling

For determination of intra-abdominal [CO], gas from the pneumoperitoneum was withdrawn from a side port of the right subcostal trocar After 50 ml of gas in the tubing was discarded, 100 ml of gas was assayed with a Sensidyne/Gastec detector tube (Sensidyne, Inc , Clearwater, Fla) using the multistroke gas sampling pump Evaluations were performed intraoperatively at the same time blood samples were drawn (every 15 minutes) Sensidyne/Gastec detector tubes relied on a colorimetric reaction with potassium polladosulfite They were designed and calibrated so that the length of stained tubing corresponded to the concentration of CO in the sample It could detect [CO] between 1 and 2000 parts per million (ppm) with an accuracy of ±25% of the measured value.[9]

Operation

Laparoscopic cholecystectomy was performed using a four-port technique as described previously.[1] Immediately after establishment of a pneumoperitoneum, adhesions on the gallbladder were taken down using electrocautery. This technique was also used to dissect the cystic duct and artery. After ligation and transection of these structures, excision of the gallbladder was completed with electrocautery Factors that might influence the length of the procedure or cautery time were recorded; these included presence of adhesions, degree of inflammation of the pericholecystic tissues, presence and management of common bile duct stones, anatomically "intrahepatic" gallbladder (lack of a definite plane between gallbladder serosa and hepatic parenchyma), and inadvertent perforation with spillage of gallbladder contents Complications that occurred during the procedure, such as bleeding and hypotension, were also noted Smoke was evacuated sparingly throughout the operation to allow visualization for the surgeon, the number and duration of times the ports were opened for this purpose were recorded At the end of each operation, all intraperitoneal gas was evacuated through the trocars prior to their removal The duration of

cautery use was recorded by a start-stop cumulative arithmetic compilation.

Postoperative Evaluation

Patients were transported to the recovery room breathing 100% oxygen by face mask On their arrival in the recovery room, they were rapidly weaned from the oxygen within 30 minutes Venous blood samples were drawn in unheparinized syringes 30 minutes after skin closure. Six hours postoperatively and prior to discharge the following morning, all patients completed a 10 cm visual analogue scale questionnaire regarding the presence of the following symptoms fatigue, abdominal pain, nausea, dyspnea, and dizziness. Nausea was treated with metoclopramide, 10 mg intravenously or by mouth every 6 hours as needed, and the amount was recorded The investigators evaluated the patients for tachycardia, tachypnea, or abnormal mental status (orientation, memory, and attention).

Statistical Analyses

The InStat statistical computer software package (GraphPad Software, Inc., San Diego, Calif) was used for data analysis. Statistical comparisons among the groups with respect to paired continuous variables were performed with the Friedman nonparametric repeated measures test. Analyses of unpaired data were performed using Kruskal-Wallis one-way analysis of variance. All specific comparisons were made using Dunn's multiple comparisons test When preoperative values were zero, intraoperative and postoperative continuous variables were analyzed using the two-tailed, one-sample Student's t test. Linear regression models with correlation coefficients were calculated to analyze the relationship between 6-hour postoperative symptoms and peak values of intraperitoneal [CO] Statistically significant differences were defined as $P < 0.05$. Summary values in the text are expressed as mean ± standard error of the mean (SEM)

RESULTS

Twenty-one patients (aged 45 ± 3 years, range 22 to 72 years, mean weight 84 ± 4 kg) underwent LC in this protocol. Two patients smoked cigarettes on a regular basis (both ~3 to 4 cigarettes/day), and another two patients drove an automobile for more than 2 hours a day The rest of the 17 patients did not have pertinent factors known to affect COHb and MetHb levels Mean duration of operation was 69 ± 5 minutes (range 40 to 110 minutes), during which 71 ± 14/ L of CO_2 (range 28 to 190 L) was used for insufflation (Table I). In all cases, electrocautery was initiated within 10 minutes after pneumoperitoneum was established, to take down adhesions around the gallbladder and to dissect the hepatocystic triangle. The predominant use of electrocautery, however, occurred 30 minutes into the operation (after intraoperative screening for choledocholithiases using laparoscopic intracorporeal ultrasound), during the dissection of the gallbladder from its bed. Mean cumulative electrocautery time was 3.0 ± 0.3 minutes (range 0 7 to 6.2 minutes). Electrocautery time was not significantly different whether the gallbladder was intrahepatic (43%, 3 3 ± 0.2 minutes) or extrahepatic (57%, 2.9 ± 0.4 minutes) Minimal adhesions and inflammation of the gallbladder were found in most patients, and there were no common bile duct stones or intraoperative complications. The intraperitoneal smoke was briefly (<10 seconds) vented through a trocar once in two patients and twice in one patient to allow better visibility for the surgeon.

Intraperitoneal [CO] rose significantly from 0 ppm at baseline to 33 ± 7 ppm at 15 minutes ($P < 0$ 0001, range 0 to 100 ppm), 130 ± 17 ppm at 30 minutes ($P < 0.01$ vs. 15 minutes, range 0 to 350 minutes), and peaked at 209 ± 19 ppm at 50 minutes ($P < 0.0001$ vs baseline, range 100 to 250 ppm; Fig. 1) COHb and MetHb levels, however, did not change· preoperative [COHb] range 0.5% to 2.6%, intraoperative and postoperative ranges 0 4% to 2 3%, preoperative [MetHb] range 0 1% to 0.8%, intraoperative and postoperative ranges 0 3% to 1 0% (Fig. 2). Mean perioperative oxyghemoglobin and total hemoglobin levels also were unchanged at 98.0% ± 0.3% and 13 3 ± 0.3 g/dl, respectively.

The surgeon's preoperative and postoperative [COHb] and [MetHb] also remained essentially unchanged. Mean [COHb] actually decreased slightly from the preoperative level of 2 9% to 2.4% postoperatively, and mean [MetHb] was 0.6% both pre- and postoperatively. Both perioperative total hemoglobin and venous oxyhemoglobin levels were unchanged at 16.0 ± 0.1 g/dl and 40% ± 3%, respectively.

There were no postoperative complications. Postoperative symptoms were evaluated on a 10 cm visual analogue scale (Fig 3). At 6 hours postoperatively,

Table I. Intraoperative data

Operating room time (min)	69 ± 5
Cautery time (min)	3 0 ± 0 3
Intrahepatic 9/21 (43%)	3 3 ± 0 2
Extrahepatic 12/21 (57%)	2 9 ± 0 4
Adhesions (scale 1-5)*	1 6 ± 0 2
Inflammation (scale 1-5)*	1 3 ± 0 2
Complications	0/21 (0%)

All values except "Complications" are expressed as mean ± standard error of the mean

*1 = none, 2 = mild, 3 = mild to moderate, 4 = moderate, 5 = severe

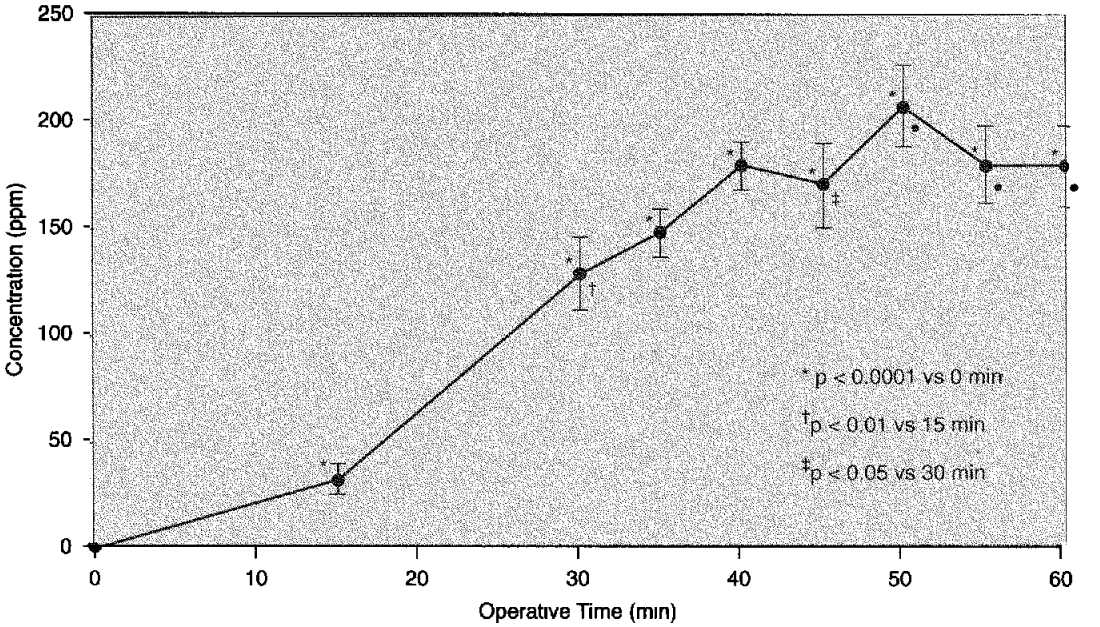

Fig. 1. Intraperitoneal [CO] during laparoscopic cholecystectomy Significant elevation occurred within 15 minutes of skin incision and remained elevated throughout the procedure

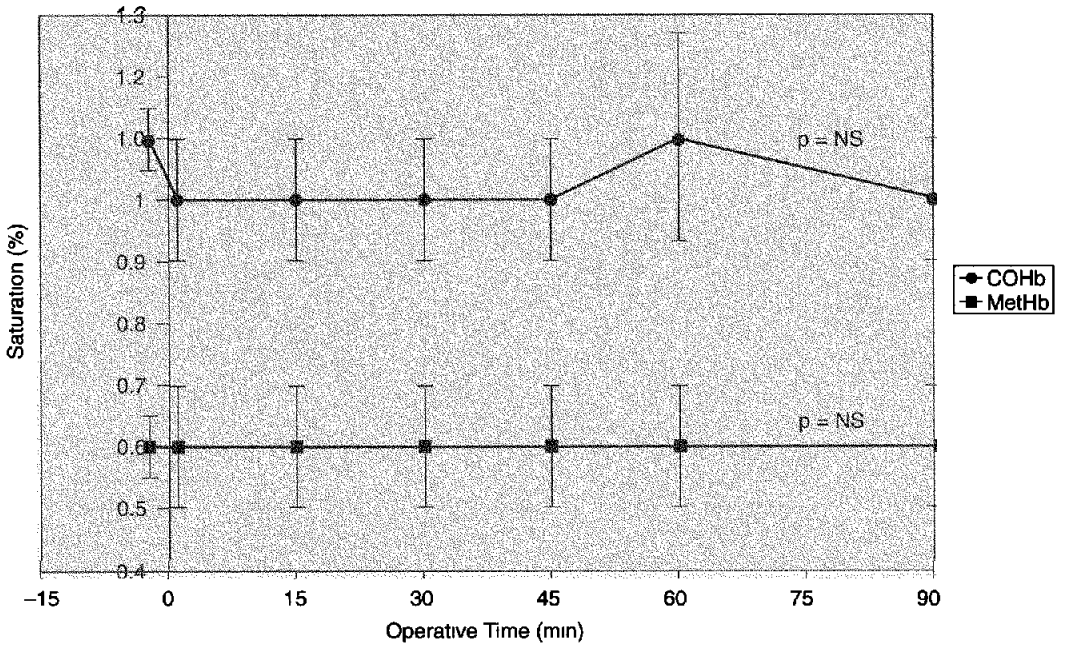

Fig. 2. Preoperative, intraoperative, and postoperative [COHb] and [MetHb] in patients undergoing laparoscopic cholecystectomy using electrocautery [COHb] and [MetHb] levels were not significantly different perioperatively

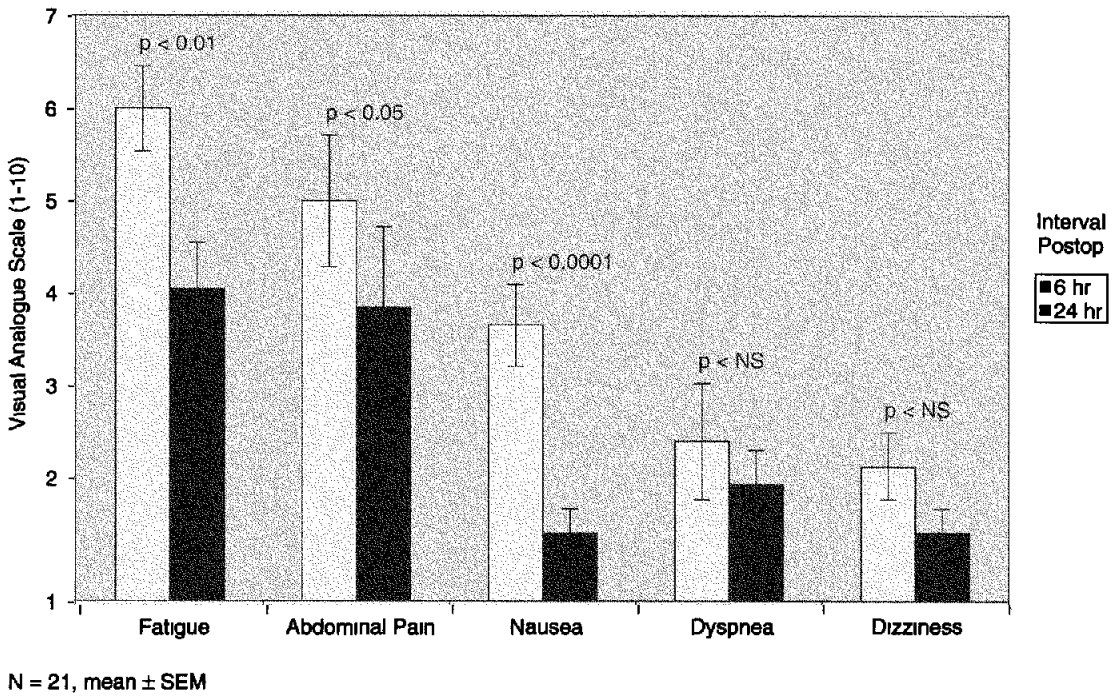

Fig. 3. Postoperative symptoms scored by patients using a visual analogue scale ranging from 1 to 10 cm There was significant reduction of scores for fatigue, abdominal pain, and nausea at 24 hours compared to scores at 6 hours

71% of patients complained of moderate-to-severe fatigue, 48% had abdominal pain, 43% had nausea, 19% had dyspnea, and 14% had dizziness. The mean scores for fatigue, abdominal pain, and nausea on a 10 cm visual analogue scale significantly decreased from 6-hour levels (5.9 ± 0.6, 4.8 ± 0.7, and 3.3 ± 0.5, respectively) to 24-hour postoperative levels (3.7 ± 0.6, 3.5 ± 0.7, and 0.8 ± 0.2, respectively, $P < 0.05$). Linear regression analyses revealed no correlation between the degree of 6-hour postoperative symptoms and either the peak concentration of intraperitoneal [CO] (correlation coefficients 0.1 to 0.2) or the cumulative exposure of intraperitoneal [CO] (correlation coefficients 0.1 to 0.4). No patients showed signs of tachycardia, tachypnea, or abnormal mental status (orientation, memory, and attention) postoperatively.

DISCUSSION

There are conflicting published data regarding the production and systemic absorption of toxic byproducts of incomplete tissue combustion in the pneumoperitoneum during laparoscopic surgery. The current study clearly demonstrated that laparoscopic cholecystectomy using electrocautery during dissection of the gallbladder resulted in "hazardous" levels of intraperitoneal CO, albeit lower than those found in other studies. In the study by Ott[18] of 25 patients undergoing laparoscopic-assisted hysterectomy or laparoscopic vaporization of endometriosis, with a similar average time of tissue combustion of 2.4 ± 1.2 minutes, intraperitoneal [CO] increased to a mean of 425 ppm within 2 minutes of initiation of cauterization (range 115 to 2100 ppm). Others have reported similar increases of intraperitoneal [CO] in patients undergoing LC.[6,7] Although there are currently no established safety limits for intraperitoneal [CO], the Environmental Protection Agency's (EPA) maximum allowable 1-hour exposure to ambient CO is 35 ppm with a ceiling concentration of 200 ppm.[10,11] The maximum allowable concentration of ambient CO set forth by the Occupational Safety and Health Administration (OSHA) is 50 ppm for 8 hours of exposure or 400 ppm per 15 minutes.[6,12]

Given the markedly elevated intraperitoneal [CO], transperitoneal absorption into the bloodstream could lead to toxic effects of end-organ hypoxia as a result of CO poisoning. If CO were absorbed systemically, one would predict either elevated blood levels of [COHb] or exhaled [CO] The basis for the generation of COHb is hemoglobin's marked affinity for CO, which is approximately 200- to 250-fold greater than that for oxygen [13] For nonsmokers the normal baseline [COHb] is less than 1%, although the EPA has set the

goal of maintaining nonsmokers' [COHb] below 2% [12] Above this level one may suffer various symptoms (e g , dizziness, nausea, dyspnea, palpitations, and impairment of judgment) and signs (e.g., tachycardia, tachypnea, and abnormal mental status) of CO toxicity[5] A few studies have shown that [COHb] of only 2% to 4% significantly decreased the time of onset of angina in persons with coronary artery disease[14,15] and decreased behavioral performance [16] The frequent postoperative complaints of headaches, dizziness, and nausea are often attributed to anesthesia. However, could CO poisoning be contributing to these symptoms? If so, patients might benefit from oxygen therapy postoperatively, since the elimination half-life of COHb is approximately 5 hours when room air is breathed but 1 hour if 100% oxygen is administered [17]

Previous studies of patients undergoing laparoscopic operations have shown variable COHb levels In Ott's series all 25 patients showed elevated [COHb] after 10 minutes of cauterization, with a mean level of 10.5% (range 2 8% to 18 5%) The patients with the highest [COHb] were noted to suffer postoperative symptoms of dizziness, nausea, headache, and weakness [18] Esper et al ,[6] however, found only a minimal but statistically significant increase in [COHb], from 0 7% ± 0.6% to 1 2% ± 0 7% (P <0 01), in their study of 15 patients undergoing LC In contrast, Beebe et al [7] demonstrated no significant elevation of [COHb] despite elevated intraperitoneal [CO] during LC in nine patients. A major criticism of the latter two LC studies was the small number of patients. In this study of 21 patients, there was no significant elevation of [COHb] If CO was being absorbed transperitoneally, one possible explanation for the minimal elevation of [COHb] was that the patients were exhaling CO We did not assess exhaled [CO] in the current study, but we have previously shown no elevation of exhaled CO in a porcine model of laparoscopic electrocautery [19]

The possibility of the development of methemoglobinemia during LC was also explored after reports by Ott[8,18] suggested elevation of [MetHb] to 2% to 3% from a baseline value of less than 1% Theoretically, elevations of MetHb (>2%) could produce the same symptoms and signs as COHb poisoning. The significance of this would mean that seriously ill patients with elevated postoperative MetHb levels might require the administration of methylene blue, since methemoglobinemia is usually unresponsive to oxygen therapy In the current study, however, MetHb was not found to be elevated intraoperatively or postoperatively Because both [COHb] and [MetHb] were unchanged throughout the study in all patients, the frequent postoperative symptoms of fatigue, abdominal pain, nausea, and dyspnea were not attributed to CO poisoning Other indirect data supporting this conclusion were the linear regression analyses showing no relationship between intraperitoneal [CO] and these untoward symptoms

Many operating room personnel have expressed concerns about exposure to smoke by its evacuation through the laparoscopic trocars into the operating room environment Therefore we also measured [COHb] and [MetHb] in the primary surgeon Although smoke evacuation was negligible during LC, all intraperitoneal gas was evacuated by the surgeon into the ambient atmosphere at the end of the procedure Nevertheless, there was no evidence of elevated [CO] in the surgeon.

In summary, this study assessed the intraperitoneal presence and systemic absorption of CO, a toxic byproduct of incomplete tissue combustion during LC Intraperitoneal [CO] reached levels above those established as safe for inhalation by the EPA and OSHA. However, there was no significant elevation of [COHb] or [MetHb]. The surgeon's exposure to CO by the evacuation of smoke through laparoscopic ports was negligible Production and release of smoke during LC using monopolar electrocautery, therefore, does not appear to pose a threat to the patient or the surgeon.

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The Pathogenesis of Port-Site Recurrences

Marc A Reymond, M D , Claus Schneider, M D , Sigrid Kastl, M D ,
Werner Hohenberger, M D , Ferdinand Kockerling, M D

The major factors underlying the seeding of tumor cells during laparoscopy are mechanical, with CO_2 playing only a secondary role The peritoneal wound is of great importance, especially in advanced tumor stages, when cells are present within the abdominal cavity Most reported port-site metastases were found within the extraction port when no protective measures were taken Gasless laparoscopy is no solution to the problem, since numerous port-site metastases have been described after thoracoscopy, during which no CO_2 is used The surgeon's role in the seeding of tumor cells is based on tumor perforation, excessive manipulation, and replacement of trocars This presumably explains the large differences (0% and 21%) in the reported incidence of port-site metastases Prospective studies now show that it is possible to keep the incidence of abdominal wall metastases to about 1%—which is comparable to that seen in open surgery—by the use of a meticulous operating technique and preventive measures (J GASTROINTEST SURG 1998,2 406-414)

Despite the explosive development of laparoscopy in many areas of surgery and surgical subspecialties, it is difficult to predict the future role of this new technique in the treatment of malignant disease It is still too early to definitively assess its advantages and problems, both known and unknown

Potential advantages of laparoscopy in cancer treatment—as compared with laparotomy—are reduced immunologic trauma[1-4] and tumor growth, as demonstrated in seven animal studies [5-11] In conjunction with adjuvant chemotherapy or immunotherapy, such effects might improve the management of minimal residual disease after curative surgery in selected groups of patients Other advantages, such as improved cosmesis or shorter hospitalization, should be considered secondary and not relevant in curative surgical procedures for cancer Indeed the clinical superiority of laparoscopy for such curative indications has not yet been convincingly demonstrated. The first long-term results of curative resections in colorectal cancer have just been published,[12,13] but actuarial survival curves are not yet widely available The few prospective randomized studies are still in progress [13,14] Current concerns focus on the quality and extent of oncologic resections [15] In the meantime, the short-term quality control results concerning number of lymph nodes harvested, resection margins, and extent of resection, obtained in a large prospective multicenter study, appear to be quite satisfactory [16]

Port-site recurrences represent another worrisome aspect that might limit the use of laparoscopic techniques in the treatment of cancer This troubling complication has been reported in numerous cases—after both curative and palliative surgery—and with different types of tumors [17] Results of clinical and experimental studies now permit some assessments of the incidence and mechanisms of these port-site recurrences [18-20]

DEFINITION

It is surprising just how poorly defined port-site recurrences have been to date We propose the following definition for port-site recurrences· early tumor recurrences that develop locally in the abdominal wall, within the scar tissue of one or more trocar sites or an incision wound, after laparoscopy or thoracoscopy for cancer They are not associated with peritoneal carcinomatosis Port-site recurrences are not cutaneous metastases, such as that which occurs in advanced cancers, but rather they are local tumor implantations that develop in the subcutis For this reason they should be termed port-site recurrences rather than metastases

From the Department of Surgery, University of Erlangen, Erlangen, Germany
Reprint requests M A Reymond, M D , Department of Surgery, University of Erlangen, P O Box 3560, D-91023 Erlangen, Germany
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A recent extensive review of the literature identified 152 such recurrences reported between 1970 and July 1996 including 52 in colorectal cancer, 45 in gallbladder cancer, and 15 in ovarian cancer Other malignancies included pancreatic, hepatic, bladder, cervical, and gastric cancer and lymphoma. In colorectal cancer most of these recurrences (90.3%) appeared in advanced tumor stages, although five developed after resection for International Union Against Cancer (UICC) stage I cancer.[21]

Clinically, palpation reveals a nodular, painful infiltration of the scar around a trocar site associated with a varying degree of inflammation. Microscopically, the incisional recurrences center around the incisional scar and initially involve the dermis and the subcutaneous fat but not the muscle [22] Most port-site recurrences develop within a few months, but some have been detected as early as 14 days after primary surgery.[17,23] To reach a palpable size (1 g = 10^9 cells), a single tumor cell requires 30 doubling cycles.[24] Doubling time for a colorectal metastasis was estimated to be approximately 100 days.[25] A mean delay of 190 days before the clinical appearance of port-site recurrences suggests therefore that initial inoculation of tumor cells at the time of surgery might have been massive.

Both the delay in the appearance and the macroscopic and microscopic patterns of port-site recurrences after endoscopic surgery are comparable to what has been reported for local recurrences in drainage tracts following cancer operations,[26,27] in gastrostomy,[28] after fine-needle biopsy,[29-31] mediastinoscopy,[21,32,33] and thoracoscopy.[21,34-39]

INCIDENCE OF PORT-SITE RECURRENCES

There is some debate about the relative incidence of wall recurrences in open and endoscopic surgery. The overall incidence of wound recurrence following laparotomy[40-42] and thoracotomy[22] varies between 0.6% and 1.6%. It is likely that the incidence of such incisional recurrences after conventional surgery might be underestimated.[41] It is also still difficult to establish the exact incidence of port-site recurrences after laparoscopy. Figures ranging from 0%[12] to 21%[43] have been reported in the literature. Wexner and Cohen[44] estimated an incidence of 4%, which is higher than that reported for open surgery. However, their calculation was based on unreliable patient selection criteria, and others at their institution report a lower incidence (Weiss EG, personal communication) Reports from large prospective trials published since then[12,45,46] also suggest a lower incidence, which would seem more accurate—at least when laparoscopic surgery is performed by experts. Results from The American Society of Colon and Rectal Surgeons Laparoscopic Registry showed five recurrences among 504 patients (1%) treated for cancer, one associated with peritoneal carcinomatosis, another with distant metastases, and all occurring in advanced tumors. A minimum follow-up of 1 year was achieved in 480 of 493 evaluable patients.[45]

Recent data from the only prospective randomized study[13] published to date showed no port-site or wound recurrence in patients undergoing laparoscopic (n = 27) or open (n = 33) surgery, after a mean follow-up of 23 months. In an ongoing randomized trial at The Cleveland Clinic, thus far there has been one wound recurrence in the laparotomy group and none in the laparoscopy group (Milsom J, personal communication). Reliable port-site recurrence rates for various types of cancer and different stages, or data comparing results achieved by different surgeons, are not available. Because of the low incidence of such complications, large numbers of patients would be necessary to ensure statistically significant differences between indications or between surgeons Nevertheless, it is already possible to state that the available data stress the role of the surgeon as a risk factor [17]

PATHOGENESIS OF PORT-SITE RECURRENCES

Fig. 1 shows that pathogenic mechanisms of port-site recurrences can be divided into the following three groups: active mechanisms, as defined by the source of tumor cells (Table I), possible vectors of tumor cells, and passive protective mechanisms in the abdominal wall that might be disturbed by local processes (Table II). In this review we have attempted to evaluate the relative importance of these different mechanisms.

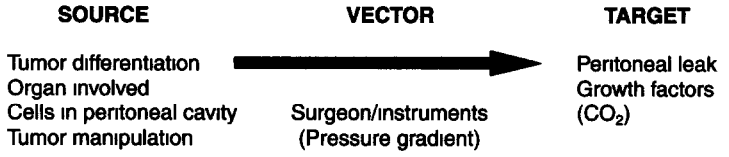

Fig. 1. Pathogenesis of port-site recurrences

Table I. Pathogenesis of port-site recurrences Source and vectors of tumor cells

Tumor cell spillage
Open resection
Section through tumor[47]
Grasping with instruments[48]
Advanced tumor stages (peritoneal cytology positive)[49]
Direct inoculation
Surgical specimen retrieval[23]
Instruments[50]
Trocar movement/removal[18]
Aerosolization (unlikely or limited)
Pressure gradient[50-52]
Systemic vectors (unlikely)
Blood-borne tumor cells

Table II. Pathogenesis of port-site recurrences Protective mechanisms and local factors

Peritoneal wound
Loss of mechanical protection (mesodermal layer)[53]
Loss of protection of proteoglycans[54,55]
Direct access to subcutaneous tissue
Scarring
Mediators of inflammation
Growth and angiogenic factors
Ischemia[56]
Adjuvant factors
CO_2 (at low concentrations)[5,11,57-61]
Inhibitory factors
Helium[60]
CO_2 (at high concentrations)
Other (betadine,[12,62] cytostatics, taurolidine,[63] etc)

Clinical Observations

Clinical observations regarding the development of port-site recurrences must be rated highly for analysis of the pathogenic mechanisms They are more important than experimental observations in animal models, which could overemphasize one aspect of the pathogenetic process as a result of experimental conditions that have been chosen Clinical observations should guide the choice of these animal models and the interpretation of their results

A recent overall review of port-site recurrences analyzing responses from 443 hospitals in Germany reported 109 cases of port-site recurrence or early peritoneal carcinomatosis, 76 (70%) of which were found after routine cholecystectomy where no carcinoma was suspected Most port-site recurrences (63%) occurred after a procedure during which no protection bag was used for specimen retrieval After cholecystectomy, 56% of the recurrences developed in the extraction port.[23] These observations underscore the role of mechanical inoculation of tumor cells into the abdominal wall, either because the surgeon was unaware of the presence of cancer or because he or she failed to protect the wound during extraction of the resected specimen In this survey 19 (17%) such local recurrences were noted after surgery for colorectal cancer, three of which should have been eliminated because they occurred in association with disseminated peritoneal carcinomatosis All port-site recurrences after colorectal operations developed after resection of advanced tumors (UICC categories T3 and T4). The mean time between curative surgery and diagnosis of local recurrence was 190 days for colorectal procedures

Port-site recurrences have also been reported after thoracoscopy We have recently emphasized that such potential complications can occur not only after laparoscopy involving a pneumoperitoneum but also after thoracoscopy without the use of CO_2 [64] This was confirmed by two recent studies involving 21[34] and 15[21] cases of metastases, respectively, following thoracoscopy On reviewing the literature we found additional cases of port-site recurrence after thoracoscopy[34-39,64] and also after thoracotomy.[22] These findings provide further pathogenic evidence that the presence of a pneumoperitoneum is not necessary for the development of port-site recurrences

Many other comparable local recurrences in the abdominal or thoracic wall have been described, these complications have been reported after mediastinoscopy[21,32,33] and in drainage tracts following cancer surgery [26,27] Incision-site metastases have also occurred after fine-needle biopsy [29-31] Tumor implantation has also been described after percutaneous gastrostomy [28] All of these situations are characterized by the creation of a channel through the body wall simultaneously with the manipulation of a tumor, but a pneumoperitoneum is used only in laparoscopy

Last but not least, the incidence of port-site recurrences varies greatly among surgeons[12,43-46,65-71] (Fig. 2), suggesting that differences in operating technique, rather than invariable factors such as pneumoperitoneum, are of greater importance In the meantime, some authors have suggested that the development of port-site recurrences might be an entirely surgeon-related variable that is dependent on experience and level of expertise [17]

Findings in Humans

Mesothelial cells have been demonstrated in the smoke created during laparoscopic surgery.[72] During staging laparoscopies for pancreatic cancer in humans,

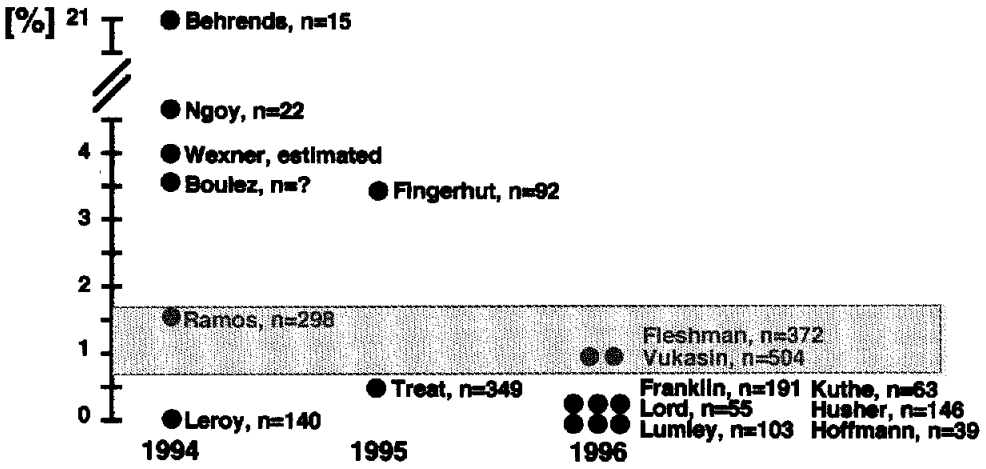

Fig. 2. Incidence of port-site recurrences Influence of the surgeon [12,43-46,65-71] (Incidence of abdominal wall metastases in open surgery is presented in the grid box)

we were able to show that the numbers of all kinds of cells aerosolized in the CO_2 at pneumoperitoneum pressures of approximately 14 mm Hg are very low, even in the presence of a massive contamination of the peritoneal liquid with tumor cells.[50] The same study showed that the surgical instruments, the suction device, and the trocars used carried approximately 10^4 times more cells than the aerosol In another study involving 25 patients,[51] analysis of CO_2 showed no cells but did show positive carcinoembryonic antigen in three samples. These results are highly consistent with findings in animal studies showing that CO_2 had no role in the aerosolization of tumor cells [52,73,74]

In advanced tumor stages, malignant cells are usually already present within the abdominal cavity at the beginning of the procedure During open and laparoscopic colorectal resections, tumor cells can be found within the peritoneal cavity even in early tumor stages. The quantity of cells does not seem to be influenced by the type of procedure or the time of sampling.[49] In our own study, undertaken during staging laparoscopies for pancreatic cancer, peritoneal cytologic examination identified tumor cells in half of the cases [50]

Accuracy of Animal Models

Since 1995 a number of experimental studies on the pathogenesis of port-site recurrences have been published. Although some results initially appear to be contradictory, careful analysis shows that most differences can be explained by the choice of the experimental model (kind of animal, location of tumor, type of cell line, and experimental conditions)

Peritoneal tumor growth and incidence of port-site recurrences are not synonymous and should be considered different outcome criteria. In contrast to some experimental findings,[57,58] clinical port-site recurrences are usually not associated with disseminated peritoneal carcinomatosis [23]

Most of the studies were performed in rodents (rats, hamsters, and mice) These animals preferentially develop peritoneal and lung metastases after injection of tumor cells into the tail vein.[75] Liver and lymph node metastases are rare in these species. Animals differ in terms of immunity, depending on the species and the supplier (e g , immunodeficiency in nude mice), which explains the finding by some authors of very high rates of port-site implantation after intraperitoneal injection of cell lines (e.g., half of the control hamsters in a trial conducted by Jones et al.).[58]

CO_2 Dependence of Cell Lines In Vitro and In Vivo

It is well known to biologists that the in vitro growth of cell lines is dependent on many factors, for example, CO_2 at a concentration of 5%, an adequate culture medium with or without growth factors, a constant temperature (approximately 37° C), humidity, and sterile conditions Nevertheless, some undifferentiated tumor cell lines can survive in vitro without CO_2. At high concentrations, CO_2 has an inhibitory effect on cell growth in vitro.

Differences in experimental conditions, for example, the choice of cell line, the concentration of CO_2, and the duration of exposure to it, may serve to explain the contradictory results obtained in animal models

Intraperitoneal Tumor Seeding or Retroperitoneal Models

Whether an intraperitoneal or a retroperitoneal model is used to study the influence of pneumoperitoneum has definite relevance As a rule, CO_2 is used intraperitoneally, but it may also be insufflated retroperitoneally, for example, in laparoscopic adrenalectomy In models of intraperitoneal seeding, tumor implantation at trocar sites is enhanced by CO_2, as compared to anesthesia alone, in the hamster[58] and rat [5,11,57,59-61] There is also a definite dose-response relationship between tumor implantation and the number of cells in the inoculum [52,58] CO_2 has no effect on tumor growth when a solid[76] or retroperitoneal[77] tumor model is used, which is similar to the clinical situation—at least in early tumor stages

Can Pneumoperitoneum Aerosolize Tumor Cells?

Only one research group[78] has shown aerosolization of tumor cells in an in vitro model. Other experimental evidence shows either no tumor cells or only very small numbers of such cells in the aerosol Using a radioactive cell line in pigs, Allardyce et al.[52] have recently shown that, although CO_2 may increase wound site implantation, the major variable influencing tumor cell deposition is whether or not the port is used by the surgeon Using filters, Hewett et al [73] were able to demonstrate that the movement of cells throughout the peritoneal cavity during laparoscopy is via contaminated instruments, with local contamination of the port by dispersion within water vapor remaining a secondary possibility Using in vitro and in vivo models, Whelan et al [74] showed that trocar site recurrence is unlikely to result from aerosolization of tumor cells

Gasless vs. CO_2 Laparoscopy

It has been well documented in the pig model, with the use of radiolabeled cells, that gasless laparoscopy does not significantly reduce contamination of the port at any site [52] Our own studies during staging laparoscopies for pancreatic cancer showed not only that no tumor cells were visible microscopically in the aerosols, but also that no human genes could be amplified by polymerase chain reaction in 6 of these 12 aerosols We saw a few mesothelial cells, as did Champault et al [72] Nevertheless, large numbers of tumor cells were detected on surgical instruments and on the trocars [50] In 25 staging laparoscopies for cancer, Bonjer et al [51] also failed to see any tumor cells in the aerosols Although two studies in the rat model documented a reduction in the incidence of port-site recurrences when gasless laparoscopy was used,[76,79] we do not believe that gasless laparoscopy will prevent the development of port-site recurrences, since numerous port-site recurrences have been described after thoracoscopy [21,34-39]

Laparoscopy vs. Laparotomy

The above-mentioned data show that CO_2 enhances intraperitoneal tumor growth only if and when cells are present in this cavity, but not if they are in the retroperitoneum. These results were obtained in comparison with anesthesia alone, which is not relevant for clinical practice. The important clinical question to ask is whether laparoscopy is superior to laparotomy in terms of intraperitoneal or systemic tumor growth. Although tumor growth is enhanced by CO_2 laparoscopy in comparison with anesthesia alone, the results of seven independent animal studies[5-11] have shown that there is less tumor growth after CO_2 laparoscopy than after conventional laparotomy. These findings might have clinical implications if they are confirmed by the disease-free survival rates achieved in prospective studies, and if the problem of port-site recurrences can be resolved in clinical practice, as appears to be the case when the surgeon is highly skilled.[12,13,45] An explanation for this reduced tumor growth in laparoscopic surgery might be less immunologic trauma[1,2,9,80] or a reduced acute-phase response [81]

Influence of Different Gases on Tumor Growth

Since palliative laparoscopy is performed in advanced tumor stages, the use of alternative gases that have no effect on tumor growth or, preferentially, have cytostatic properties might be a promising approach Interestingly, laparoscopy involving the use of air enhances intraperitoneal tumor growth more markedly than does the use of CO_2.[7] Helium has been shown to have inhibitory effects on tumor growth [57,60] Explanations for these differences might be the use of cell lines with different degrees of CO_2 dependence, or a possible inhibitory effect of CO_2 at high concentrations This point merits further investigation to identify possible consequences in clinical practice The clinical use of helium, however, carries a possible risk of lethal gas embolism [82,83] Comparative clinical trials will be difficult to organize because of the

low incidence of port-site recurrences: a 50% reduction in the incidence of port-site metastases (from 2% to 1%) would require more than 6000 patients to reach statistical significance

Disruption of the Peritoneal Barrier

After open surgery, intra-abdominal recurrences usually develop in the laparotomy wound or anastomosis.[53] Intra-abdominal recurrences after laparoscopy develop preferentially in serosal lesions (port sites[58,61] or on the damaged liver surface[58]), which underscores the importance of an intact peritoneal barrier for preventing the implantation of free cancer cells in the peritoneal cavity.[54] It has been postulated that pericellular hyaluronate produced by mesothelial cells plays an important role in preventing tumor cells from adhering in the peritoneal cavity[55] Presence of growth and angiogenesis factors in the subcutaneous tissue would be a further explanation for this preferred localization of tumor recurrence Vukasin et al.[45] believe that drain sites, stoma sites, and any other peritoneal disruptions carry the same tendency toward enabling cancer recurrences as primary incisions and that all such abdominal wall recurrences should be considered related to the surgical wound.[49] This option is shared by Heald[84] who believes that seeding of malignant cells into the lumen, or from the ulcerated peritoneal surface of a cancer, may contaminate raw surfaces created by surgery and thus lead to malignant implantation and local recurrence, as in the case of port-site recurrences after laparoscopic surgery, but also in conventional surgery after abdominoperineal excision. If this proves to be true, and if it becomes accepted by the surgical community, the implications might be enormous.

Differentiation and Adhesion Potential

It appears that most port-site recurrences develop in advanced cancer stages[17,23,45] and in locally invasive types of tumors (e g., gallbladder carcinoma). This is in accordance with current knowledge that underscores the role of successive mutations in the metastatic cascade. The discovery of genetic defects in cancer cells,[85,86] tumor metastasis–related genes,[87] and tumor suppressor genes,[88] now permits better understanding of the process that allows a tumor cell to detach from the primary lesion, invade the extracellular matrix, migrate, readhere to a specific organ, avoid immune response mechanisms, and finally grow. Intraoperative spillage is one possible way in which tumor cells can migrate However, numerous cells might be present within the peritoneal cavity in advanced tumors and might then inoculate the subcutaneous tissue even after the surgical procedure has been completed

Prevention of Port-Site Recurrences

New approaches have been proposed recently to prevent the development of port-site recurrences. Besides technical surgical measures,[12,62] chemotherapeutic agents have also been advocated to reduce port-site implantations in the animal model [63] Experimental trials are ongoing in Europe, in the United States, and in Australia that might provide exciting information in the near future.

CONCLUSION

The preceding data illustrate the pathogenesis of port-site recurrences and their correlation with clinical findings. Although a stimulatory effect of CO_2—as compared to anesthesia alone—on intraperitoneal tumor growth is clearly documented in numerous animal studies, we believe this factor is of only secondary importance in clinical practice Intraperitoneal tumor growth is slower after laparoscopy than after laparotomy. No negative effect of CO_2 has been demonstrated for retroperitoneal (subserosal) tumors. Gasless laparoscopy was not able to eliminate contamination to the ports at any site The incidence of port-site recurrences differs greatly among surgeons, suggesting differences in operating technique Incisional metastases occur after thoracoscopy, during which no CO_2 is used, and they also occur in a number of other situations. CO_2 is not capable of aerosolizing large numbers of tumor cells at the pressures used in the clinical setting.

On the basis of the preceding data, we believe that the following principles apply to the development of port-site recurrences after laparoscopy or thoracoscopy·

1. Tumor cells are already present within the abdominal cavity—as is the case in advanced cancer stages—or are spilled as a result of inadequate surgical technique.
2. The peritoneal wound breaches the mechanical and chemical protection provided by the mesodermal layer
3. Implantation of tumor cells into the wound can occur by direct contact, by direct inoculation via surgical instruments or unprotected extraction of the surgical specimen, or even postoperatively by the contaminated peritoneal liquid The role

of pneumoperitoneum in tumor cell seeding appears to be secondary.

4. Finally, local favorable conditions in the scar, such as the presence of inflammation mediators, and growth and angiogenic factors, promote the growth of the tumor cells. CO_2 might have a borderline effect on tumor growth at this stage—at least in animal models when CO_2-dependent cell lines are used and at low concentrations

Port-site recurrences are no longer a mysterious complication that is understood by no one As documented in several reviews, most of these complications have occurred within the extraction port, in the absence of suitable precautions Measures have been proposed[18,62,65] that might help the surgeon to prevent port-site recurrences Large prospective studies[12,45] and a limited prospective randomized trial[13] have shown that it is possible to maintain the incidence of incisional recurrences at a level comparable to that seen in open surgery by using meticulous operating technique

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Reasons for Intracranial Hypertension and Hemodynamic Instability During Acute Elevations of Intra-Abdominal Pressure: Observations in a Large Animal Model

Raul J Rosenthal, M D , Richard L Friedman, M D., Akram M Kahn, M D , Joseph Martz, M.D., Somasundavam Thiagarajah, M D., Douglas Cohen, M D , Qiuhu Shi, M S , Moses Nussbaum, M D

In previous studies we reported that an acute elevation in intra-abdominal pressure (IAP) is responsible for the elevation in intracranial pressure (ICP) and mean blood pressure (MBP). Thus far, the reasons for the increased ICP during an acute elevation in IAP and the combined effects of increased IAP and ICP on hemodynamics have not been reported Five large animals (swine) were studied Each animal served as its own control. A subarachnoid screw was placed for ICP monitoring The jugular vein, femoral vein, and femoral artery were cannulated. ICP, MBP, central venous pressure above (CVPA) and below (CVPB) the diaphragm, and $PaCO_2$ were monitored after a pneumoperitoneum with CO_2 was established at 5, 15, and 30 mm Hg of IAP Cavography was performed to evaluate the morphology of the inferior vena cava at different increments of IAP Measurements were obtained in reverse Trendelenburg (group 1), supine (group 2), and Trendelenburg (group 3) positions Multiple regression analysis was used to examine the effects of IAP and positioning in separate models with different blood pressures as dependent variables Increased IAP significantly increased CVPA, CVPB, ICP, and MBP There were no changes in cerebral perfusion pressure. The change in position (from group 1 to group 3) significantly increased CVPA and decreased the CVPB Cavograms performed on animals in the supine position with increased IAP showed a narrowing of the IVC at the level of the diaphragm Increases in IAP will increase ICP and MBP without altering the cerebral perfusion pressure A mechanical effect mediated by compression of the inferior vena cava at the level of the diaphragm with increased central venous pressure and decreased drainage from the lumbar plexus and central nervous system is responsible for this effect (J GASTROINTEST SURG 1998,2 415-425)

In 1901 Georg Kelling[1] postulated that the establishment of a pneumoperitoneum would achieve hemostasis for gastrointestinal bleeding. He performed this process in 20 experimental animals. Among other observations he concluded that "while the femoral blood flow remained unchanged or slightly decreased, the carotid blood flow increased 10%." This was the beginning of laparoscopy and since then the hemodynamic response to increased intra-abdominal pressure (IAP) has been the subject of intensive research.

During the past 50 years many papers have been published describing the important hemodynamic and cardiorespiratory changes that occur in response to an increase in IAP secondary to the establishment of a pneumoperitoneum or other clinical situations such as the abdominal compartment syndrome. In 1987 Caldwell and Ricotta[2] measured the perfusion of all abdominal organs after an elevation in IAP in dogs. The elevation in IAP was found to cause a decrease in the absolute blood flow to all intra-abdominal organs measured except the adrenal glands where the blood flow increased. As in Kelling's experiment, these observations remained without a physiopathologic explanation. Thus far, there has not been a sat-

From the Departments of Surgery (R J R , R L F, A.M K., J.M , and M N), Anesthesia (S T), and Biostatistics (Q S), and the Department of Neurology and Neurosurgery (D C), Institute of Neurology and Neurosurgery, Beth Israel Medical Center, Albert Einstein College of Medicine, New York, N Y

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Reprint requests Raul J Rosenthal, M D , Department of Surgery, Mount Sinai Medical Center, Mount Sinai School of Medicine, One Gustave Levy Place, New York, NY 10029-6574

isfactory explanation of the hemodynamic changes observed during acute elevations of intra-abdominal pressure Some authors showed evidence that a neurohormonal response mediated by chemoreceptors and osmoreceptors was involved but others concluded that a mechanical effect was responsible for most of the hemodynamic changes [3-7] In fact, since the mean blood pressure (MBP) to intra-abdominal organs ranges from 70 to 105 mm Hg, it seems difficult to justify that the effects of elevated IAP alone would decrease the blood flow to all of the intra-abdominal organs with exception of the adrenal glands at IAP levels of 20 mm Hg Furthermore, the parallel and paradoxical increase in blood flow to the carotid arteries during acute elevations in IAP is also a subject of discussion. In 1994 Josephs et al.[8] described in a large animal model how acute elevation of IAP produced an immediate increase in intracranial pressure (ICP) [8] Their report was followed by ours, which yielded similar results showing that at 5 mm Hg of IAP there was already an immediate and significant increase in ICP[9,10] This study examines the reasons for increased ICP during acute elevations of IAP as well as the "combined" effects of increased IAP and ICP on hemodynamics

MATERIAL AND METHODS

All experimental procedures and protocols were reviewed and approved by the appropriate institutional committees This study used five female farm pigs with an average weight of 60 pounds Each animal served as its own control Measurements were carried out in reverse Trendelenburg (group 1), supine (group 2), and Trendelenburg (group 3) positions ICP, MBP, and central venous pressure above (CVPA) and below (CVPB) the diaphragm as well as arterial pressure of carbon dioxide ($PaCO_2$) were measured at various time points during each phase. The cerebral perfusion pressure (CPP) was calculated based on a standard formula CPP = MBP − ICP Measurements were carried out before and after a pneumoperitoneum with CO_2 was established up to pressures of 5, 15, and 30 mm Hg.

Animals were fasted overnight prior to surgery Preoperative medications used as sedatives/anesthetics included acepromazine (0.6 mg/kg), ketamine (20 mg/kg), and atropine (0 05 mg/kg), all of them administered intramuscularly After anesthesia was induced, the airway was kept open by means of an endotracheal tube, and animals were mechanically ventilated using a model 30170 Proportioner anesthesia machine (Airco Inc , Madison, Wis). Mechanical ventilation was performed with a tidal volume of 500 ml/kg at 35 breaths per minute aimed at maintaining baseline $PaCO_2$ values below 35 mm Hg Anesthesia was maintained with an isoflurane/oxygen mixture (1 5% to 5%). During the experimental procedure 0.9% sodium chloride was infused at a rate of 100 ml/hr For monitoring of arterial blood gases and MBP, the right femoral artery was cannulated with a 7 F triple-lumen catheter (20 cm in length and 0.032 inches in diameter, Arrow Precision Products, Inc., Reading, Pa) To record the CVPA and CVPB, the right internal jugular and right femoral veins were cannulated with a 7 F triple-lumen catheter (Arrow Precision Products, Inc.). Catheters placed in the jugular vein and in the femoral vein and artery were attached to a disposable pressure transducer (Baxter Healthcare Corp , Melrose Park, Ill.), which was attached to a model 870 Datascope monitor (Datascope Corp , Paramus, N.J) and calibrated. For continuous monitoring of ICP, a twist drill hole was made in the skull through a 1 cm incision in the right prefrontal area, and a Camino fiberoptic ICP transducer system was inserted intracranially and connected in the standard manner to a Camino V420 monitor (Camino Laboratories, San Diego, Calif) and calibrated.

Experimental Procedure

Group 2. Animals in this group were placed in the supine position A 1 cm incision was made in the navel area, and a Veress needle (Karl Storz Endoscopy-America, Inc , Culver City, Calif) was inserted into the abdominal cavity CO_2 was introduced by means of a Laparoflator (Karl Storz Endoscopy-America, Inc), and a pneumoperitoneum was established to a pressure of 15 mm Hg A 5 mm trocar (Karl Storz Endoscopy-America, Inc) was inserted into the abdominal cavity for better control of insufflation and desufflation during the experimental procedures The abdomen was deflated and the animal kept in the supine position After a stabilization period of 10 minutes, baseline measurements of ICP, MBP, CVPA, CVPB, and arterial blood gases were obtained The abdomen was then insufflated to IAP levels of 5, 15, and 30 mm Hg, and all previously mentioned measurements were repeated at each increment of IAP Also, at each elevation of IAP cavography was performed to assess the diameter of the inferior vena cava A diluted solution of 50 ml of 43% Iothalamate meglumine injection (Conray, Mallinckrodt Chemical, St Louis, Mo) was injected through the catheter placed in the right femoral vein. Radiologic documentation was obtained with a GE Amx II C-arm device (Machein Medical Systems, Milwaukee, Wis) exposing Kodak Laner regular film on a Kodak X-9 M cassette (Eastman Kodak Company, Rochester, N Y)

Group 1. The abdomen was deflated and the animals were placed in a 30-degree reverse Trendelenburg position After a stabilization period of 15 min-

utes, baseline measurements of ICP, MBP, CVPA, CVPB, and arterial blood gases were obtained. Pneumoperitoneum was then restored to levels of 5, 15, and 30 mm Hg of IAP, and all measurements were repeated as described for group 2.

Group 3. The abdomen was deflated and after a stabilization period of 15 minutes, animals were placed in a 30-degree Trendelenburg position. Baseline measurements of ICP, MBP, CVPA, CVPB, and arterial blood gases were obtained Pneumoperitoneum was then restored to levels of 5, 15, and 30 mm Hg of IAP, and all measurements were repeated as described for groups 1 and 2

Statistical Analysis

All five pigs involved in this experiment were included in the analysis The mean and standard deviation at each increment of IAP and each animal positioning as well as the different recorded ICPs were considered dependent variables and were assessed The residual analyses were used to assess the appropriateness of the regression assumptions and to detect outliers [11] The nonlinear effects have also been analyzed. Statistical analysis of significance was performed with the Statistical Analysis System [12]

RESULTS

Effects of IAP and Positioning on ICP

The increase in IAP produced an immediate increase in ICP in all groups (Table I) The highest mean values reached were in the animals in the Trendelenburg position (see Table I, group 3). The lowest means were achieved when animals were placed in the reverse Trendelenburg position (see Table I, group 1). The estimated regression coefficients for predictors of ICP are presented in Table II. Two independent variables, IAP and positioning (reverse Trendelenburg, supine, or Trendelenburg), were tested in the models The results showed that increased IAP significantly increased ICP. The change in position also significantly increased (group 3, Trendelenburg) or decreased (group 1, reverse Trendelenburg) the ICP. All of the above-mentioned parameters returned to baseline values contiguously after IAP was released.

Effects of IAP and Positioning on CVPA and CVPB

The estimated regression coefficients for predictors of CVPA and CVPB are presented in Table II. Means and standard deviation are depicted in Table I Two independent variables, IAP and positioning, were tested in the models The results showed that increased IAP produced an immediate and significant increase in CVPA and CVPB (see Table I) The change in position (from group 1 to group 3) will produce a significant increase in CVPA and decrease in CVPB (see Table I). All of the above-mentioned parameters returned to baseline values contiguously after IAP was released

Effects of IAP and Positioning on MBP

The increase in IAP produced an immediate increase in MBP in all three groups (see Table I) The estimated regression coefficients for predictors of MBP are presented in Table II Two independent variables, IAP and positioning, were tested in the models. The results showed that increased IAP produced an immediate and significant increase in MBP There was no statistical significance between the positioning of the animals and the MBP in any of the groups (see Table II). All of the above-mentioned parameters returned to baseline values contiguously after IAP was released.

Effects of ICP on MBP

The estimated regression coefficients for predictors of MBP are presented in Table III Means and standard deviation are depicted in Table I. Two independent variables, ICP and positioning, were tested in the models The results showed that increased ICP produced a significant increase in MBP. Changes in position did not significantly affect the MBP All of the above-mentioned parameters returned to baseline values contiguously after IAP was released

Effects of IAP and Positioning on CPP

The estimated regression coefficients for predictors of CPP are presented in Table II Means and standard deviations are indicated in Table I. Two independent variables, IAP and positioning, were tested in the models. The results showed that increased IAP or positioning did not significantly affect the CPP.

Cavography

The increase in IAP produced a narrowing of the inferior vena cava at the level of the diaphragm when compared to a native picture without increased IAP The narrowing of the inferior vena cava was increased as IAP was elevated. With IAP at 0 mm Hg the diameter of the inferior vena cava at the level of the diaphragm was 1 5 cm (Fig 1). As IAP was increased to 5 mm Hg, the diameter of the inferior vena cava was reduced to 1.3 cm (Fig. 2) At IAP of 15 mm Hg the diameter of the inferior vena cava at the level of the diaphragm was 0 8 cm (Fig. 3) When IAP was in-

Table I. Effects of intra-abdominal pressure and positioning

	IAP (mm Hg)	CVPA Mean	CVPA SD	CVPB Mean	CVPB SD	MBP Mean	MBP SD	ICP Mean	ICP SD	CPP Mean	CPP SD
Group 1 (reverse Trendelenburg-head up)	0 baseline	4 80	1 48	11 80	1 30	70 80	9 31	8 40	3 21	61 00	10 56
	5	9 00	2 35	15 80	1 48	84 00	12 51	13 40	2 70	70 80	11 08
	15	13 60	2 19	22 20	3 11	92 60	16 89	18 20	3 27	75 20	14 31
	30	14 20	3 42	31 60	7 44	92 00	14 37	24 00	5 34	65 20	16 81
Group 2 (supine)	0 baseline	7 60	4 10	7 20	4 71	71 00	13 36	16 60	5 41	56 00	11 40
	5	10 80	3 96	9 80	3 96	80 20	11 21	19 80	5 26	61 80	9 04
	15	14 40	4 04	17 60	6 47	83 20	10 66	25 20	4 66	60 60	7 57
	30	18 60	5 59	25 40	12 92	82 80	7 66	28 80	5 93	51 80	8 76
Group 3 (Trendelenburg-head down)	0 baseline	10 00	3 32	5 40	3 91	80 40	6 54	20 20	7 85	59 40	8 38
	5	13 00	4 69	8 40	4 04	85 00	7 48	24 40	8 05	62 20	9 50
	15	15 80	6 22	17 40	3 78	85 00	6 28	28 40	7 96	57 40	10 11
	30	18 60	2 88	29 80	4 21	93 60	10 14	31 40	8 47	59 20	7 73

CVPA = central venous pressure above the diaphragm, CVPB = central venous pressure below the diaphragm, MBP = mean blood pressure, ICP = intracranial pressure, CCP = cerebral perfusion pressure, IAP = intra-abdominal pressure, SD = standard deviation

Table II. Estimated regression coefficients for predictors of mean blood pressure

	CVPA	CVPB	MBP	ICP	CPP
IAP	0 31 (0 04)*	0 70 (0 06)*	0 45 (0.13)*	0 42 (0 06)*	NS
Group	1 98 (0 60)†	−2 55 (0 86)†	NS	5 05 (0 90)*	−4 25 (1 75)‡
Interception	4 75 (1 41)†	13 2 (3 01)*	7 66 (4 16)	6 26 (2 11)†	71 0 (4 10)*
Adjusted multiple R^2	0 50*	0 70*	0 15†	0 55*	0 07

NOTE IAP and group (changes in position) are independent variables, CVPA, CVPB, MBP, ICP, and CPP are dependent variables
IAP = intra-abdominal pressure, CVPA = central venous pressure above the diaphragm, CVPB = central venous pressure below the diaphragm, MBP = mean blood pressure, ICP = intracranial pressure, CPP = cerebral perfusion pressure, NS = nonsignificant
*P <0 001
†P <0 01
‡P <0 05

Table III. Intracranial pressure as a predictor of mean blood pressure and estimated regression coefficient

	Mean blood pressure
ICP	0 64 (0 20)*
Group	NS
Interception	74 84 (4 54)†
Adjusted multiple R^2	0 12‡

NOTE ICP and group (changes in position) are independent variables, mean blood pressure is dependent variable
ICP = intracranial pressure, NS = nonsignificant
*P <0 05
†P <0 001
‡P <0 001

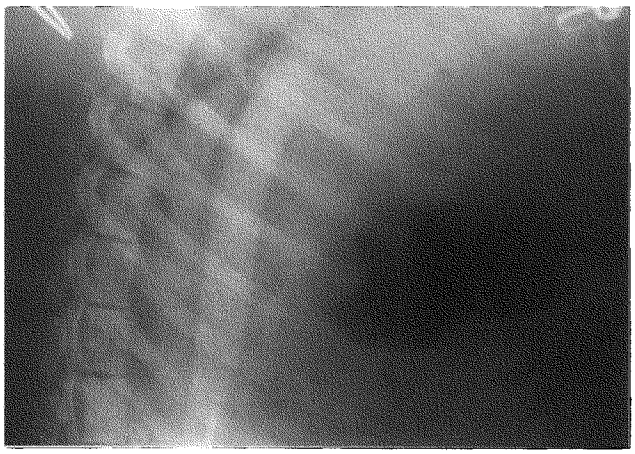

Fig. 1. Cavogram at 0 mm Hg of intra-abdominal pressure Diameter of the inferior vena cava at the level of the diaphragm is 1 5 cm

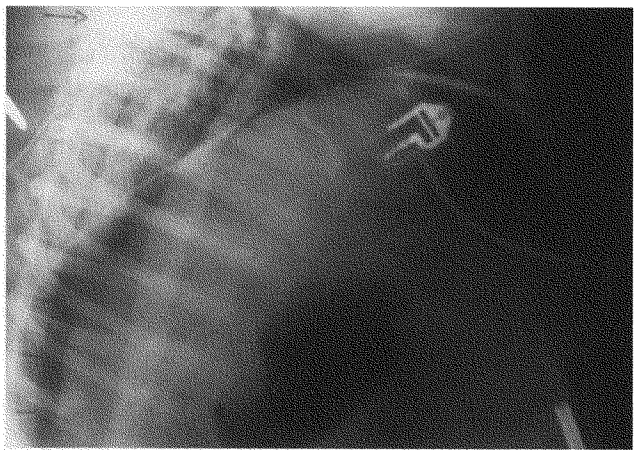

Fig. 2. Cavogram at 5 mm Hg There is a slight narrowing of the inferior vena cava at the level of the diaphragm to 1 3 cm

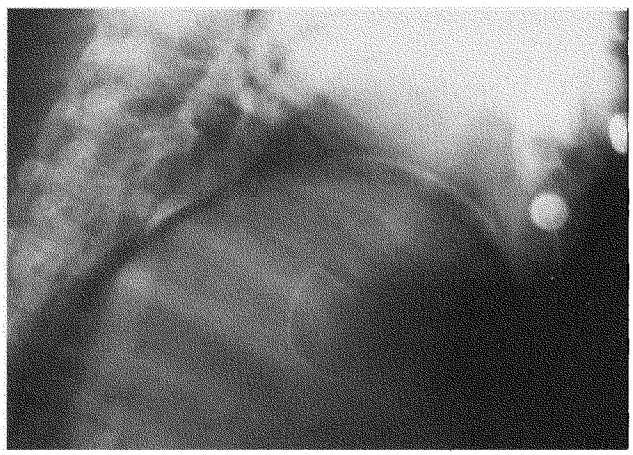

Fig. 3. Cavogram at 15 mm Hg There is an increased narrowing of the inferior vena cava at the level of the diaphragm to 0 8 cm

creased to 30 mm Hg, the diameter of the inferior vena cava at the level of the diaphragm was 0 4 cm (Fig. 4) All of the above-mentioned parameters returned to baseline values contiguously after IAP was released

Effects of IAP and Positioning on $PaCO_2$

Means and standard deviation are depicted in Table IV. Two independent variables, IAP and positioning, were tested in the models. The results showed that increased IAP or positioning did not significantly affect the $PaCO_2$ There was an increase in $PaCO_2$ as IAP with a CO_2 pneumoperitoneum was increased

DISCUSSION

In recent years numerous investigators have reported in both animal and human studies that an increase in IAP produces an increase in ICP[8-10,13] Most authors attributed these changes to a mechanical effect on the large vessels of the abdomen and lumbar plexus Our group performed a large animal model experiment showing a significant and immediate linear increase in ICP at all levels of IAP The Trendelenburg position further increased the ICP Although there was a parallel increase in MBP, the CPP remained above critical levels throughout the experiment [10] As in other studies,[8-10] we could demonstrate that there is an immediate effect from changes in IAP on ICP The fact that the rise in ICP was immediate and that in our study the $PaCO_2$ was maintained below 40 mm Hg negates the possibility that the fluctuation in $PaCO_2$ alone was responsible for this increase in ICP.

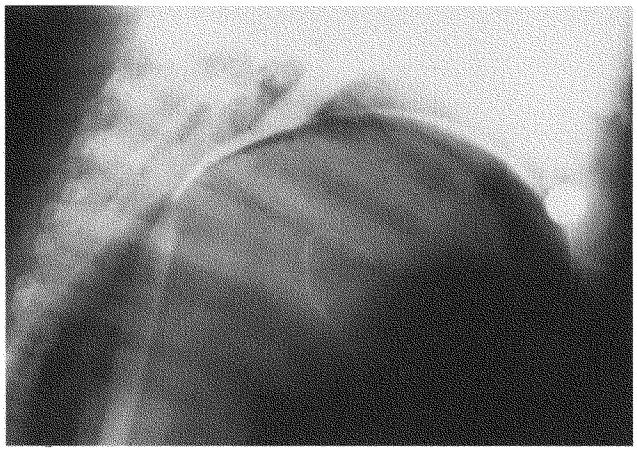

Fig. 4. Cavogram at 30 mm Hg The narrowing of the inferior vena cava at the level of the diaphragm becomes most exaggerated to 0 4 cm

It has been demonstrated that it takes at least 10 to 15 minutes for the $PaCO_2$ to rise after a pneumoperitoneum has been established.[14] In a recent publication Schob et al.[15] demonstrated in a swine model that establishment of a pneumoperitoneum with nitrous oxide or helium produced a lesser increase in ICP than with CO_2 However, the fact that all three gases increased the ICP supports our mechanical theory that not only the arterial cerebral vasodilatation produced by hypercarbia will increase ICP

To better understand the effects of increased IAP on the central nervous system, we postulated that the increase in ICP is mediated by two mechanisms. The first is a passive, early, mechanical, or venous effect seen in the abdominal compartment syndrome and with creation of a pneumoperitoneum with or without CO_2 for laparoscopic procedures The second is an active, late, arterial, or chemical effect seen mainly during laparoscopic procedures using a CO_2 pneumoperitoneum and with a prolonged compartment syndrome where hypercarbia ensues as a result of compression of the lower lobes of the lungs with ventilation/perfusion mismatch It is important to distinguish between an active increase in ICP and a passive increase in ICP. The active phase is seen with cerebral vasodilatation indicating a functional autoregulation to hypercarbia. The passive increase in ICP is seen when there is venous stasis and increased venous pressure in the sagittal sinus [16] The increased venous pressure in the sagittal sinus will decrease the absorption of cerebrospinal fluid from the arachnoid villi,

Table IV. Correlation between intra-abdominal pressure and positioning in relation to $PaCO_2$

	$PaCO_2$ (mm Hg)			
	0	5	15	30
Group 1 Head up	24 7 ± 3 2	25 2 ± 3 5	30 8 ± 5 7	32 9 ± 6 9
Group 2 Supine	25 9 ± 3 8	27 7 ± 4 0	31 7 ± 6 8	33 8 ± 7 3
Group 3 Head down	25 2 ± 4 0	28 7 ± 5 7	32 4 ± 5 6	34 0 ± 6 6

NOTE All animals were hyperventilated to maintain $PaCO_2$ below 35 mm Hg
IAP = intra-abdominal pressure, $PaCO_2$ = arterial pressure of carbon dioxide
Values are mean ± standard deviation

thus causing an increase in the cerebrospinal fluid pressure [16,17] We will now describe in detail the early and late phases of the increase in ICP.

Early Stage (Venous, Mechanical, or Passive Effect). The increase in ICP during this stage has two components· an intra-abdominal effect and an intrathoracic effect In the intra-abdominal effect, the establishment of an elevated IAP (Fig. 5, *A1* and *A2*), compresses the inferior vena cava (see Fig. 5, *A3*) and produces an increase in central venous pressure (CVP) (see Fig. 5, *A4A*), which reduces venous drainage from the central nervous system and lumbar plexus (see Fig. 5, *A6* and *A7*) increasing the cerebrospinal fluid pressure. Doppman et al.,[18] showed that the increase in IAP caused by fluids or gas will produce a narrowing of the inferior vena cava at the level of the diaphragm. Rubinson et al.[19] came to similar conclusions. This caval obstruction disappeared when the IAP was released. Similar findings were described by other authors.[19-21] During pneumoperitoneum with IAPs at 5, 15, and 30 mm Hg the IVC became narrowed at the level of the diaphragm (see Figs 1 to 4). CVP monitored during acute elevations of IAP showed a simultaneous increase above and below the diaphragm (see Table I) Further variations in CVP could be observed in both regions based on animal positioning (see Table I).

The second component of the mechanical effect or intrathoracic effect causing an increase in ICP correlates with the elevation in CVP above the diaphragm (see Table I). The cranial displacement of the diaphragm (see Fig. 5, *A2*) increases intrathoracic pressure (see Fig. 5, *A3*) by reducing the intrathoracic space and compressing the right atrium. This increases the filling pressures and the CVP in the superior vena cava (see Fig 5, *A4C* and *A5*) [19,22-24] The intra-abdominal and intrathoracic components together decrease the venous drainage from the central nervous system increasing the pressure in the sagittal sinus, where the arachnoid villi empties, thereby increasing the ICP.[16,17] The increase in ICP related to the acute increase in the CVP and the cerebrospinal fluid pressure can be further explained by the Monroe-Kellie hypothesis.[25-27]

Late Stage (Active, Arterial, or Chemical Effect). In this stage the increase in ICP is mediated by hypercarbia, which results from two separate mechanisms (see Fig 5) The first mechanism relates to CO_2, which is absorbed by simple diffusion through the peritoneal membrane (see Fig. 5, *B1* and *B2*) into the preperitoneal capillary beds and cannot be removed with ventilation. This increase in $PaCO_2$ will produce a reflex arterial vasodilatation of the central nervous system vasculature (see Fig. 5, *B4* and *B5*), which increases the ICP (see Fig. 5, *A9*) [28-30]

The second mechanism that produces an increase in ICP during this stage is the cranial excursion of the diaphragm, with increases in IAP (see Fig. 5, *A2* and

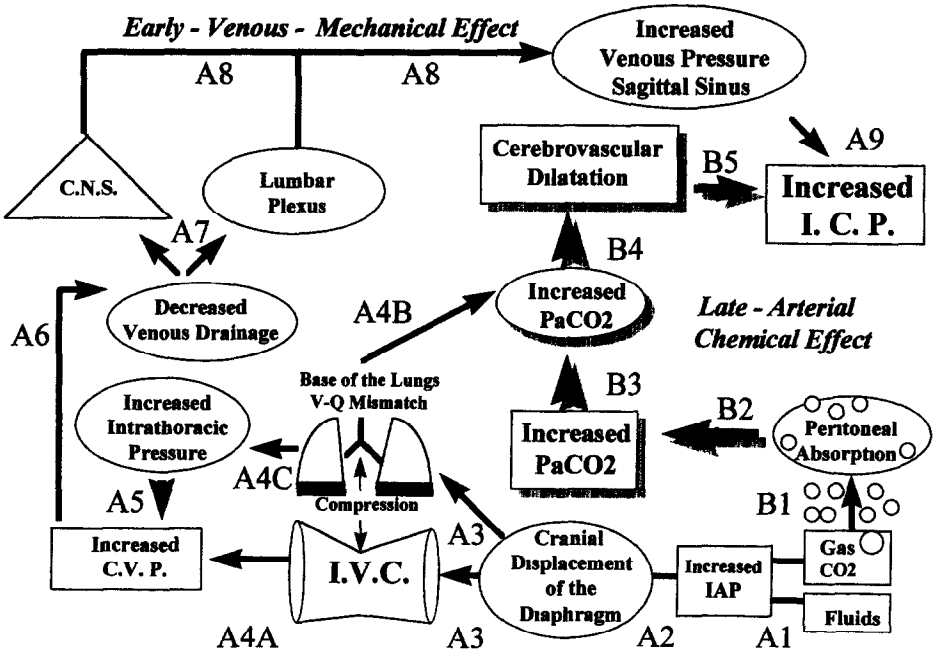

Fig. 5. Reasons for increased intracranial pressure *(ICP)* during acute elevation of intra-abdominal pressure *(IAP)* CNS = central nervous system, CVP = central venous pressure, IVC = inferior vena cava

A3) combined with Trendelenburg position that will compress the lower lobes of the lungs, thus altering the ventilation/perfusion ratio (see Fig. 5, *A4B*) This ventilation/perfusion mismatch will further increase the $PaCO_2$ (see Fig 5, *B4*). In the present study the effects of hypercarbia were antagonized by hyperventilating the animals maintaining a $PaCO_2$ below 35 mm Hg (see Table IV) However, there is sufficient evidence in the literature supporting a direct effect of an elevated $PaCO_2$ on ICP.[31-33] Recently Fuji et al [34] concluded that creation of a CO_2 pneumoperitoneum produced hypercapnia and reflex vasodilatation of the central nervous system with increased flow through the middle cerebral artery [35] Fuji et al [34] showed that cerebral blood flow increased 10 minutes after peritoneal insufflation parallel to the rise in $PaCO_2$ [36] The work of Fuji et al. gives credence to our second mechanism for increase in ICP.

The influence of positioning with regard to ICP has been widely discussed in the neurologic and neurosurgical literature, and it has been shown that the head-down position increases ICP, whereas the head-up position decreases ICP [37-40] In the present study the reverse Trendelenburg position produced a decrease in ICP at baseline levels (without increased IAP) and after a pneumoperitoneum was established when compared to the same IAP and position Elevation of the head as a common practice to decrease ICP has been discussed and is controversial because of its simultaneous risk in decreasing cerebral blood perfusion [33,37,41] However, Schneider et al [37] demonstrated that 92% of the possible effect created by the head-up position with respect to ICP was already detected at 30 degrees From the present study and Schneider's observations, it appears that a 15- to 30-degree head-up position would benefit patients with increased IAP or the potential for increased ICP.

Most of the adverse effects caused by an acute elevation in IAP are hemodynamic, cardiorespiratory, and renal, and they have been widely described in both the clinical and experimental literature [3,42-46] Diebel et al [47-49] conducted numerous large animal studies demonstrating that all splanchnic vascular beds except those of the adrenal glands showed an increased peripheral vascular resistance with decreased blood flow to the affected organs. Similar observations were made by other investigators in animal and human studies [50-55] The previously mentioned studies also found an increase in peripheral vascular resistance, CVP, and MBP as signs of a sympathetic response to increased IAP In the present study we also corroborated these findings

The response of the central nervous system to elevated ICP has been extensively documented in the neurosurgical literature of the preceding century In 1881 Naunyn[56] first described a pressor response where a mean arterial pressure was stabilized at a level above that of an elevated ICP This response was confirmed by Cushing[57] in 1901 and has since been termed the Cushing reflex. The etiology and location of the receptors initiating the Cushing reflex have been identified by Hoff and Reis[58] and are located in the lower brainstem [56,58,59] This hemodynamic response is mediated by a sympathetic stimulus.[60-65] In this study the increase in ICP originated by increased IAP showed a simultaneous increase in MBP. Multiple regression analysis showed that the changes were statistically significant and had a positive correlation

From the previously mentioned literature one can infer that all of the hemodynamic changes observed during the acute elevation of IAP combined with the acute elevation in ICP are mainly mediated by the central nervous system and not by the IAP itself.[16] The increase in ICP will result in narrowing of the cerebrovascular system and produce a stimulus to the C1 neurons of the medulla oblongata (Fig. 6, *C1* and *C2*), which releases a sympathetic response (Fig 6, *C3*) mediated by release of catecholamines and vasopressin (see Fig 6, *C4* and *C5*) [57-66] The release of these vasoactive hormones produces venous and arterial vasoconstriction with increased MBP (see Fig 6, *C6*, *C7*, and *C8*) and increased peripheral vascular resistance (see Fig 6, *C10*) to maintain adequate arterial cerebrovascular blood flow and cerebral perfusion (see Fig 6, *C8* and *C9*) [16,57-66] At the same time, the increase in peripheral vascular resistance produces splanchnic vasoconstriction mobilizing blood from the intra-abdominal organs toward the central venous system to increase preload and attempt to reopen the narrowed vena cava (see Fig 6, *C11* and *C13*)

CONCLUSIONS

We believe that the following conclusions have been demonstrated

1 The acute increase in IAP produces an acute increase in ICP without affecting the CPP
2 Two mechanisms, a mechanical effect and a chemical effect, are responsible for the increased ICP during acute elevation of IAP Positioning will further increase or buffer the elevated ICP during increased IAP
3 The increase in IAP produces a progressive diaphragmatic excursion with narrowing of the inferior vena cava and with increased intrathoracic pressures and CVPs above and below the diaphragm This results in elevation of venous pressures in the sagittal sinus that will increase cerebrospinal fluid pressures
4 The systemic hemodynamic response characterized by increased MBP observed during

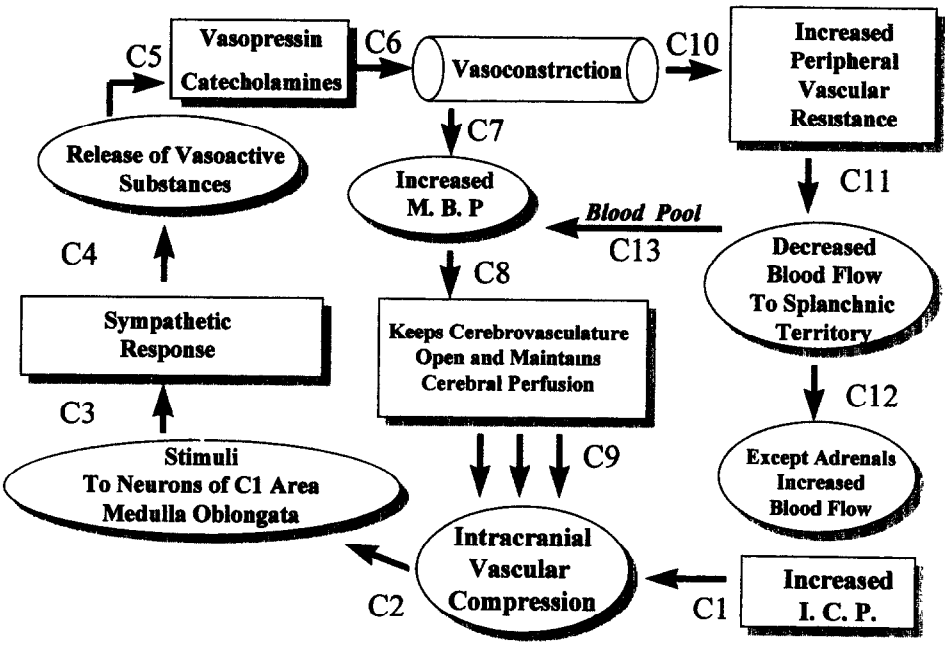

Fig. 6. Hemodynamic response to combined increased intracranial pressure *(ICP)* and intra-abdominal pressure MBP = mean blood pressure

acute elevation of IAP is a response of the central nervous system to the elevated ICP to maintain CPP.

5. Laparoscopy with a CO_2 pneumoperitoneum is contraindicated in patients with suspected or documented intracranial injuries.
6. Laparoscopic procedures with pneumoperitoneum being performed in patients with the potential for increased ICP should be carried out at low IAPs and in a 15- to 30-degree reverse Trendelenburg position to buffer the increased ICP caused by the acute elevation in IAP.

Further studies analyzing the effects of the combined increase in IAP and ICP on blood flow of intra-abdominal organs and systemic hemodynamic responses as well as the role of these pathophysiologic mechanisms in the chronic elevation of IAP are under way

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Laparoscopic/Endoscopic Repair of Rectal Stricture

Robert A Kozol, M D , Mary Ann Kosir, M D

Although uncommon, anastomotic stricture after low anterior resection may require additional repair beyond dilatation Two alternate approaches are described wherein laparoscopic and endoscopic techniques were utilized to avoid repeat pelvic surgery in two cases These can be used whether a stapled or hand-sewn approach was used for the initial anastomosis Photo documentation demonstrates a widely patent anastomosis after repair There is early return of bowel function by these methods, and long-term results (3 years) are excellent (J GASTROINTEST SURG 1998,2 426-429)

Anastomotic stricture is a recognized, infrequent complication of colonic surgery [1,2] An anastomotic stricture at the level of the rectum is often amenable to dilatation. When repeated dilatation fails, surgical repair is indicated Surgical repair through an abdominal approach (in a scarred pelvis) can be a formidable procedure Several novel methods have been reported to facilitate repair of strictures without takedown of the anastomosis [3-6] This report describes two additional innovative approaches using laparoscopic/endoscopic methods to repair a rectal anastomotic stricture that had failed dilatation therapy

CASE REPORTS

Case 1

A 64-year-old man underwent a stapled low anterior resection for a Dukes' B adenocarcinoma of the rectum The patient recovered nicely after surgery Follow-up colonoscopy revealed an anastomotic stricture 1 year postoperatively Biopsy of the stricture showed no evidence of recurrent carcinoma The patient developed constipation and thin-caliber stools 2 years postoperatively Colonoscopic examination at the time revealed a stricture that would not permit insertion of a standard colonoscope (Fig 1) The patient underwent endoscopic dilatation of this stricture on four occasions over a 14-month period Balloon dilatation was unsuccessful, but the stricture could be dilated with the obturator of a rigid sigmoidoscope under direct vision via an adjacent flexible scope in the rectum The patient remained symptomatic and surgical repair of the stricture was undertaken using a laparoscopic approach The transverse colon was identified A 4 cm upper abdominal incision was made and a loop of transverse colon was delivered through the abdominal wall A transverse colotomy was performed and the anvil of an end-to-end stapling instrument was delivered into the colon A colonoscope was advanced transanally past the stricture into the transverse colon A silk suture previously tied to the anvil was grasped with a snare and the anvil was pulled down the colon to the stricture (Fig 2, *A*) The shaft of the 31 mm stapler was then passed transanally, joined with the anvil by having the surgeon hold the anvil with fingers in the rectum, and the stapler was fired across the stricture (Fig 2, *B*) The circular stapler had cut out the stricture resulting in a new enlarged anastomotic lumen The transverse colotomy was closed as was the 4 cm incision

The patient had a bowel movement on postoperative day 2 He began a liquid diet on postoperative day 3 and was discharged on postoperative day 5 He is currently asymptomatic Repeat colonoscopy at 1 and 3 years revealed no recurrent stricture (Fig 3)

Case 2

A 74-year-old man underwent a low anterior resection for a large (5 cm) tubulovillous adenoma with atypia in the rectum The specimen showed a 4 5 cm well-differentiated adenocarcinoma arising in the tubulovillous adenoma and focal invasion of the submucosa A double-stapling technique was used with a linear stapler and circular stapling device His postoperative recovery was unremarkable No radiation or chemotherapy was given postoperatively He was seen for follow-up endoscopy at 6 months when a stricture was noted 7 cm proximal to the anal verge (Fig 4, *A*) Biopsies of the stricture revealed focal areas of granulation tissue and mild chronic inflammation The patient had symptoms of constipation 5 to 6 months postoperatively, at which time a barium enema showed stricture Under gen-

From the Surgical Service, VA Medical Center, and Wayne State University School of Medicine, Detroit, Mich
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Reprint requests Robert A Kozol, M D , VA Medical Center (112), 4646 John R, Detroit, MI 48201

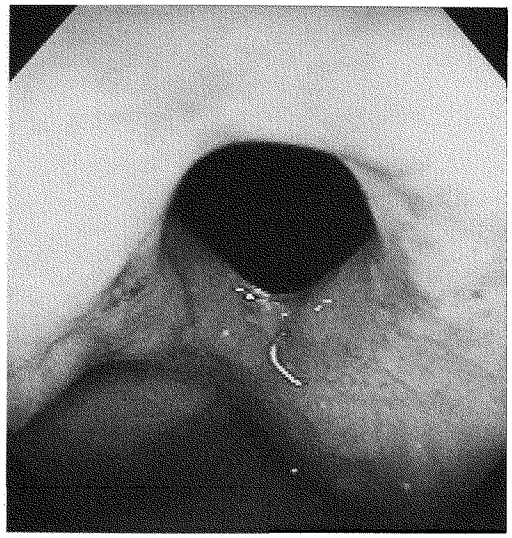

Fig. 1. Tight fibrotic stricture (case 1)

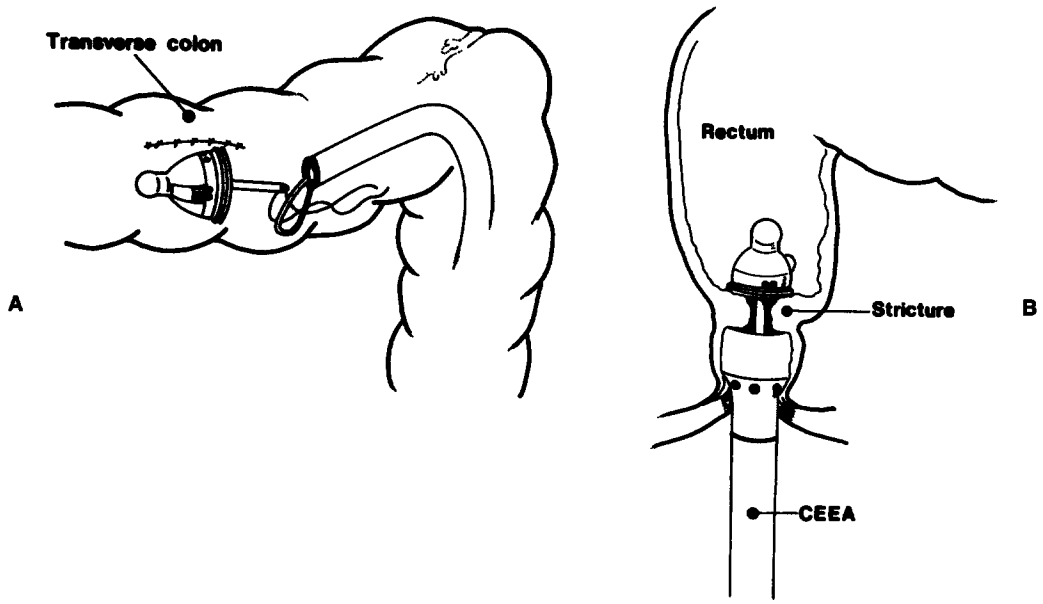

Fig. 2. A, Schematic drawing of the snared stapling anvil within the colon **B,** Schematic drawing of the circular stapler in place over the stricture CEEA = circular end-to-end anastomotic instrument

eral anesthesia with the patient in the lithotomy position, the area of the stricture was dilated with the obturator of a rigid sigmoidoscope to admit a colonoscope, which was inserted to the midtransverse colon A 4 cm midline incision was made over the point of transillumination of the anterior abdominal wall The anvil of a 31 mm EEA stapler was inserted through a transverse colotomy with a silk tie in place on the anvil rod The anvil was directed distally and the colotomy as well as the abdominal incision was closed The silk suture on the anvil was grasped with a snare and pulled to the area of the stricture by the colonoscope By holding the anvil with the fingers of the left hand (within the rectum), the EEA stapler was introduced into the rectum and attached The EEA stapler was fired and a crescent-shaped piece of the rectal stricture was excised Colonoscopic examination verified that the colon was intact and hemostatic. An enlarged anastomosis was confirmed (Fig 4, *B*) Within 2 days the patient was passing flatus, had a small bowel movement, and was tolerating a liquid diet He is without symptoms at 3 months

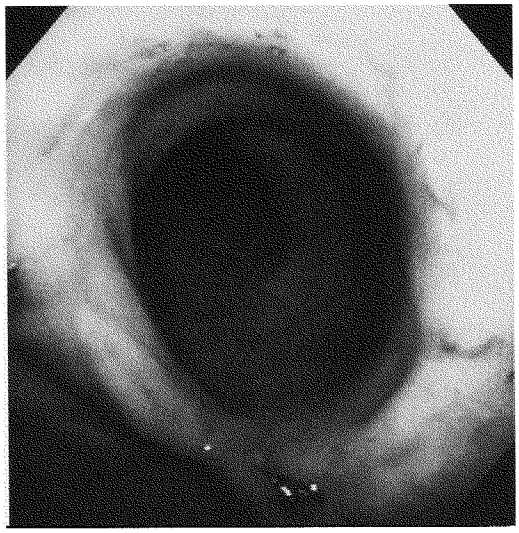

Fig. 3. Postoperative view of the new anastomotic lumen (case 1)

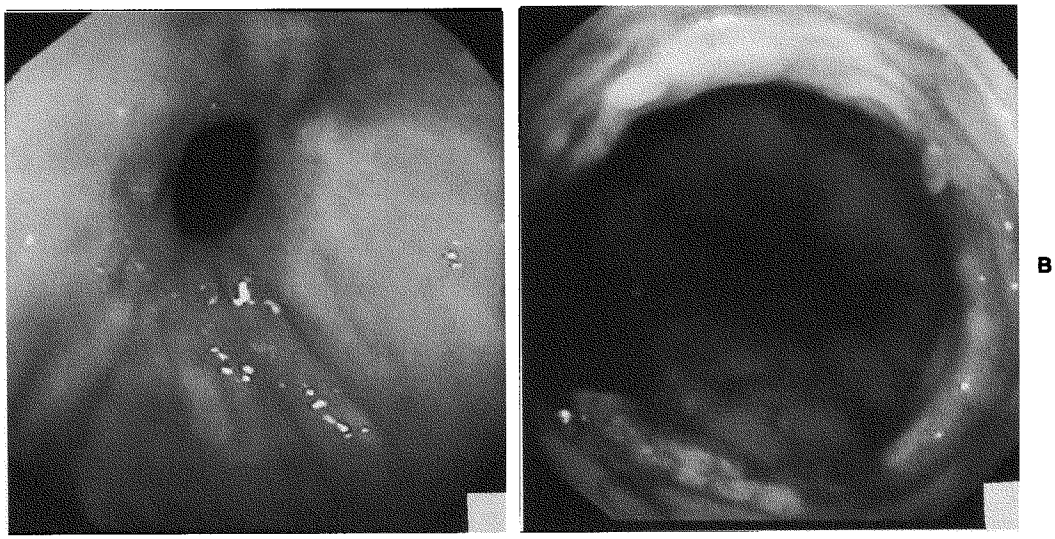

Fig. 4. A, Stenosis of low rectal anastomosis before repair (case 2) **B,** Widely patent low rectal anastomosis after resection of stricture by EEA (case 2)

DISCUSSION

The development of the end-to-end intestinal stapler allows another approach to complete resections of very low-lying rectal carcinomas with reestablishment of colonic continuity Overall, colorectal anastomoses are associated with a stricture rate reported to range from 1% to 16% [1,2,7,8] With dilatation, most patients require repeated therapy and some strictures become tighter over time

The technique of combined laparoscopic/endoscopic repair as described in this report has several advantages over formal open anastomotic revision These include avoidance of a large abdominal incision, avoidance of pelvic dissection, and possibly a shorter hospital stay with less postoperative ileus If the transverse colon allows transillumination of the abdominal wall, this identifies the location for a 4 cm incision (thus precluding the need for laparoscopy) If transillumination is unsuccessful, then laparoscopy allows identification of the transverse colon and the sight for the small incision There are other methods described in the literature for avoiding pelvic dissection in the treatment of anastomotic stricture Shimada et al [6] described a staple-cutting device that can

be used repeatedly as restricturing occurs, although the device may not yet be commercially available These methods are similar in concept to previously reported methods of restapling the anastomotic strictures using end-to-end stapling devices or an Endo-GIA stapler [2-5] However, our technique offers an approach for cases where the stricture is too tight for passage of an end-to-end stapler In fact, one could argue that a stricture which is amenable to dilatation to stapler size does not need revision at all. For those strictures that require revision, these laparoscopic/endoscopic approaches offer good alternatives to repeat pelvic surgery

CONCLUSION

Two laparoscopic/endoscopic methods are described for repair of symptomatic rectal anastomotic stricture, which offer the advantage of avoiding open pelvic dissection. These will offer the surgeon additional approaches to the uncommon problem of anastomotic stricture, whether by stapled or hand-sewn technique.

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Hepatic Kupffer Cell Blockade Reduces Mortality of Acute Hemorrhagic Pancreatitis in Mice

Beat Gloor, M D , Karen E Todd, M D , John S Lane, M.D ,
Michael PN Lewis, FR C S , Howard A Reber, M D

Inflammatory cytokines derived from the liver may cause distant organ failure and death in severe pancreatitis To minimize liver cytokine release, we studied the effects of Kupffer cell blockade on the mortality rate and severity of inflammation in a model of that disease Thirty mice were divided into three groups Group 1 received gadolinium chloride (1 mg/100 g intravenously), which blocks Kupffer cell activity, and regular food Groups 2 and 3 were fed a choline-deficient, ethionine-supplemented diet and developed severe pancreatitis Group 2 (control) received intravenous saline solution, and group 3 received gadolinium chloride Animals were killed at 72 hours Serum levels of tumor necrosis factor-α and interleukin-1β, interleukin-6, and interleukin-10 were determined by enzyme-linked immunosorbent assay Lung neutrophil infiltration was assessed by myeloperoxidase assay Pancreatic inflammation was scored in a blinded manner In a separate experiment, mortality rates were determined in saline- and gadolinium-treated animals (n = 100) Gadolinium reduced the levels of all the cytokines and lung myeloperoxidase ($P < 0.05$) Gadolinium also reduced the mortality rate (52% vs 86%, $P < 0.001$) However, the degree of pancreatic inflammation was unchanged by gadolinium treatment These data support the hypothesis that mortality in severe pancreatitis may in part be related to the secondary release of hepatic cytokines (J GASTROINTEST SURG 1998,2 430-435)

Acute pancreatitis is a serious disease, the causes of which remain obscure. The overall mortality rate is approximately 10%, but in its most severe form 20% to 30% of patients die The cause of death in most of these patients is not related specifically to the pancreatic inflammation, or even to pancreatic infection Rather, death is often the result of multiorgan system failure, which appears to be the same as the organ failure seen in other seemingly unrelated conditions (e g , sepsis, major trauma, burns) The processes that influence the degree of local pancreatic inflammation as well as the spread of inflammation to involve distant organ systems is unclear, but evidence suggests that activated pancreatic macrophages may release inflammatory cytokines (e.g , interleukin [IL]-1, IL-6, and tumor necrosis factor-alpha [TNF-α]) as a response to the local tissue damage These cytokines would be expected to act locally to aggravate the pancreatitis, and could act systemically to increase capillary permeability, and promote leukocyte adherence and extravasation, which could lead to organ dysfunction Thus the local response could produce far-reaching effects throughout the body

In pancreatitis the release of endogenous inflammatory mediators from the inflamed pancreas is a very early event The serum levels of these cytokines correlate well with the degree of pancreatic inflammation, and their source was assumed to be the inflamed pancreas We suggest that the liver may be the principal source of the systemic cytokine elevation that is characteristic of severe pancreatitis

In this study we tested that hypothesis We examined the effects of selective hepatic Kupffer cell inactivation on systemic cytokine levels, local pancreatic inflammation, and mortality rate in an animal model of the disease

From the Departments of Surgery, Sepulveda VA Medical Center and UCLA School of Medicine, Los Angeles, Calif
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Reprint requests Howard A Reber, M D , Division of General Surgery, UCLA School of Medicine, 10833 Le Conte Ave , Los Angeles, CA 90095

MATERIAL AND METHODS

Animal Model

All experiments were conducted with the prior approval of the Animal Research Committee at Sepulveda Veterans Administration Medical Center (VAMC), Sepulveda, California. Animals were cared for in accordance with treatment guidelines established by the VAMC Office of Research and Development. Female Swiss-Webster mice (Simonsen Laboratories, Gilroy, Calif.) weighing 22 ± 1 g were used. Animals were allowed to acclimatize for a minimum of 1 week Acute hemorrhagic pancreatitis was induced by feeding the mice a choline-deficient diet (Harlan Teklad, Madison, Wis.), supplemented with 0 5% DL-ethionine (Sigma Chemical Co , St. Louis, Mo) (CDE diet) for 72 hours The CDE diet was replaced every 6 hours to ensure its constant availability. Mice had free access to water at all times Gadolinium chloride (Sigma Chemical Co) (1 mg/100 g of body weight) or saline solution was injected into the tail vein at the start of the study and again after 36 hours in both experiments.

Experiment 1

Mice were randomly divided into three groups. Group 1 (control, n = 6) received gadolinium chloride (1 mg/100 g intravenously) and regular chow. Groups 2 and 3 (n = 12 each) were fed a CDE diet for 72 hours. Group 2 received intravenous saline solution, and group 3 received gadolinium. After 72 hours, following anesthesia with sodium pentobarbital (50 mg/kg intraperitoneally), mice were killed by exsanguination Blood samples from the inferior vena cava were collected in heparinized tubes (Becton Dickinson, Franklin Lakes, N J) containing aprotinin (0 009 trypsin inhibitory units/ml of blood). Blood was centrifuged at 5000 rpm for 10 minutes. The serum was separated and stored at −80° C. Lung and pancreatic tissue samples were taken and immediately further processed or snap-frozen in liquid nitrogen and stored at −80° C. Serum TNF-α and IL-1β, IL-6, and IL-10 were measured by means of an enzyme-linked immunosorbent assay technique using commercially available kits for mouse cytokines (Genzyme, Cambridge, Mass.). Serum amylase levels were determined spectrophotometrically at 37° C using an enzymatic assay kit (Sigma Chemical Co). All assays were run in duplicate

Neutrophil infiltration in the lung was determined by myeloperoxidase (MPO) assay using a modification of the technique of Andrews and Krinsky.[1] Fresh lung tissue was obtained, immediately washed in saline solution, weighed, and immersed in 4 ml of ice-cold hexadecyltrimethylammonium-bromide buffer (0.5% in 50 mmol/L phosphate buffer at pH 6 0). Hexadecyltrimethylammonium-bromide is a detergent that releases MPO from the granules of the neutrophils.[2,3] The tissue was then homogenized for 30 seconds. The samples were transferred to standard 5 ml polyethylene tubes and centrifuged at 3000 rpm at 4° C for 10 minutes to remove cellular debris. The subsequent supernate was saved for further assay MPO activity was determined spectrophotometrically at 650 nm (Beckman Instruments, Inc , Fullerton, Calif.) by incubating 50 μl of the supernate with 1 ml of a 1 76 mmol/L tetramethylbenzidine solution and 1 ml of 10 mmol/L hydrogen peroxide dissolved in potassium acetate at pH 5 6 The change in absorbance with time was then recorded and MPO activity was calculated by dividing the change of absorption through the tissue weight. Hexadecyltrimethylammonium-bromide, phosphate buffer, 3,3′,5,5′-tetramethylbenzidine, hydrogen peroxide, and potassium acetate were all obtained from Sigma Chemical Company

Pancreatic sections were stained with hematoxylin and eosin and graded in a blinded manner by two observers using a scale of 0 to 4. The degree of edema, inflammation, hemorrhage, and necrosis were each evaluated (score of 0 to 16; normal to most abnormal). This technique was previously validated and described in detail [4]

Experiment 2

In a separate study, 100 mice were randomly divided into two groups (50 each) and fed the CDE diet Group 1 received intravenous injections of saline solution, group 2 received gadolinium chloride at the beginning of the diet and again after 36 hours After 72 hours the CDE diet was replaced with regular chow. The mortality rate was determined for each group every 6 hours for 10 days.

Statistical Analysis

Serum cytokine levels are expressed as means ± standard error of the mean and were compared using the analysis of variance test Histologic grading was analyzed with the Mann-Whitney U test. Survival analysis included the Kaplan-Meier curve, the log-rank test, and the chi-square test. P values <0 05 were considered significant

RESULTS

Experiment 1

Serum cytokine levels for animals in groups 1, 2, and 3 are shown in Table I. The mean serum levels of

Table I. Serum cytokine levels (mean ± standard deviation) in control animals (group 1), in CDE diet and saline-injected animals (group 2), and in CDE diet and gadolinium-injected animals (group 3)

Cytokines (detection limit*)	Group 1	Group 2 (saline)	Group 3 (gadolinium)
TNF-α (15 pg/ml)	14 6 ± 2	605 ± 188	361 ± 86†
IL-1β (10 pg/ml)	10 ± 6 7	1159 ± 209	592 ± 112†
IL-6 (5 pg/ml)	43 ± 8 3	794 ± 351	481 ± 231†
IL-10 (15 pg/ml)	58 ± 18	1423 ± 1203	597 ± 424

*The detection limit is determined after statistical analysis of enzyme-linked immunosorbent assay results The mean absorbance with the value indicated as detection limit was greater than two standard deviations above the mean baseline absorbance obtained from replicate zero control wells (i e , wells containing all assay components except cytokine standard)
†P <0 05 vs group 2 and P <0 0001 vs group 1

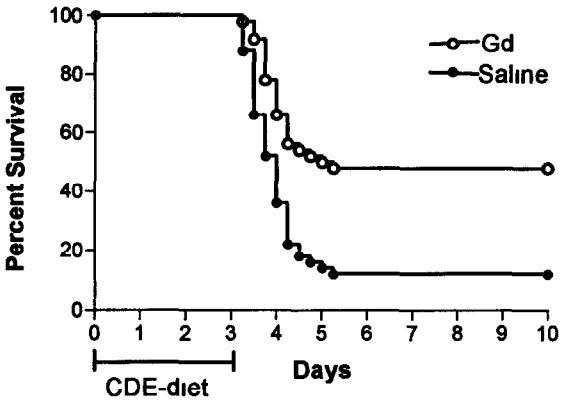

Fig. 1. Ten-day cumulative survival in mice after severe hemorrhagic pancreatitis (CDE diet for 72 hours) Intravenous gadolinium chloride *(Gd)* injections vs saline injections After 10 days, 86% of the control animals were dead compared to 52% of the gadolinium-treated animals (P <0 001)

TNF-α and IL-1β, IL-6, and IL-10 in the gadolinium-treated mice were all lower than the values in the animals that received saline solution (P <0 05)

The CDE diet–induced pancreatitis increased the lung MPO content This increase was attenuated by treatment with gadolinium (1 678 ± 0 226 U/g in group 2 vs 0 953 ± 0 114 U/g in group 3, P <0 01)

As expected, serum amylase levels increased in animals with pancreatitis (P <0 0001). Gadolinium treatment had no effect on this (23,090 ± 2380 U/L in group 2 vs 20,930 ± 1577 U/L in group 3, P = 0 39)

Significant pancreatic injury (edema, inflammation, hemorrhage, and necrosis) was seen in all animals with pancreatitis. The extent of this local response was unaffected by treatment with gadolinium The inflammatory scores were 9 8 ± 1 7 for group 2 animals vs 10 5 ± 1 4 for group 3 (P = 0 47).

Experiment 2

Consumption of the CDE diet for 72 hours resulted in a 10-day mortality rate of 86% in control animals that received saline solution (group 2). In the group 3 animals that received the gadolinium, the mortality rate was 52% (P <0 001) (Fig 1)

DISCUSSION

The CDE diet model of acute pancreatitis reproduces some of the morphologic and physiologic changes of the most severe form of the human disease, and it has been widely used [5,6] One advantage of the model is that the severity of the pancreatic inflammation, the systemic response, and the mortality rate can be modified somewhat by limiting the period of exposure to the diet [7] The animals in the present study were fed the diet for 72 hours This avoided a uniformly fatal outcome in the animals and allowed a significant effect of gadolinium treatment to be demonstrated [4,8] The fact that the relevance of the model to human pancreatitis is unclear is a potential disadvantage For that reason it would be important to repeat these experiments in other models as well

There was no evidence that the gadolinium treatment itself affected the well-being of the animals The mice in group 1, which received gadolinium and a normal diet, appeared well and ate all of their chow Most important, there was no difference in the amount of the CDE diet consumed by groups 2 and 3

The mechanism of action of the gadolinium has been investigated by others The compound is taken up highly selectively by the Kupffer cells, where it profoundly depresses their phagocytic activity and eventually kills the cells [9-12] The result is a near-total inhibition of the usual hepatic response to a variety of toxins and noxious substances [13,14] For example, the liver normally responds rapidly to the portal venous infusion of endotoxin by releasing TNF-α and IL-6, both of which are proinflammatory cytokines Evi-

dence that the Kupffer cells are the origin of these substances includes the facts that messenger RNA for both TNF-α and IL-6 is upregulated in these cells after endotoxin exposure and that gadolinium pretreatment prevents that upregulation in Kupffer cells along with the hepatic release of the cytokines [15,16] Because the Kupffer cell population is replenished within 3 to 4 days, we repeated the gadolinium treatment after 36 hours. This ensured that Kupffer cell activity was minimal for the entire 72-hour period of the CDE exposure. In addition to the well-documented effect of gadolinium on Kupffer cells, Naito et al [17] recently investigated the toxicity of several substances on macrophages. Of interest for our study is the fact that gadolinium was not cytotoxic to murine peritoneal macrophages As a result of all these data, gadolinium appears to be highly specific with respect to the Kupffer cells, with only minor or no effect on peritoneal macrophages or other cells within the portal system

There was a mortality rate of 52% in the gadolinium-treated mice, and serum cytokine levels were markedly elevated in this group as compared to the control group Our study did not investigate the origin of these cytokines There are several possible explanations for this finding and they all seem to contribute to the systemically measured cytokines Cytokines released from the local inflammatory response can reach the systemic circulation through the abdominal lymphatic vessels via the thoracic duct Cytokines are not only released from Kupffer cells but also from the pancreas or from other sites (i.e., peritoneal macrophages, monocytes, or enterocytes) within the abdominal cavity. Saad et al.[18] reported that after lipopolysaccharide stimulation, hepatocytes, in addition to Kupffer cells, have the ability to produce TNF-α and IL-6.

We have stressed that gadolinium treatment affected the function of the hepatic Kupffer cells and concentrated on the role of the liver in this disease Indeed there is a large body of literature that supports this Nevertheless, it is important to point out that there also may have been an effect of gadolinium treatment on pulmonary macrophage function. Data in the literature concerning this topic are sparse and conflicting Bannenberg et al [19] studied the effects of gadolinium treatment in rats on pulmonary macrophage function They measured phagocytosis and nitroblue tetrazolium reduction by alveolar and interstitial macrophages At the same dose that we used (10 mg/kg intravenously, 48 hours before study), no effect on pulmonary macrophages was observed. On the other hand, Pendino et al [20] pretreated rats with gadolinium (7 mg/kg intravenously) and found that this decreased nitric oxide production by pulmonary macrophages Thus the question remains unresolved, and the possibility of an additional effect of gadolinium on pulmonary macrophage function remains

As has been noted earlier, many of the clinical manifestations of acute necrotizing pancreatitis can be attributed to the high systemic levels of a variety of inflammatory mediators including cytokines (e.g , IL-1α and β, IL-6, IL-8, IL-12, and TNF-α) [21] These are produced by a growing list of different cells but principally by monocytes and macrophages, activated lymphocytes, and endothelial cells.[22] The presumed purpose of these mediators is to limit the extent of the local tissue damage. However, it has also become clear that when these substances are released from leukocytes in the pancreatic and peripancreatic tissue, they may play an important role in the determination of the local severity and progression of the disease. If they continue to be elaborated in greater amounts or for longer periods than is considered appropriate, tissue destruction can be enhanced.[21] Indeed we and others have shown recently that the local severity of the pancreatic inflammation can be ameliorated by modification of cytokine activity. Thus administration of IL-10, an anti-inflammatory cytokine, improved the severity of pancreatitis in mice and rats [4,23] Pretreatment with an anti–TNF-α antibody attenuated the expected increase in serum TNF-α levels in rats [24] Blockade of the cytokine cascade at the level of the IL-1 receptor before or soon after induction of pancreatitis attenuated the rise of IL-6 and TNF-α levels and reduced intrinsic pancreatic damage in mice.[25]

The preceding studies focused on the local pancreatic damage and the intrapancreatic production of the cytokines Although systemic cytokine levels often were measured and their importance in regard to distant organ dysfunction was recognized, their source was generally assumed to be the inflamed pancreas.[25] In the present study we have stressed the role of the liver in the release of cytokines during acute pancreatitis There are several reasons for this It is known that inflammatory cytokines, pancreatic enzymes, endotoxin, and a variety of poorly defined inflammatory mediators are released from the pancreas into the portal venous circulation during an episode of acute pancreatitis, where they enter the liver directly The concentration and amounts released are probably a function of the local severity of the pancreatitis.[26] Hepatic Kupffer cells, which represent the largest concentration of fixed tissue macrophages in the body, respond to a variety of substances that reach them via the portal circulation These include ethanol, endotoxin, TNF-α, and other inflammatory cytokines Kupffer cell gene expression (messenger RNA) of TNF-α, IL-6, and transforming growth factor β1 were all found to be elevated after ethanol infusion So too was the

hepatic Kupffer cell release of these three cytokines [10,15,16,27]

A recent report by Closa et al.[28] is consistent with our observations and strengthens our hypothesis about the role of the liver These investigators induced hemorrhagic pancreatitis in two groups of rats by retrograde injection of bile salt into the pancreatic duct. One group had no other intervention, the other underwent portacaval shunt placement before the pancreatitis was created. Rats with shunts had minimal pulmonary damage, those with the portal circulation intact developed significant lung injury The authors concluded that the lung changes were "related to the passage through the liver of substances released from the damaged pancreas " They did not pursue the possibility that cytokines derived from the liver might be involved In our view this was the primary mechanism of pulmonary injury In their model it was interesting that the inflammatory cytokines derived from the inflamed pancreas that were diverted into the systemic circulation had little deleterious effect on the lungs This may be due to the quantity of these substances that perfused the pulmonary circulation, which would be expected to be less than those derived from the liver, or the cytokines themselves could be different.

We found that Kupffer cell blockade lowered serum cytokine levels of both proinflammatory (IL-1β, IL-6, and TNF-α) and anti-inflammatory (IL-10) cytokines Indeed the serum concentration of IL-10 fell by more than 50% in the treated group Since the systemic administration of IL-10 recently has been shown to reduce the severity of inflammation and the mortality rate in different animal models of pancreatitis, this may seem to be a reason for concern [4,8,23] Presumably the overall salutary effect of treatment reflected the primary importance of the lowering of the proinflammatory cytokines in this model

The absence of any effect of Kupffer cell blockade on either the serum amylase levels or the degree of pancreatic inflammation is an important observation It suggests that the mortality rate in severe pancreatitis can be improved by interventions that are not directed at efforts to improve the local severity of the pancreatitis, which has been the customary goal Perhaps a more productive clinical approach would be to attempt to modify the secondary responses that influence survival, as we did in these experiments

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Discussion

Dr. E. Bradley (Buffalo, N Y) The search for the pathogenesis of acute pancreatitis is replete with false passages and disappointments This study seems to offer some real substance The first question deals with your concentration on the fixed macrophages There are some inferential data in your study to suggest the relative importance of the fixed macrophages vs the circulating type I noticed a 50% reduction in cytokines so you would have to make an assumption that the gadolinium only blocked 50% of the Kupffer cells, or perhaps the wandering macrophages might also be important The second point is of some therapeutic interest Would you care to speculate on the signal for cytokine released from the Kupffer cells? It is that area that I think would be most amenable to blockade rather than an "across-the-board" cytokine blockade, which has not worked in other experimental preparations

Dr. B. Gloor. First, to the role of fixed tissue macrophages and the other macrophages, or let us say other sources of cytokines Yes, there are other sources and the method of the gadolinium blockade has been used by many others With the two injections, as we conducted our experiments, we can expect that the Kupffer cells have been knocked out to a greater degree than just 50% So there must be other sources as well for the cytokines that we measured in the gadolinium-treated group With respect to your second question, for the additional cytokine release, there are mediators We do not know exactly which they are in acute pancreatitis, but we know from other studies that, for example, endotoxins or TNF-α in the portal venous blood causes cytokine release from hepatic macrophages So we think that these substances or other similar ones are responsible for the release of cytokines from the liver

Dr. C. Baker (Chapel Hill, N C) We have had similar results in a femur fracture in terms of Kupffer cell activation Have you looked at the cellular paracrine effects of cytokine release in the liver itself? Also, given your focus on the MPO model in the lung, have you looked at IL-8 release?

Dr. Gloor. We have not yet studied either paracrine effects of cytokine release or IL-8 release

Dr. M. Korc (Irvine, Calif) This is potentially a very important study Have you studied other animal models of acute pancreatitis? Is it possible that the CDE diet somehow damages the Kupffer cells?

Dr. Gloor. The CDE model has been widely used by many others We do believe that the gadolinium damages the Kupffer cells

Dr. Korc. Did you actually measure the cytokine levels in hepatic outflow? It was not clear to me from your previous answer that it is coming from the liver

Dr. Gloor. They are systemic serum levels measured in the vena cava

Dr. M. Steer (Boston, Mass) This is an interesting model of pancreatitis that was developed initially as a way of inducing liver cancer, so it is a hepatotoxin It is a "tricky" model We have learned some of the pitfalls, the biggest of which are that the severity and all of the complications of the pancreatitis are directly related to the amount of the diet that is consumed by the mouse, so it becomes critical to be absolutely certain that the gadolinium-fed mice, or injected mice, actually eat the same amount of the diet as the saline-treated control mice

Dr. Gloor. I agree with your comment regarding the CDE model and that it is important to check the amount of food that has been consumed We determined that all animals in all groups ate the same amount of food

Are Vitamin B_{12} and Folate Deficiency Clinically Important After Roux-en-Y Gastric Bypass?

R E Brolin, M D, J H Gorman, M D, R C Gorman, M D, A J Petschenik, M D, L J Bradley, M S, R D, H A Kenler, Ph D, R P Cody, Ph D

Although iron, vitamin B_{12}, and folate deficiency have been well documented after gastric bypass operations performed for morbid obesity, there is surprisingly little information on either the natural course or the treatment of these deficiencies in Roux-en-Y gastric bypass (RYGB) patients During a 10-year period, a complete blood count and serum levels of iron, total iron-binding capacity, vitamin B_{12}, and folate were obtained in 348 patients preoperatively and postoperatively at 6-month intervals for the first 2 years, then annually thereafter The principal objectives of this study were to determine how readily patients who developed metabolic deficiencies after Roux-en-Y gastric bypass responded to postoperative supplements of the deficient micronutrient and to learn whether the risk of developing these deficiencies decreases over time Hemoglobin and hematocrit levels were significantly decreased at all postoperative intervals in comparison to preoperative values Moreover, at each successive interval through 5 years, hemoglobin and hematocrit were decreased significantly compared to the preceding interval Folate levels were significantly increased compared to preoperative levels at all time intervals Iron and vitamin B_{12} levels were lower than preoperative measurements and remained relatively stable postoperatively Half of the low hemoglobin levels were not associated with iron deficiency Taking multivitamin supplements resulted in a lower incidence of folate deficiency but did not prevent iron or vitamin B_{12} deficiency Oral supplementation of iron and vitamin B_{12} corrected deficiencies in 43% and 81% of cases, respectively Folate deficiency was almost always corrected with multivitamins alone No patient had symptoms that could be attributed to either vitamin B_{12} or folate deficiency Conversely, many patients had symptoms of iron deficiency and anemia Lack of symptoms of vitamin B_{12} and folate deficiency suggests that these deficiencies are not clinically important after RYGB Conversely, iron deficiency and anemia are potentially serious problems after RYGB, particularly in younger women Hence we recommend prophylactic oral iron supplements to premenopausal women who undergo RYGB (J GASTROINTEST SURG 1998,2 436-442)

Patients who undergo Roux-en-Y gastric bypass (RYGB) for treatment of morbid obesity are prone to deficiencies in iron, vitamin B_{12}, and folate [1-5] Although prophylactic multivitamin (MVI) supplements are routinely prescribed for RYGB patients, there are virtually no data in the medical literature demonstrating the efficacy of oral MVI supplements in prevention of either iron or vitamin B_{12} deficiency after RYGB. There is also a paucity of longitudinal data on the clinical consequences of metabolic deficiencies after RYGB The primary goals of this study were to determine how readily patients with these deficiencies responded to postoperative supplementation of the deficient micronutrient and to learn whether the risk of developing these deficiencies decreases over time, which would suggest that the nonexcluded bowel eventually becomes more efficient in absorption of these substances A secondary goal was to utilize this information to make recommendations for prophylaxis and treatment of the common metabolic sequelae of RYGB.

PATIENTS AND METHODS

We have followed several hematologic parameters in 348 patients who underwent RYGB during a 10-

From the Departments of Surgery (R E B, A J P, L J B, and H A.K.) and Environmental and Community Medicine (R P C), University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, N J, and the Department of Surgery (J H G and R C G), University of Pennsylvania, Philadelphia, Pa
Reprint requests Robert E Brolin, M D, UMDNJ-Robert Wood Johnson Medical School, CN 19, New Brunswick, NJ 08903

year period including 321 patients who had a primary RYGB and 27 (7.7%) who had revision procedures. Our RYGB incorporated an upper pouch with a capacity of 30 ml or less with Roux limbs ranging from 50 to 150 cm in length Limb length in this range does not affect the incidence of post-RYGB metabolic deficiencies [6] A complete blood count and serum levels of iron, total iron-binding capacity, vitamin B_{12}, and folate were obtained in each patient preoperatively. Postoperatively these tests were performed at 6-month intervals during the first 2 years and annually thereafter. Nearly all of these tests were performed in the laboratory at Robert Wood Johnson University Hospital, New Brunswick, New Jersey Postoperative follow-up and dietary counseling were carried out according to our usual protocol for patients who undergo RYGB at our institution All patients were told to take a liquid or chewable MVI supplement daily during the first month. Most patients switched to a solid MVI supplement with minerals at 4 weeks postoperatively when the transition from pureed to solid food was completed.

Postoperative deficiencies were defined according to the following parameters iron deficiency by serum levels below 45 μg/dl (normal = 45 to 135 μg/dl), vitamin B_{12} deficiency by serum levels below 210 pg/dl (normal = 210 to 700 pg/dl), serum folate deficiency by levels below 4.0 ng/dl (normal = 4 to 16 ng/dl), and anemia by hemoglobin levels below 12.3 g/dl for women and 14 0 g/dl for men (normal = 12 3 to 15 5 g/dl for women and 14 0 to 16.2 g/dl for men). A positive response to treatment was defined as return of the value to a level at or above the lower limit of the normal range for our laboratory.

Postoperative laboratory results were collapsed into the following four time periods the first 12 months (n = 305), the second 12 months (n = 215), 24 through 60 months (n = 175), and more than 60 months (n = 85) Mean length of follow-up was 42 ± 14 months and ranged from 6 to 128 months. Statistical analysis of data was performed using the chi-square test, unpaired Student's *t* test, and two-way analysis of variance

RESULTS

Table I shows the changes in the various hematologic parameters over time. Deficiencies were recognized in 268 (82%) of the 348 patients postoperatively including 155 patients (47%) with iron deficiency, 122 (37%) with vitamin B_{12} deficiency, 115 (35%) with folate deficiency, and 177 (54%) with anemia Hemoglobin and hematocrit values were significantly decreased compared to preoperative levels at all postoperative intervals Moreover, at each successive postoperative interval through 5 years, hemoglobin and hematocrit were decreased significantly compared to the preceding interval. Conversely, serum iron levels remained relatively stable through the first 3 years postoperatively Although mean iron levels at 36 months or more were significantly lower than at previous intervals, they remained well within the normal range Changes in total iron-binding capacity were generally consistent with serum iron levels throughout the study Although microcytic hypochromic indices were found in most anemic patients, only 63% of low iron levels were associated with microcytic indices Moreover, 50% of low hemoglobin levels were not associated with iron deficiency No patient had macrocytic anemia. Only three patients (0 8%) had macrocytic indices.

Fig 1 shows the changes in mean hemoglobin, iron, and vitamin B_{12} values over time in 85 patients who were followed for 5 or more years Postoperative changes in hematocrit were virtually the same as the pattern observed for hemoglobin. After 5 years both hemoglobin and hematocrit were increased relative to values obtained between 3 and 5 years postoperatively Vitamin B_{12} levels were more variable showing an initial decline during the first 24 months postoperatively

Table I. Changes in hematologic parameters over time

Time (mo)	No of patients	Hemoglobin (g)	Hematocrit (%)	Iron (μg/dl)	TIBC (μg/dl)	Vitamin B_{12} (pg/dl)	Folate (ng/dl)
Preoperative	348	13 8 ± 1	41 4 ± 4	79 ± 35	343 ± 61	450 ± 341	5 5 ± 3 4
Postoperative							
12	304	13 2 ± 2*†	39 5 ± 4*†	74 ± 31	328 ± 62*	350 ± 205*	8 1 ± 5 2*
24	213	12 8 ± 2*†	38 4 ± 5*†	77 ± 37	352 ± 73	337 ± 192*	9 0 ± 6 3*
≥36	195	12 4 ± 2*†	37 7 ± 5*†	65 ± 36*†	378 ± 73*†	357 ± 217*	9 2 ± 5 2*

TIBC = total iron-binding capacity
Data are expressed as mean ± standard deviation
*Significant difference vs preoperative measurement ($P < 0.05$ by analysis of variance with Student's–Newman-Keuls test)
†Significant difference vs the preceding time interval(s) ($P < 0.05$ by analysis of variance with Student's–Newman-Keuls test)

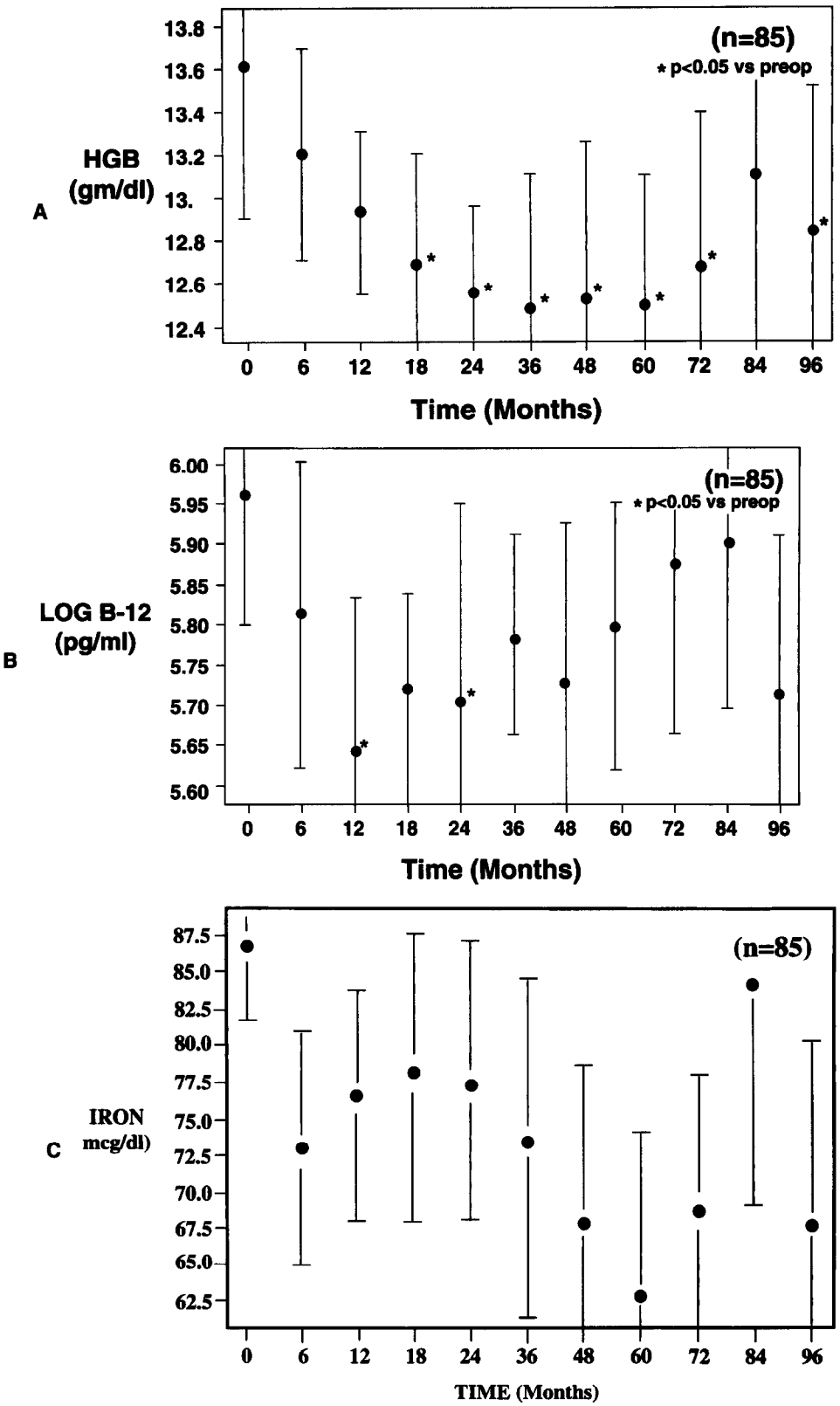

Fig 1. Changes in mean hemoglobin **(A)**, vitamin B_{12} **(B)**, and iron **(C)** values in 85 patients followed for ≥5 years (data expressed as mean ± standard deviation) * = Significant difference vs preoperative measurement ($P < 0.05$ by analysis of variance with Student's–Newman-Keuls test) Log scale E was used to normalize the distribution of the vitamin B_{12} values

with a subsequent increase after 48 months. However, vitamin B_{12} levels were significantly lower than mean preoperative values only at 12 and 24 months postoperatively. Although iron levels declined during the first 12 months postoperatively, there were no significant differences in mean iron levels over time. Mean postoperative folate levels in this group were significantly higher compared to preoperative measurements at all time periods.

Although iron deficiency was noted in 51% of female vs. 22% of male patients ($P < 0.001$ by chi-square test), there was no significant difference between sexes in terms of the incidence of vitamin B_{12} deficiency or anemia. Iron saturation levels were significantly lower in women than in men throughout the study. Only three of the eight anemias that developed in men postoperatively were associated with iron deficiency. The mean time of recognition of anemia in men was at 29 months postoperatively, nearly 2 years later than in women. The incidence of folate deficiency was higher in women (35%) vs. men (22%) at a level that approached significance ($P = 0.058$). Low iron levels were significantly less common in women who had a total abdominal hysterectomy prior to RYGB compared to those who did not ($P \leq 0.02$ by chi-square test) However, low hemoglobin levels did not correlate with having a total abdominal hysterectomy suggesting that post-RYGB anemia in some women has causes other than perimenstrual blood loss

Twenty-four of the 27 patients who had revision procedures had some form of gastroplasty as their initial operation, whereas three had revision of jejunoileal bypass to RYGB. There was no significant difference in the incidence of iron deficiency, folate deficiency, or anemia between patients who had primary vs. revision operations. However, the incidence of postoperative vitamin B_{12} deficiency was significantly greater in the revision group ($P \leq 0.004$ by chi-square test).

There was no correlation between regular ingestion of MVI supplements and the potential for developing deficiencies in either iron or vitamin B_{12}. Only 115 patients (33%) complied with the MVI supplement regimen throughout the study period Conversely, 27 patients (7.7%) never took MVI supplements. Compliance was defined as taking supplements five or more times per week Compliance with a MVI regimen also did not prevent anemia postoperatively. Conversely, there was a significant difference in the incidence of folate deficiency between patients who regularly took MVI supplements compared to noncompliant patients (31% vs. 52%; $P \leq 0.005$ by chi-square test) Compliance with a MVI regimen was associated with improvement of 41% of iron deficiencies and 22% of anemias, whereas deficient levels became normal in only 16 iron-deficient patients (7%) and one patient with anemia who were not taking MVI supplements.

Low serum levels of iron, vitamin B_{12}, and folate were treated with either MVI or supplements of the deficient micronutrient. Although there was a significant correlation between the taking of oral iron supplements and improvement of postoperative iron deficiency, oral iron supplements corrected iron deficiency in only 43% of cases. Conversely, vitamin B_{12} supplements (94% oral) resulted in improvement of 81% of vitamin B_{12} deficiencies. Folate deficiency was almost always corrected with MVI supplements alone.

DISCUSSION

Table II summarizes the data in several published articles that focus on vitamin and mineral deficiencies after RYGB The incidence of folate deficiency and anemia in the present report is substantially higher than in previously published series including our earlier reports.[4] Longer postoperative follow-up may explain the higher incidence of these deficiencies in the present series since the incidence of low iron, folate, and hemoglobin levels nearly doubled in our own patients with a proportional increase in follow-up time. Conversely, the incidence of vitamin B_{12} deficiency remained constant over time among our patients There was little difference in the mean time of recog-

Table II. Published reports of metabolic deficiencies after gastric bypass. Mean incidence, time of recognition, and duration of follow-up

Reference	No. of patients	Iron	Vitamin B_{12}	Folate	Anemia	Follow-up
Halverson et al [1] (1981)	69	20%/17 mo	26%/20 mo	9%/13 0 mo	18%/—	20 mo
Amaral et al [2] (1985)	150	49%/15 6 mo	70%/13 0 mo	18%/—	35%/20 mo	33 2 mo
Brolin et al [4] (1991)	124	33%/13 4 mo	37%/12 8 mo	16%/10 7 mo	22%/12 mo	24 2 mo
Brolin et al (1997)	348	47%/11 0 mo	37%/12 7 mo	35%/11 5 mo	54%/10 8 mo	42 3 mo

Mean incidence and time of deficiency recognition are listed under each micronutrient with mean follow-up shown in far right column

nition of iron, B_{12}, and folate deficiency among the three series. The onset of deficiencies was rapid in most of our patients as the median time interval for recognition of low iron, B_{12}, folate, and hemoglobin levels was the 6-month visit

Causes of Post-RYGB Deficiencies

Post–gastric bypass vitamin B_{12} deficiency occurs primarily as a consequence of maldigestion of dietary B_{12} Dietary B_{12}, which is protein bound, must be enzymatically cleaved from the protein before absorption can occur [6] Both pepsin and hydrochloric acid are required to separate food-bound vitamin B_{12} from the protein moiety in the stomach. After gastric bypass, enzymatic cleavage of the food-bound vitamin B_{12} moiety is limited by both absence of hydrochloric acid in the upper gastric pouch and exclusion of the distal stomach and duodenum, where pepsin and pancreatic secretory enzymes facilitate binding of the freed vitamin B_{12} to intrinsic factor Several investigators have demonstrated that food-bound vitamin B_{12} is less well absorbed than orally administered crystalline B_{12} after both partial gastrectomy and RYGB [6-8] Other investigators have reported normal Schilling tests in RYGB patients, suggesting that intrinsic factor secretion occurs in the bypassed stomach [8,9] Consequently oral supplements of crystalline B_{12} can be expected to provide effective treatment for vitamin B_{12} deficiency after RYGB

Iron deficiency after RYGB results from both malabsorption and maldigestion of dietary iron Dietary iron is primarily absorbed in the duodenum and upper jejunum, which are excluded from the functional digestive tract in RYGB In the normal stomach, absorption of dietary iron is facilitated by hydrochloric acid Several investigators have shown markedly reduced acid production in the upper pouch of gastric bypass patients [10,12] Hence it seems likely that decreased acid secretion in the small gastric pouch also contributes to the development of iron deficiency after RYGB.

The incidence of post-RYGB folate deficiency in clinical reports has varied widely ranging from 0% to 38% [1-3,5,13] Although folate absorption occurs predominantly in the upper third of the small intestine, there is evidence that absorption can occur in the mid and distal small bowel [14] Because folate absorption is also facilitated by hydrochloric acid in the stomach, low acid production in the upper pouch of RYGB patients may predispose them to development of folate deficiency postoperatively Russel et al [15] have suggested that increased bacterial synthesis of folate in the upper small bowel may compensate for diminished absorption of dietary folate in achlorhydric patients. This finding suggests that folate absorption may gradually improve over time after RYGB

Changes in postoperative dietary habits may also contribute to the development of micronutrient deficiencies following RYGB Red meat and milk are major sources of iron and vitamin B_{12}, respectively, in the diet. Red meat is generally recognized as the most difficult type of food to eat after gastric restrictive operations, whereas milk product intolerance is common following gastric bypass [16] Avinoah et al [17] reported a significantly higher incidence of iron, vitamin B_{12}, and folate deficiency in postoperative RYGB patients who ate red meat less than once per week in comparison with patients who ate red meat more than once per week These authors concluded that decreased meat consumption is a major factor contributing to both iron and vitamin B_{12} deficiency after gastric bypass

Updegraffe and Neufeld[18] obtained pre- and postoperative diet histories from 12 patients who underwent gastric bypass and found that postoperative intake of protein and folate were significantly decreased in comparison with preoperative intake. However, postoperative serum folate levels were significantly higher than the preoperative measurements The investigators attributed the increase in postoperative folate levels to MVI supplementation since none of the 12 patients were taking MVI supplements prior to operation

Although the estimated blood loss in revision procedures was usually two to three times greater than that in primary operations, the incidences of postoperative iron deficiency and anemia were similar in these two groups However, the incidence of vitamin B_{12} deficiency was significantly greater after revision procedures This finding was surprising since 24 of the 27 patients had some form of gastroplasty as their primary operation Because there was no difference in serum vitamin B_{12} levels between primary and revision patients prior to RYGB, this difference suggests that B_{12} stores were depleted in the revision group Reduced dietary intake of vitamin B_{12} after the primary procedure provides a plausible explanation for the significant difference in postoperative serum levels between revision and primary RYGB patients

Patient noncompliance may be the most important factor contributing to both development and persistence of metabolic deficiencies after RYGB. Only 33% of patients were consistently compliant in taking MVI supplements throughout the study, whereas 35% and 54% were compliant in taking iron and vitamin B_{12} supplements, respectively, for treatment of their deficiencies Development of severe anemia, defined as a hemoglobin level of 10 g or less, was invariably associated with not taking MVI and iron supplements and missing scheduled follow-up visits This

frequency of noncompliance occurred despite a detailed preoperative discussion regarding the potential for developing metabolic deficiencies after RYGB. The risks of metabolic deficiencies are also emphasized at each postoperative visit.

Clinical Consequences and Treatment Recommendations

Although low vitamin B_{12} and folate levels were common in this series, no patient had symptoms that could be attributed to either deficiency. This finding suggests that vitamin B_{12} and folate deficiencies are not clinically important after RYGB. On the basis of these results, we do not recommend prophylactic supplementation of vitamin B_{12} or folate to our RYGB patients Moreover, because folate deficiency is consistently prevented by taking MVI supplements, we no longer routinely measure serum folate levels before or after surgery

Conversely, many patients had fatigue and weakness associated with iron deficiency and anemia Women comprised 93.5% of the patients who developed iron deficiency in this series Iron deficiency was significantly less prevalent in women who had a total abdominal hysterectomy, suggesting that menstrual blood loss is an important factor contributing to the development of post-RYGB iron deficiency Low iron stores in menstruating women are probably the primary cause of iron deficiency and anemia in this group In men anemia was much less common Moreover, the mean time of onset of anemia in men was at 2½ years postoperatively, which explains why anemia was not recognized in men in two earlier reports [1,4]

Megaloblastic anemia was not recognized in any of our patients as compared with a respective incidence of 5% and 7% in two earlier reports [2,5] The absence of megaloblastic anemia in the present report may be due to better compliance in taking MVI supplements postoperatively and to earlier treatment intervention in patients with vitamin B_{12} and folate deficiency.

Because mean follow-up in most previous reports was relatively short, there is little published information on the results of treatment of these deficiencies In the present series more than 80% of the vitamin B_{12} deficiencies responded to oral supplementation. Rhode et al [10] have shown that a minimum daily dose of 350 μg of crystalline B_{12} is necessary to maintain normal serum levels after RYGB We have found that 500 μg of oral vitamin B_{12} is sufficient to correct the majority of deficiencies Intramuscular supplements are usually reserved for patients who refuse to take oral vitamin B_{12} MVI supplements, which typically contain 400 μg of folate, consistently corrected low folate levels.

There are no published data on the efficacy of prophylactic iron supplements after RYGB. In the present study low serum iron levels did not respond consistently to treatment with MVI and oral iron supplements Treatment of severe anemia (hemoglobin ≤10 g) was particularly problematic No patient with severe anemia was successfully treated with oral iron supplements alone Three severely anemic patients eventually responded to intramuscular iron injections, three patients required blood transfusion, and one patient responded after a total abdominal hysterectomy. Intravenous iron dextran was not used in this study. The resistance of iron deficiency to oral iron supplements coupled with the high incidence of iron deficiency anemia in menstruating women has led us to prescribe prophylactic oral iron supplements containing 50 mg or more of elemental iron to premenopausal women after RYGB.

An important heretofore unanswered question regarding post-RYGB metabolic deficiencies is whether there is steady progression of untreated deficiencies over time. Data in the present study weakly suggest that most deficiencies tend to either stabilize or improve after the fourth or fifth year postoperatively. However, these data are muddled by haphazard compliance with treatment regimens and inconsistent long-term follow up

In summary, these results show that iron deficiency and anemia are common after RYGB and that MVI prophylaxis does not consistently protect against the development of these deficiencies The results also show that anemia can be a serious clinical problem after RYGB. Although iron deficiency was the most common factor predisposing patients to development of anemia, 50% of low hemoglobin levels in this series were not associated with iron deficiency This finding suggests that further studies are needed to elucidate the mechanisms involved in the evolution of anemia after RYGB so that more effective strategies for prophylaxis can be developed

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Biliary Dyskinesia: A Study of More Than 200 Patients and Review of the Literature

Anthony J. Canfield, M.D., Stephen P Hetz, M D., F.A C S., John P Schriver, M D, Hubert T Servis, M D., Trent L Hovenga, M D, Paul T. Crangle, M D, Brian S Burlingame, M D.

The diagnosis and treatment of biliary dyskinesia, defined as symptoms of biliary colic in the absence of gallstones, remains controversial and has been the subject of several previous retrospective reviews The diagnosis and treatment of biliary dyskinesia based on the CCK-HIDA scan, and the outcome with cholecystectomy for biliary dyskinesia, are reviewed We add more than 200 cases of cholecystectomy for biliary dyskinesia, and compare our results with those of previous reports We retrospectively reviewed 295 patients with biliary dyskinesia who underwent cholecystectomy at three military hospitals between 1988 and 1995 All patients had symptoms consistent with biliary colic and preoperative evaluations that revealed no evidence of cholelithiasis Pathology specimens were reviewed for cholelithiasis and pathologic changes Data were retrieved by chart review and clinic evaluation of new patients Individual follow-up of each patient was attempted Follow-up was achieved in 218 of the 295 patients for a rate of 74% The mean duration of follow-up was 506 days with a range of 22 days to 6 years Two hundred patients (92%) had CCK-HIDA scans with an ejection fraction (EF) <50% Eighteen patients (8%) had an EF >50% but did have reproduction of their symptoms with CCK injection In the group with an EF <50%, 94 5% were improved or cured with cholecystectomy In the group with an EF ≥50% and pain reproduction, the improved or cured rate was 83 4% CCK-HIDA scans are useful for diagnosing biliary dyskinesia and predicting improvement after cholecystectomy Patients presenting with biliary dyskinesia and an EF <50% on CCK-HIDA scan have 94% improvement or resolution of their symptoms after cholecystectomy CCK-HIDA scans should be employed early in the evaluation of biliary colic with no evidence of cholelithiasis (i.e , with a normal ultrasound scan) When test results are abnormal, cholecystectomy should be performed, since the results in this setting approach those of cholecystectomy for stone disease (>90% cured/improved) In the current climate of cost containment, these excellent results would obviate the need for extensive and expensive medical testing before surgical therapy is recommended (J GASTROINTEST SURG 1998,2 443-448)

Biliary dyskinesia has been defined as the presence of biliary colic symptoms (postprandial right upper quadrant pain, fatty food intolerance, nausea, and bloating),[1-3] without evidence of cholelithiasis. Unfortunately the diagnosis of biliary dyskinesia is still often not considered in patients with ultrasound-negative right upper quadrant pain. In fact, several major textbooks of general surgery do not even reference the term "biliary dyskinesia" in the index. Others refer to poor emptying of the bile ducts, implicating ampullary dysfunction as a cause [4-7] Many of these patients have a history consistent with biliary colic, with symptoms of right upper quadrant pain, nausea, vomiting, and bloating occurring after ingestion of fatty foods If the ultrasound scan is normal, other tests are usually ordered (e.g , esophagogastroduodenoscopy, upper gastrointestinal series, CT scan, and intravenous pyelogram). However, if their test results are normal, many

From the Departments of Surgery, Evans Army Community Hospital (A.J C , H T S , T L H , and P T C), Fort Carson, Colo , William Beaumont Army Medical Center (S P H and B S B), El Paso, Tex , and Womack Army Medical Center (J P S), Fort Bragg, N C
The opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the United States Army or the Department of Defense
Reprint requests Stephen P Hetz, M D , F.A.C S , Department of Surgery, William Beaumont Army Medical Center, El Paso, TX 79920-5001

of these patients undergo no further testing and are not referred to a general surgeon for evaluation, despite continued symptoms consistent with biliary colic

This report details the results of a retrospective review of more than 200 patients who underwent cholecystectomy for biliary colic without evidence of cholelithiasis (i e , biliary dyskinesia) The preoperative CCK-HIDA results are evaluated and correlated with the patient's reported outcome after cholecystectomy These results are then compared with those from previously published reports on surgical treatment of biliary dyskinesia

MATERIAL AND METHODS

Records were reviewed after they were identified by a computer search of patients undergoing cholecystectomy for biliary dyskinesia The following three military hospitals participated in the review Evans Army Community Hospital (Fort Carson, Colo), William Beaumont Army Medical Center (El Paso, Tex), and Womack Army Medical Center (Fort Bragg, N C.) The charts of patients undergoing cholecystectomy (open or laparoscopic) between 1988 and 1995 for biliary dyskinesia were reviewed. A total of 295 records were obtained for review and the patients were contacted by telephone, office visit, or mailed questionnaire These patients were asked whether they were asymptomatic, improved, or not improved after cholecystectomy The inpatient records were reviewed for CCK-HIDA ejection fraction (EF), reproduction of pain by cholecystokinin (CCK) injection, result after cholecystectomy, pathology report, and complications. The EF in normal individuals is approximately 74% [8,9] An EF of 50% was chosen because it is two standard deviations below the mean for normal individuals Other authors have selected this as well [10]

RESULTS

The follow-up rate was 74%, with 218 patients out of 295 being contacted either by telephone or personal interview The length of time between the patient's surgery and the follow-up ranged from 22 days to 6 years, with an average time after cholecystectomy of 1 4 years Patients were questioned about whether they were free of their preoperative symptoms, were significantly improved, or had no improvement after cholecystectomy The results were then compiled and divided into two major groups based on the results of their preoperative CCK-HIDA scans. Previous studies have used values between 35% and 50% to indicate abnormal gallbladder function [10,11] Group 1 had an EF $<50\%$ (n = 200, 92%) and group 2 had an EF $\geq 50\%$ (n = 18, 8%) Group 1 was then subdivided into those who had their pain reproduced with CCK injection and those who did not In group 1 (EF $\leq 50\%$), 96% of patients who had their pain reproduced by CCK injection had a satisfactory result (pain free or significantly improved), and 89% of those in group 1 who did not have their pain reproduced by CCK had a satisfactory result The outcome of patients in group 1 is shown in Fig 1 In group 2 (EF $>50\%$), 83% had a satisfactory result after cholecystectomy, these results are shown in Fig 2 Most of the patients in group 2 had undergone extensive workups prior to cholecystectomy for their right upper quadrant pain.

Pathologic examination of the gallbladder in these patients yielded the following results chronic cholecystitis in 158 (72%), normal findings in 101 (46%) and cholesterolosis in 53 (24%) Thirteen specimens (6%) had small stones (not found preoperatively on ultrasound examination) and three specimens had cholesterol polyps There was one specimen that contained a pancreatic rest Many of these patients had multiple pathologic findings, most commonly chronic cholecystitis and cholesterolosis

There were nine complications out of 218 procedures (4%). These included the following three wound infections (open cholecystectomies), one enterotomy, one case of postoperative pneumonia, one hematoma, one incisional hernia (open cholecystectomy), one case of intravenous site phlebitis, and one conversion to open cholecystectomy because of bleeding After cholecystectomy three patients reported increased loose bowel movements severe enough to require medical attention One patient noted increased bloating and belching

DISCUSSION

Biliary disease without stones has been recognized by surgeons since the early 1920s. Whipple[12] published a study identifying 47 patients with biliary colic who underwent cholecystectomy but did not have cholelithiasis He followed these patients and found that 36 (76%) of 47 were relieved of their symptoms following cholecystectomy, whereas 89% of the patients with cholelithiasis were asymptomatic following cholecystectomy Blalock[13] also demonstrated that in a series of 103 patients followed after cholecystectomy without stones, 68 (66%) were without symptoms, 17 (16 5%) were improved, seven (6 8%) were not improved, nine (8 7%) died after the operation, and two (2%) died of other causes within 1 year These patients were all operated on for symptoms alone

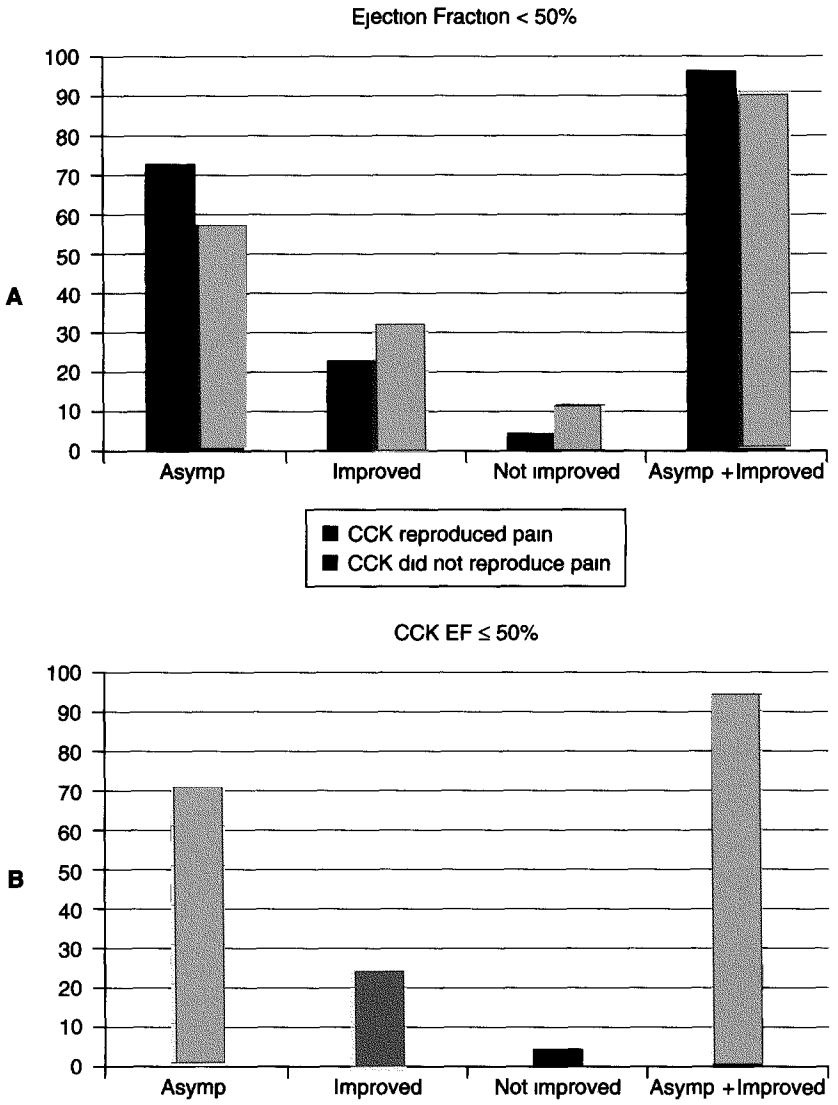

Fig. 1. A, Results in 200 patients who underwent cholecystectomy for biliary dyskinesia with an EF <50% Black bars represent those who experienced pain reproduction with CCK injection Gray bars represent those who did not have their pain reproduced by CCK injection The asymptomatic plus improved rates are 96% and 89% for those with and without pain reproduction, respectively **B,** Results in 200 patients with an EF <50%, combining those with and without pain reproduction The asymptomatic plus improved rate is 94 5%

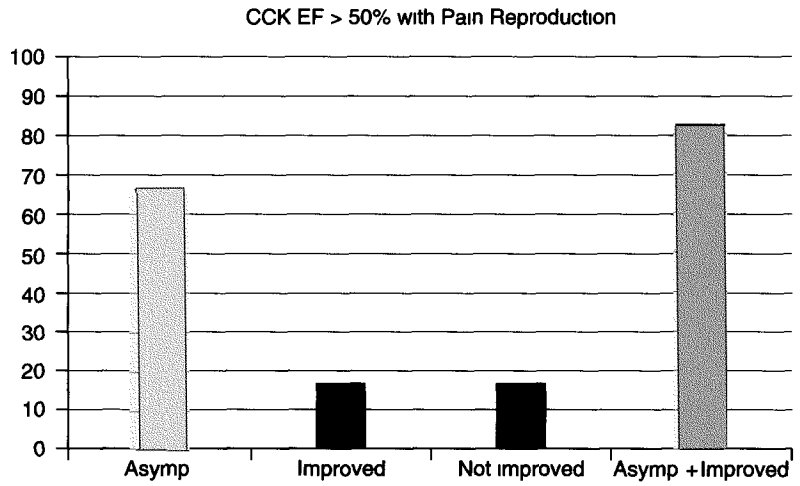

Fig. 2. Results in 18 patients with an EF >50% and pain reproduction Note that the asymptomatic plus improved rate is 83%, whereas the asymptomatic rate is 67%

In 1924 Graham and Cole[14] introduced cholecystography, which changed the way biliary disease was diagnosed. Before cholecystography, surgeons relied on patient history and physical examination to diagnose biliary pathology. After 1924, they had a test to determine the presence or absence of stones before surgery. In 1934 Mackey[15] reviewed 243 cholecystectomies performed without evidence of cholelithiasis. He found that 60% were improved or cured, 37% had unsatisfactory results, and 3% died. He advised that cholecystectomy be performed only for gallstones or a deformed gallbladder on preoperative cholecystography. This school of thought persisted as diagnostic tests became more accurate in demonstrating cholelithiasis. In 1956 Glenn and Mannix[16] recommended that the gallbladder not be removed if stones or cholecystitis were not found at surgery.

Although the focus of surgical treatment was directed at cholelithiasis, patients with symptoms of biliary colic but no gallstones were still seen by a physician. A diagnostic test to identify patients with biliary dysfunction was needed. CCK was identified as the hormonal trigger for gallbladder contraction in 1928 by Ivy and Oldberg [17]. However, CCK was not available for clinical use until 1958 when Broden[18] injected porcine CCK during cholecystography to evaluate the motor function of the gallbladder. In 1975 Freeman and Cohen[19] used CCK injected during cholecystography to predict which patients would benefit from cholecystectomy for biliary dyskinesia. They found that out of 22 patients with either a decreased ejection fraction, bile crystals, or symptoms that were reproduced with CCK injection, 95% had relief or improvement of symptoms after cholecystectomy. Griffen et al [1] reported similar results in 1980 with 95% of patients becoming asymptomatic or improved following cholecystectomy. Burnstein et al [20] reported improvement or complete resolution of symptoms in 21 patients with hypocontraction of the gallbladder or presence of bile crystals. In 1984 Lennard and Farndon[21] used CCK injection versus placebo to identify patients with acalculous biliary pain. They found 100% of 26 patients to be asymptomatic following cholecystectomy.

Nuclear imaging of the gallbladder with technetium-99m disofenin became available in the 1980s. Fink-Bennett et al.[22] combined CCK injection with this imaging modality to accurately measure the ejection fraction of the gallbladder. They reported on 14 patients with low gallbladder ejection fractions who underwent cholecystectomy. All were clinically improved after surgery.[22] Since 1985 there have been several other reports of similar results and these are shown in Fig. 3 for comparison. Including our study we reviewed 14 reports that identified patients with biliary dyskinesia by using CCK injections combined with imaging studies (Table I). The results are surprisingly similar when these reports are compared. The combined percentage of 621 patients who underwent cholecystectomy for biliary dyskinesia who were asymptomatic or improved was 97%. The results of our study closely matched the combined results previously published. This supports our contention that patients with biliary dyskinesia identified by low ejection fractions or reproduction of symptoms during CCK-HIDA scans can be treated successfully with cholecystectomy.

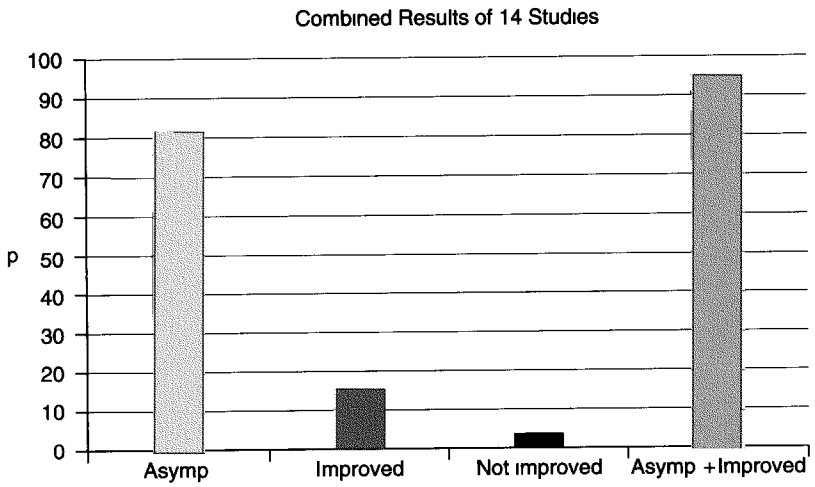

Fig. 3. Results of 13 similar studies in the literature combined with our study. Note that the asymptomatic plus improved rates are 97% for the combined studies and 94.5% for our studies. Also, the marked similarity in results for these studies should be indicative of results in clinical practice.

Table I. Biliary dyskinesia Results from 14 studies similar in design*

Year	Reference	No. of patients	Criteria	Asymptomatic	Improved	No change	Asymptomatic + improved
1975	Freeman and Cohen[19]	22	CCK OCG decreased EF, CCK pain, or bile crystals	19 (86%)	2 (9%)	1 (5%)	21 (95%)
1980	Griffen et al [1]	16	CCK EF <50%	13 (81%)	2 (13%)	1 (6%)	15 (94%)
1982	Burnstein et al [20]	21	CCK OCG EF decreased	16 (76%)	5 (24%)	0	21 (100%)
1982	Rajagopalan and Pickleman[23]	16	CCK OCG EF <50%	15 (94%)	1 (6%)	0	16 (100%)
1984	Lennard and Farndon[21]	26	CCK OCG EF <50%	26 (100%)	0	0	26 (100%)
1985	Pickleman et al [24]	14	CCK-HIDA EF <50%	13 (93%)	0	1 (7%)	13 (93%)
1985	Fink-Bennett et al [22]	14	CCK-HIDA EF <35%	14 (100%)	0	0	14 (100%)
1985	Proudfoot et al [10]	31	CCK OCG EF <50%	22 (71%)	6 (19%)	3 (10%)	28 (90%)
1991	Zech et al [25]	59	CCK-HIDA EF <50%	56 (95%)	2 (3%)	1 (2%)	58 (98%)
1991	Misra et al [2]	69	CCK-HIDA EF <35%	58 (84%)	9 (13%)	2 (3%)	67 (97%)
1991	Fink-Bennett et al [26]	111	CCK-HIDA EF <35%	N/A	N/A	1 (1%)	110 (99%)
1991	Yap et al [8]	11	CCK-HIDA EF <40%	10 (91%)	1 (9%)	0	11 (100%)
1993	Sorenson et al [3]	11	CCK-HIDA EF <35%	11 (100%)	0	0	11 (100%)
1997	Canfield et al	200	CCK-HIDA EF <50%	140 (70%)	49 (14 5%)	11 (5 5%)	189 (94 5%)
14 Studies combined		621		413/510 (81%)	77/510 (15%)	20/510 (4%)	600/621 (97%)

CCK = cholecystokinin, OCG = oral cholecystogram, EF = ejection fraction
*Only the results in patients who underwent cholecystectomy and had follow-up are included in is table For further details concerning each study, refer to the individual references cited

CONCLUSION

Patients who have symptoms of biliary colic but whose ultrasound scans do not show gallstones should then have a CCK-HIDA scan performed If the ejection fraction is less than 50%, with or without pain reproduction by the CCK injection, approximately 94% to 96% will be cured or improved after cholecystectomy This was evident in our results and in the combined data from numerous investigators These patients with symptoms of biliary colic and an abnormal CCK-HIDA scan should undergo cholecystectomy If the ejection fraction is greater than 50% and their pain is reproduced by CCK injection, other causes for the pain should be investigated If a thorough search for other causes of upper abdominal pain is negative, cholecystectomy should relieve or improve their symptoms in 83% of these patients We searched retrospectively and did not evaluate patients who were diagnosed with symptoms of biliary colic, had an abnormal CCK-HIDA scan, but did not undergo cholecystectomy This could only be adequately achieved by a large prospective randomized trial The only study that did follow patients who did not undergo cholecystectomy was that of Misra et al ,[2] who followed 29 patients with abnormal CCK-HIDA scans Of these 29 patients, 97% continued to have symptoms A controlled randomized study has yet to be performed Our study represents the largest retrospective study to date

Overall, the CCK-HIDA scan is an excellent diagnostic tool for patients with symptoms of biliary colic but who have no stones on their ultrasound scans In patients with a low ejection fraction (<50%) and biliary colic, cholecystectomy should be performed, since the results in this setting approach those of cholecystectomy for stone disease (>90% cured/improved) In the current climate of cost containment, these excellent results would obviate the need for extensive and expensive medical testing before surgical therapy is recommended

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Glucocorticoids Upregulate Intestinal Nutrient Transport in a Time-Dependent and Substrate-Specific Fashion

Pasquale Iannoli, M D , Jen-nie H Miller, M.S., Charlotte K Ryan, M D , Harry C Sax, M D

Glucocorticoids mediate skeletal muscle proteolysis during critical illness to provide substrates for hepatic acute-phase protein synthesis and gluconeogenesis The effects of hypercortisolemia on splanchnic substrate uptake are not well defined This study characterizes intestinal nutrient transport in response to acute elevations of plasma glucocorticoid levels New Zealand White rabbits were randomized to receive either dexamethasone (2 mg/kg intramuscularly) or vehicle and were killed 8, 16, or 24 hours after steroid treatment Brush-border membrane vesicles were prepared from pooled small intestinal mucosa and the uptake of tritiated substrates was quantified. Serum insulin-like growth factor 1 (IGF-1) levels, mucosal DNA content, and mucosal morphology were determined Glucocorticoids increased glucose and leucine uptake at 8 hours (80% and 24%, respectively) and 24 hours (147% and 50%, respectively) Glutamine, alanine, and arginine transport increased by 42%, 96%, and 236%, respectively, at 24 hours Sodium-*independent* transport (diffusion) of all substrates was increased by 240% by dexamethasone treatment at 24 hours Mucosal DNA content increased by 32%, whereas microvillus heights decreased by 27% at 24 hours No effects were noted on IGF-1 levels or gross villus heights Glucocorticoids acutely accelerate intestinal nutrient transport in a time-related and substrate-specific fashion Although the mechanism of glucocorticoid action remains unclear, both genomic and plasma membrane effects are implicated (J GASTROINTEST SURG 1998,2 449-457)

The concept of physiologic adaptation to stress was first proposed 50 years ago.[1] Accordingly, increased adrenal cortisol secretion has been considered an essential component of the stress response.[2] Clinical practice supported supplementing adrenal-insufficient patients with high-dose glucocorticoids during periods of operative or metabolic insult [3]

The metabolic stress response is characterized by negative nitrogen balance, skeletal muscle proteolysis, and amino acid flux to the liver [4] Glutamine and alanine are mobilized from skeletal muscle stores via the splanchnic bed to support hepatic acute-phase protein synthesis and gluconeogenesis [5] Catabolic states alter the hormonal milieu that influences amino acid and protein metabolism. Concentrations of the counter-regulatory hormones glucagon, cortisol, growth hormone, and the catecholamines are increased during acute illness.[6] Insulin concentrations are variable, and a relative tissue insulin insensitivity is frequently present.[7]

A great deal is known about the role of the liver, lung, and skeletal muscle in amino acid metabolism during critical illness, but little is known about the role of the intestinal mucosa in amino acid metabolism during stress states. We have recently demonstrated that surgical stress enhances mucosal nutrient uptake in the small intestine and that a nonspecific stress or inflammatory response may be responsible.[8] This catabolic response is mediated, in part, by glucocorticoids [9] If glucocorticoids serve to mobilize amino acids from skeletal muscle to liver, it seems logical that they would also influence the liver's primary source of amino acids—splanchnic nutrient transport This study characterizes intestinal nutrient transport

From the Departments of Surgery (PI , J H.M , and H C S) and Pathology (C K.R), University of Rochester Medical Center, Rochester, N Y
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Reprint requests Harry C Sax, M D , F A C S , University of Rochester Medical Center, Department of Surgery, 601 Elmwood Ave , Rochester, NY 14642-8410

and investigates the potential mechanisms of transport upregulation in response to acute elevations in plasma glucocorticoid concentrations

MATERIAL AND METHODS

Subjects

Eighteen male New Zealand White rabbits (Hazelton Research Products, Inc, Denver, Pa), each weighing 2 kg, were housed in individual cages in light/dark-cycled, temperature-controlled rooms in accordance with institutional guidelines and the "Guide for the Care and Use of Laboratory Animals" (Department of Health and Human Services, National Institutes of Health) All experimental protocols were approved by the Institutional Animal Care and Use Committee Animals were provided with 170 g of standard Purina Rabbit Chow (Purina Mills Inc, St. Louis, Mo.) per day and water ad libitum up to the time they were killed

The rabbits were randomized to either the glucocortocoid (dexamethasone, 2 mg/kg intramuscularly, n = 14) or the control (no treatment, n = 4) group Control animals were killed immediately, whereas the experimental animals were killed 8 (n = 5), 16 (n = 4), or 24 (n = 5) hours after glucocorticoid treatment The entire length of small bowel distal to the duodenum was rapidly harvested and rinsed in ice-cold saline solution. The mucosa was scraped with a glass slide and immediately frozen at −70° C The steroid injections were administered so that all animals were killed during midmorning, thereby minimizing circadian hormonal effects

Reagents and Chemicals

All reagents and chemicals used were of analytic quality and were purchased from Sigma Chemical Company (St Louis, Mo.) Radiolabeled L-[4,5-^{3}H]-leucine, L-[G-^{3}H]-glutamine, L-[2,3-^{3}H]-alanine, L-[2,3,4,5-^{3}H]-arginine, and D-[6-^{3}H]-glucose were purchased from Amersham Corporation (Arlington Heights, Ill.)

Membrane Vesicle Preparation

Nutrient transport of the small intestinal mucosa was determined in brush-border membrane vesicles (BBMVs) As previously described, BBMVs were prepared by means of magnesium aggregation and serial differential centrifugation [8] All steps were carried out at 0° to 5° C Each gram of thawed mucosal scraping was homogenized in 8 ml of buffer containing 300 mmol/L mannitol and 1 mmol/L *N*-(2-hydroxyethyl) piperazine-*N'*-2 ethanesulfonic acid (HEPES)–Tris (pH 7 4) with a Polytron homogenizer (maximal setting) for 45 seconds (Brinkman Instruments, Inc, Westbury, Conn) Homogenates from each group were treated with 100 mmol/L magnesium dichloride/1 mmol/L HEPES-Tris to yield a final magnesium concentration of 10 mmol/L After stirring for 20 minutes, the homogenate was centrifuged for 10 minutes at 2200 ×*g* (5000 RPM in a Sorvall SS-34 rotor, Du Pont Co, Wilmington, Del) The supernate containing brush-border material was decanted and centrifuged for 5 minutes at 3300 ×*g* (6000 RPM) The supernate was then centrifuged at 45,000 ×*g* (19,000 RPM) for 35 minutes The brush-border membrane pellet was resuspended in 350 mmol/L mannitol and 50 mmol/L HEPES-Tris and centrifuged again at 45,000 ×*g* (19,000 RPM) for 35 minutes The final pellet was resuspended in the same buffer to yield a final protein concentration of 10 to 15 mg/ml

Transport Measurement

The uptake of tritiated substrates (glucose, glutamine, leucine, alanine, and arginine) was measured by a rapid mixing/filtration technique in the presence and absence of a sodium gradient For each uptake measurement, 10 μl of BBMV and 40 μl of radioactive uptake buffer were placed separately at the bottom of a 12 × 75 mm polystyrene tube (VWR Scientific, San Francisco, Calif) The uptake buffer components were adjusted so that the final concentration mixture contained initial gradients of 120 mmol/L sodium chloride or potassium chloride and 100 μmol/L substrate An electronically controlled device initiated the reaction by rapidly vibrating the tube After 10 seconds, 1 ml of ice-cold stop buffer (150 mmol/L NaCl and 10 mmol/L HEPES-Tris) was added to quench the reaction This time point was chosen to ensure measurement of the rapid initial influx before equilibration of the sodium gradient. The quenched reaction mixture was vacuum filtered onto a prewetted and chilled 0 45 μm nitrocellulose filter (Gelman Sciences, Inc., Ann Arbor, Mich) to separate intravesicular from extravesicular radiolabeled substrate, washed with 8 ml of ice-cold stop buffer, and dissolved in Cytoscint scintillation cocktail (ICN Biomedicals, Inc, Costa Mesa, Calif.) Radioactivity trapped by the vesicles (representing transport) was measured by liquid scintillation spectrometry (LS 8000, Beckman Instruments, Inc, Fullerton, Calif) Values for nonspecific retention of radioactivity by the filter and the vesicles were obtained from zero time uptakes and subtracted from total filter radioactivity

The radioactivity was converted to units of uptake and expressed as picomoles of substrate per milligram of vesicle protein per unit of time

The sodium-dependent component of substrate transport was calculated by subtracting uptake in the presence of potassium (sodium-independent uptake, quadruplicate measurements) from that determined in the presence of sodium (total uptake, quadruplicate measurements). The osmolarity of varying concentrations of amino acids was adjusted with mannitol All substrate uptakes into BBMVs were normalized to BBMV protein concentration.

BBMV Purity

BBMV purity as compared to crude homogenates of mucosa was confirmed by enrichment of the activity of the brush-border membrane-specific enzyme alkaline phosphatase (AP) with no increase in the activity of the basolateral membrane-specific enzyme sodium/potassium–adenosine triphosphatase (Na^+/K^+-ATPase) Photometric absorption was read at 410 nm for AP and at 340 nm for Na^+/K^+-ATPase

Morphology

Villus heights of standard 1 cm jejunal segments fixed in hematoxylin and eosin were determined for each animal by light microscopy by a surgical pathologist (C K.R) who was blinded to the groups. Microvillus heights were determined by electron microscopy of identical specimens fixed in 10% formalin solution (C.K R.)

Mucosal DNA Content

Mucosal DNA content was quantitated spectrophotometrically in 50 mg aliquots of mucosa using the QIAamp tissue kit (catalogue No 29304, Qiagen Inc , Chatsworth, Calif.)

Serum IGF-1 Determination

Vena caval blood specimens were collected at the time of harvest. Serum insulin-like growth factor 1 (IGF-1) levels were determined by a nonextraction immunoradiometric assay (IGF-1 IRMA 100T Kit, catalogue No. 40-2250, Nichols Institute Diagnostics, San Juan Capistrano, Calif)

Statistical Analysis

Results are reported as mean values ± standard error of the mean with significance determined by analysis of variance (with post hoc Student–Newman-Keuls pairwise multiple-comparison procedure where appropriate) at the $P < 0.05$ level.

RESULTS

BBMV Purity

The BBMV preparations demonstrate a sevenfold increase in AP activity but no change in Na^+/K^+-ATPase activity ($P < 0.05$) (Fig. 1)

Sodium-Dependent Transport

Sodium-dependent transport is illustrated in Fig. 2. Glucocorticoid treatment accelerated sodium-dependent glucose and leucine transport by 77% and 20%, respectively, compared to values in control animals 8 hours following treatment ($P < 0.05$) These changes normalize by 16 hours (P = NS) but are further accelerated by 140% and 36%, respectively, compared to control values 24 hours following treatment ($P < 0.05$). Sodium-dependent glutamine transport exhibits a profile similar to that of glucose and leucine transport but does not achieve significance despite a 24% increase at 8 hours and a 29% increase at 24 hours compared to control values (P = NS). Sodium-dependent alanine uptake is upregulated by 70% at 24 hours following treatment compared to control values ($P < 0.05$) There were no differences in sodium-dependent arginine transport (P = NS).

Sodium-Independent Transport

Glucocorticoids increased sodium-independent transport of all substrates by approximately 240% at 24 hours following treatment compared to values in control animals ($P < 0$ 05, Fig. 3). There were no differences for any substrate at 8 hours and 16 hours following glucocorticoid administration compared to control values (P = NS)

Integrated Transport

To draw some analogy to the living animal, sodium-dependent and sodium-independent transport values were pooled for each substrate to simulate total substrate transport (Fig 4). The effect of glucocorticoids on total glucose and leucine transport parallels both the pattern and magnitude of change seen in sodium-dependent transport alone ($P < 0.05$). Total glutamine and alanine transport upregulation also parallels sodium-dependent transport alone at 8 and 16 hours (P = NS) but attains significant 42% and 96% increases, respectively, at 24 hours ($P < 0$ 05).

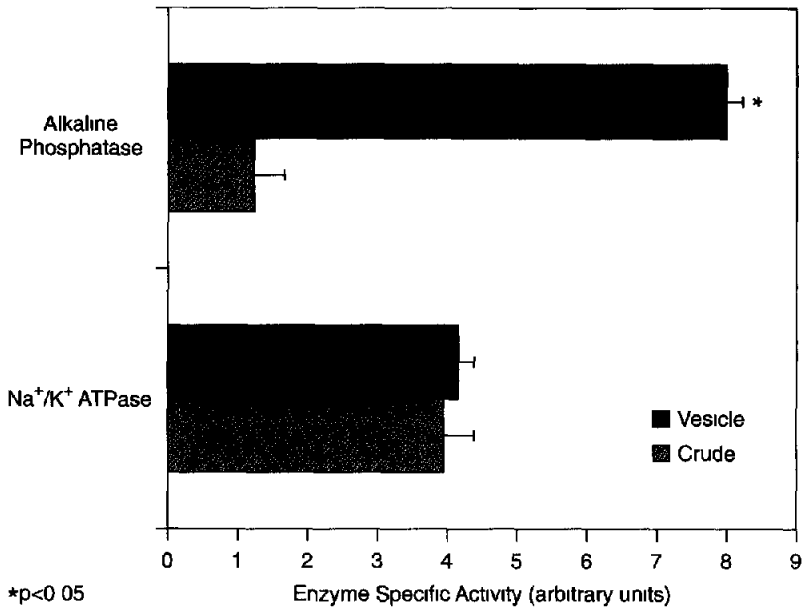

Fig. 1. Specific activity of marker enzymes for brush-border and basolateral membranes The activities for alkaline phosphatase (brush-border membrane) and Na^+/K^+-ATPase (basolateral membrane) in vesicles were compared to those of crude homogenates Values are expressed as relative ratios to crude homogenate Asterisk (*) denotes $P < 0.05$ vs crude homogenate

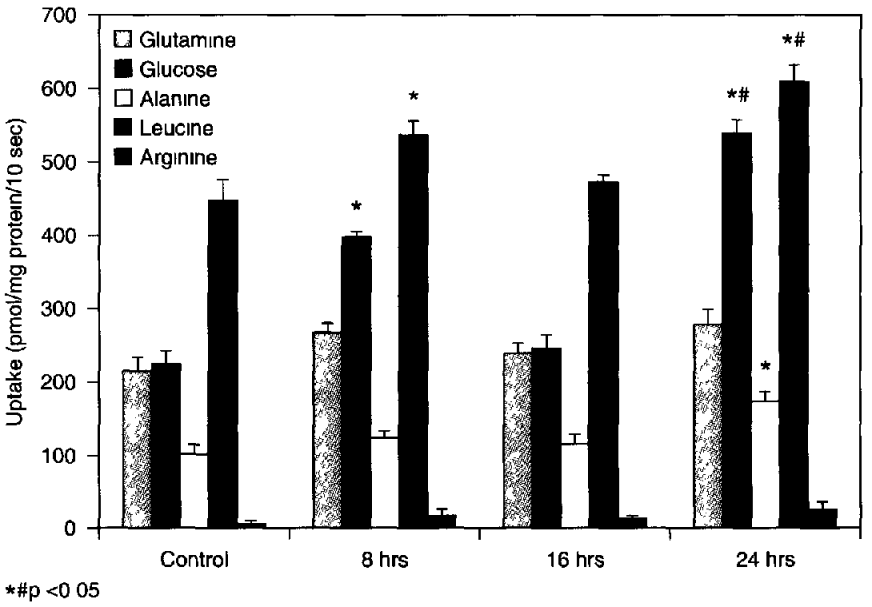

Fig. 2. Sodium-dependent substrate transport into BBMVs The figure is a composite of quadruplicate BBMV preparations Asterisks (*) and number signs (#) denote $P < 0.05$ vs unmarked groups for each time point

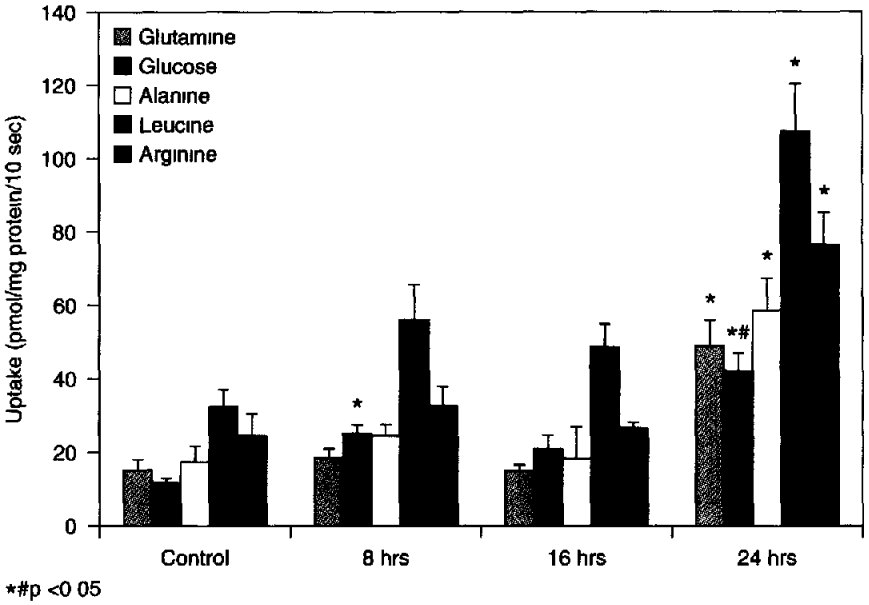

Fig. 3. Sodium-independent substrate transport into BBMVs The figure is a composite of quadruplicate BBMV preparations Asterisks (*) and number sign (#) denote $P < 0.05$ vs unmarked groups for each time point

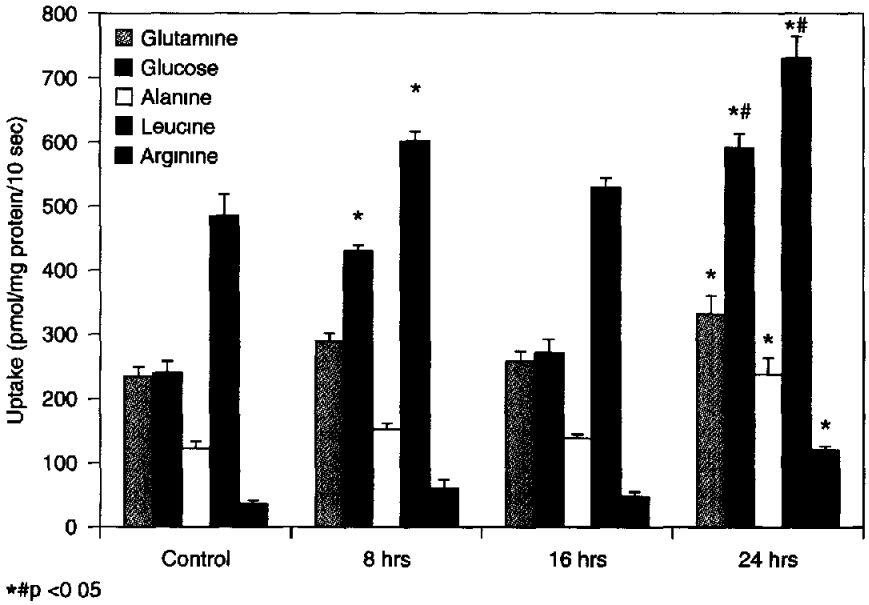

Fig. 4. Total substrate transport representing pooled sodium-dependent and sodium-independent uptake into BBMVs The figure is a composite of quadruplicate BBMV preparations Asterisks (*) and number sign (#) denote $P < 0.05$ vs unmarked groups

Total arginine transport at 8 and 16 hours following glucocorticoid treatment is not different from values in control animals but increases by 236% ($P < 0.05$) at 24 hours compared to control values, mainly as a consequence of sodium-*independent* (diffusion) arginine transport upregulation

Morphologic Assessment

Villus heights were not different among the experimental groups (P = NS, data not shown) Gross cellular histology was qualitatively normal throughout (P = NS, data not shown) Microvillus heights at 8 hours (6.56 ± 0.08 μm) were not different from values in control animals (6.89 ± 0.36 μm, P = NS) but were decreased by 27% at both 16 hours (5.08 ± 0.09 μm) and 24 hours (5.01 ± 0.11 μm) compared to control values ($P < 0.05$)

Mucosal DNA Content

When standardized for crude mucosal protein concentration (μg DNA/mg mucosal protein), total DNA content at 8 hours (99.72 ± 4.80 μg) and 16 hours (119.29 ± 6.28 μg) following treatment was not different from control values (106.57 ± 6.90 μg, P = NS) but was 75% greater (186.84 ± 12.12 μg) at 24 hours after glucocorticoid administration ($P < 0.05$)

Serum IGF-1 Concentration

Glucocorticoid treatment exerted no measurable effect on serum IGF-1 concentrations in any experimental group (data not shown)

DISCUSSION

To our knowledge, this is the first study demonstrating a time-dependent and substrate-specific glucocorticoid effect on mucosal brush-border membrane nutrient transport Total uptake of both glucose and leucine (active transport plus diffusion) demonstrates an initial significant upregulation at 8 hours followed by normalization at 16 hours There is further significant upregulation at 24 hours Total glutamine, alanine, and arginine uptake does not exhibit the bimodal pattern of glucose and leucine uptake but increases 24 hours following treatment Sodium-*independent* transport is the major mechanism for arginine uptake, whereas sodium-dependent transport assumes minimal importance

Amino acid transport into the cytoplasm occurs via functionally and biochemically distinct transport systems [10] Sodium-dependent transport mechanisms comprise the majority of free amino acid transport under physiologic conditions [11] Active amino acid transport is a carrier-mediated process that depends on an electrochemical gradient, which is maintained by an ATP-dependent Na^+/K^+ pump [10] Glucocorticoids have been shown to increase small intestinal net sodium and water absorption in rodents, probably by augmenting mucosal Na^+/K^+-ATPase activity at the basolateral membrane of villus cells [12] This mechanism probably accounts for the vast majority of glucocorticoid-mediated glucose, glutamine, alanine, and leucine uptake in our model

We chose the BBMV model because it has been well validated in previous investigations [10] Transport activity representative of that occurring in intact cells is well preserved, and alterations in transport following treatment with hormones, nutrients, growth factors, and cytokines reflect the changes that occur in vivo [13-15] The vesicle model permits clear assessment of intrinsic plasma membrane transport activity without confounding influences from active metabolism, substrate delivery, and cellular trans-effects.

Amino acids can also diffuse into cells, but this component of uptake is a minor pathway at physiologic amino acid concentrations In our model, sodium-*independent* transport represents both facilitated and passive diffusion of substrates across the plasma membrane [11] Our data demonstrate marked increases in substrate diffusion in response to dexamethasone administration This may represent steroid-induced changes in vivo in plasma membrane fluidity or permeability, allowing increased substrate flux through passive conduits and destabilized junctions [16-18] This effect is especially marked with respect to arginine transport, inasmuch as sodium-*independent* uptake comprises the vast majority of the uptake of this clinically relevant substrate.

The liver is the central organ of amino acid metabolism, assuming particular importance during septic and inflammatory states Dexamethasone increases system A (alanine), system y^+ (arginine), and system N (glutamine) transport activity in isolated hepatocytes [19,20] Dexamethasone may also play a permissive role in the regulatory effects of cytokines, especially interleukin-1, interleukin-6, and tumor necrosis factor, on hepatic acute-phase protein synthesis [21,22] Glucocorticoids mediate glutamine and alanine flux to the liver from skeletal muscle and lung parenchyma [23,24]

Our data suggest that dexamethasone induces intestinal transport system B and system y^+, as well as sodium-glucose cotransport Augmented leucine, glutamine, and alanine uptake values are all consistent with upregulated system B transport [25,26] System B is affected in a differential fashion, as leucine transport demonstrates a bimodal profile of upregulation, whereas glutamine and alanine transport is signifi-

cantly increased only 24 hours after treatment with glucocorticoid. We have previously demonstrated this differential system B upregulation in response to epidermal growth factor and human growth hormone treatment following massive enterectomy in the rabbit.[27] The ability to enhance the uptake of these specific nutrients may represent a means of reversing the catabolic state and improving overall nutritional status during critical illness [28-31]

The mechanisms by which glucocorticoids augment amino acid uptake are poorly defined Stress states are accompanied by alterations in the secretion and levels of several hormones that may influence amino acid and protein metabolism Stress-related increases in endogenous glucocorticoids are generally associated with hyperglucagonemia, hyperinsulinemia, altered fatty acid metabolism, hypersympathetic adrenergic tone, relative tissue insulin resistance, and hyperglycemia.[6] Glucocorticoids could augment intestinal nutrient uptake by increasing splanchnic oxidative fuel requirements, increasing mesenteric blood flow, upregulating enterocyte membrane transport, or enhancing mucosal and mitochondrial enzymatic activity responsible for amino acid utilization [32]

Glucose and lucine transport both exhibit a unique bimodal pattern of upregulation with an intervening period of normalization Glucocorticoid-mediated changes in small intestinal electrolyte transport reflect time-dependent effects on both crypt and villus cells in the mucosa [33] These different time-dependent effects may represent genomic and nongenomic effects of steroids on cellular function.[16] As the plasma half-life of dexamethasone in the rabbit is approximately 86 ± 21 minutes, the pulse dose-induced transport changes at times when plasma concentrations should have normalized [34] The classical explanation of steroid hormone action involves activation of high-affinity intracellular receptors, which then modulate gene expression and protein synthesis (genomic effect).[35] The rapidity with which steroids exert their electrophysiologic actions strongly suggests that these hormones also act through nongenomic mechanisms, potentially by binding to specific membrane receptors.[36]

We propose that the initial glucocorticoid-mediated glucose and leucine transport effects at 8 hours are nongenomic in etiology. Potentially, a pool of preformed transport proteins is mobilized from cytoplasmic stores and recruited to the plasma membrane, thereby effecting greater substrate uptake. By 16 hours, substrate uptake rates normalize as transport protein reserves are depleted or degraded without replenishment. Steroid-mediated genomic effects become manifest by 24 hours following treatment as de novo transport protein synthesis is stimulated. Our data illustrate modest increases in mucosal DNA content 24 hours following steroid treatment Cellular proliferation increases the total number of nutrient transporters available in the intestinal mucosa (V_{max} upregulation), accounting for increased substrate transport. A change in carrier affinity for its substrate (K_m shift) is unlikely.

Improved nutrient transport within 24 hours following glucocorticoid infusion appears to be secondary to biochemical alterations rather than structural changes Although intestinal mucosa may adapt to conditions of stress by morphologic changes, villus and microvillus hypertrophy was not noted Further, microvillus heights were decreased following steroid treatment. Alterations in cell surface adhesiveness, electrophoretic properties, and antigen binding characteristics may be responsible for the observed microvillus changes [37]

IGF-1 modulates gut function by complex interactions with stress hormones and growth factors [38] IGF-1 receptors that mediate the growth effects of IGF-1 in gastrointestinal epithelial cells are present in all segments of the gastrointestinal tract.[39] We demonstrated no changes in serum IGF-1 levels in response to acute dexamethasone treatment. In contrast, Read et al [40] reported depressed plasma IGF-1 levels and total gut wet weight in rats undergoing prolonged dexamethasone infusion Although we did not quantitate gut weight, we demonstrated an increased proliferative index (i e., increased mucosal DNA content) and augmented transport function These disparate findings may represent the differential effects of acute versus prolonged glucocorticoid treatment, in addition to dose-response and species-specific steroid effects.

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Discussion

Dr. J. Rombeau (Philadelphia, Pa) My questions relate to the specificity of your results If you inhibit or block the glucocorticoids, do you in turn abrogate the transport effects shown in the studies? Second, have you had the opportunity to look at other counter-regulatory hormones such as glucagon or the catecholamines? Finally, have you looked at other amino acids besides those shown in this study, such as glycine or lysine, to see if indeed these are specific changes?

Dr. P. Iannoli With respect to the issue of blocking steroid action, we have not done those studies yet The use of RU486, an inhibitor of the steroid receptor, has been shown to downregulate amino acid transport, but those studies were not performed in the gut There is no question, nonetheless, that the steroid receptor is central to this effect I am not aware of a specific blocker for the cytosolic 94 KD receptor We do plan to block portions of protein synthesis to define where this effect is regulated For exam-

ple, using such agents as methotrexate, actinomycin D, or cycloheximide, we can pinpoint whether it is protein synthesis or whether it is RNA transcription or translation We have not looked at a glucagon or the catecholamines, assuming that would be very interesting data We have looked at hormones such as growth hormone and epidermal growth factor and have documented changes in amino acid transport We have not looked at other amino acids but chose these to represent multiple, different carrier systems.

Dr. S. Ashley (Boston, Mass) I think there is some evidence from other studies that once enterocytes move up from the crypt to the villus, the molecular expression of the transporter is already set and all that changes is the amount at the brush border That is consistent with what you found I wonder if you have done anything to try and separate crypt cells from villous cells and to see whether these changes are specific to one area

Dr. Iannoli. We have not specifically looked at the effects of glucocorticoids on villous vs crypt cell function We have, however, studied the effects of acute intestinal ischemia on nutrient transport We have clearly documented that acute intestinal ischemia of 1 hour causes uniform loss of villous tips with retention of crypt cells and maintenance of completely normal transport in those cells Those crypt cells likely do retain the ability to adapt to a changing hormonal status

Trends in Bile Duct Injuries From Laparoscopic Cholecystectomy

R Matthew Walsh, M D , J Michael Henderson, M D , David P Vogt, M D , James T Mayes, M D , Sharon Grundfest-Broniatowski, M D , Michel Gagner, M D , Jeffrey L Ponsky, M D , Robert E Hermann, M D

Bile duct injuries are a serious complication of cholecystectomy Laparoscopic cholecystectomies (LC) were originally associated with an increased incidence of injuries Patients referred to a tertiary center were reviewed to assess the trends in the number, presentation, and management Seventy-three patients were referred over a 6-year period with a maximum of 17 patients referred in 1992, but the number has not declined substantially over time The persistent number of referrals is a consequence of ongoing injuries One third of injuries were diagnosed at LC, and the use of cholangiography has not increased The number of cystic duct leaks has not decreased and they represent 25% of all cases The level of injury has remained unchanged with Bismuth types I and II in 37% and types III and IV in 38% Excluding patients with cystic duct leaks, 58% were referred after a failed ductal repair Definitive treatment with biliary stenting was successful in 37%, and 34 patients (47%) required a biliary-enteric anastomosis Complications occurred in 18 patients (25%) including seven with postoperative stricture or cholangitis No biliary reoperations have been performed at a mean follow-up of 36 months (J GASTROINTEST SURG 1998, 2 458-462)

Within a span of several years, laparoscopic cholecystectomy (LC) has largely replaced an operation that has been in use for a century Benefits that include less pain and more rapid recovery have hastened the acceptance of LC [1-3] The introduction of the operation was associated with an increased incidence of biliary complications, which were reported to be three times more frequent than those that occur after traditional cholecystectomy The incidence of major bile duct injury following LC is generally agreed to be 0 6%,[4] whereas the established incidence after open cholecystectomy is 0 2% [5,6] It is possible that with increased utilization and familiarity with the operation (i e , progression to the plateau of the "learning curve"), the frequency and type of biliary injuries will be decreased as compared to those initially reported Alternatively, the incidence of biliary tract complications may remain elevated and they may be viewed as an inherent risk of LC

The recognized increase in biliary tract morbidity following LC may have altered the performance of the operation with increased use of operative cholangiography, or it may have changed the initial management of a recognized injury A review of patients treated at a tertiary referral center for biliary tract injuries following LC was undertaken to determine whether the passage of time has had any impact on the number of injuries, altered the performance of the operation, or given any indication of the inherent limitations of the procedure.

MATERIAL AND METHODS

A prospective database is maintained for all patients evaluated for a laparoscopic bile duct injury in the Department of General Surgery at The Cleveland Clinic The initial patient referral for a bile duct injury following LC occurred in January 1991, and all subsequent patients evaluated through December 1996 were reviewed Nearly all patients were referred from outside hospitals Attempts were made to retrieve operative reports, relevant x-ray films, and lab-

From the Department of General Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio
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Reprint requests R Matthew Walsh, M D , The Cleveland Clinic Foundation, Department of General Surgery, 9500 Euclid Ave , Cleveland OH 44195

oratory data. The database contains information regarding operative findings, use and success of cholangiography, time to diagnosis, initial evaluation and management, time to referral and presentation, subsequent evaluation and management, complications, and current status Follow-up consisted of a combination of chart review, telephone contact, and laboratory data from primary care physicians.

To assess significant changes over time, statistical comparisons were made for the first 3 years, 1991 to 1993, and the more recent 3 years, 1994 to 1996. Group comparisons were made for single variables by the exact chi-square test and continuous variables by the Wilcoxon rank-sum test Statistical significance was determined at $P < 0.05$

RESULTS

Over a 6-year period, from January 1991 through December 1996, a total of 73 patients were evaluated in the Department of General Surgery at The Cleveland Clinic for biliary complications following LC Patients were separated by year of referral to assess trends over time in regard to patient characteristics, presentation, and management. Patient characteristics are presented in Table I. Results are recorded when accurate information was available concerning cholecystitis or performance and outcome of cholangiography based on the operative report. The number of patients evaluated per year has ranged from a low of nine in 1991 to a maximum of 17 in 1992. There has been no substantial reduction since 1993. The age range is 19 to 81 years with a mean of 47 years. The percentage of patients originally operated on for acute cholecystitis has not significantly decreased over time, ranging from a high of 50% in 1991 to 9% in 1996 (1991 to 1993 vs. 1994 to 1996, $P = 0.25$).

The role of cholangiography was investigated without the benefit of intraoperative films or operative videos Less than half of the patients had cholangiography attempted and approximately three quarters of these attempts were successful. Correct interpretation of an abnormal cholangiogram was one method of making the intraoperative diagnosis of a bile duct injury. There was no significant increase in the utilization of cholangiography over time in those patients who sustained a bile duct injury ($P = 0.55$). There also did not appear to be a correlation between frequency of cholangiography and ability to make the intraoperative diagnosis of a bile duct injury.

The intraoperative diagnosis of a bile duct injury was made in 33% of cases (Table II) and ranged from 24% to 50% per year The incidence has not changed significantly over time ($P = 0.36$) Review of the operative records indicates that unexplained bile was the

Table I. Laparoscopic bile duct injuries Patient characteristics

Year	No of patients	Mean age (yr)	Acute cholecystitis (%)	Cholangiography	
				Attempted (%)	Successful (%)
1991	9	45	4 (50)	2 (29)	1 (50)
1992	17	46	6 (38)	9 (60)	7 (78)
1993	10	49	1 (10)	4 (44)	3 (75)
1994	16	48	5 (31)	8 (57)	4 (50)
1995	10	54	1 (10)	2 (25)	2 (100)
1996	11	39	1 (9)	3 (27)	3 (100)
TOTAL	73	47	10 (14)	28 (44)	20 (71)

Table II. Laparoscopic bile duct injuries Presentation

Year	Leak	Obstruction	Both	Intraoperative diagnosis No (%)	Prior repair No. (%)	Months to transfer (median)	
						Repair	No repair
1991	3	4	2	3 (33)	5 (56)	1 6	1 2
1992	7	5	5	4 (24)	6 (35)	4 1	0 9
1993	3	6	1	3 (30)	6 (60)	12 0	0 9
1994	7	6	3	6 (38)	7 (44)	0 8	0 3
1995	5	5	0	5 (50)	3 (30)	23 4	0 6
1996	4	5	2	3 (27)	5 (45)	2 1	1 1
TOTAL	29 (40%)	31 (42%)	13 (18%)	24 (33)	32 (44)	4 7	0 7

most common manner in which an injury was recognized All patients with an injury recognized at LC underwent conversion to an open procedure and repair

Patients were characterized at referral by their predominant type of presentation, either as a leak, biliary obstruction, or complex type of injury that included elements of both (Table II) The median time to diagnosis of a bile duct injury for those not diagnosed intraoperatively has not changed significantly, with an average of 4.5 days. The proportion of isolated biliary leaks has remained constant, representing 40% overall Some component of biliary obstruction predominated at referral, with 60% presenting as an obstruction or in combination Forty-four percent of all patients presented with a prior biliary repair, and if patients with an isolated cystic duct injury are excluded, 58% of our referral population had a failed repair The type of biliary repair was either a primary duct to duct, or biliary-enteric anastomosis The time to referral has remained similar over time, at a median of 4 7 months following a failed repair and a median 0 7 months if no repair was performed. In Table III patients were separated by Bismuth level into isolated cystic duct leaks (type 0), relatively easier to manage common bile duct and common hepatic duct strictures (types I and II), and complex injuries (types III and IV) [7] The incidence of cystic duct leaks has not significantly decreased over time, representing approximately 25% of all patients Lower bile duct injuries (types I and II) and proximal injuries (types III and IV) represent an equal proportion of injuries, 37% and 38%, respectively, which have remained uniform over time ($P = 0\ 67$)

The principal methods of treatment (see Table III) for these injuries included either endobiliary stenting or biliary-enteric bypass Definitive treatment with biliary stenting alone (achieved by percutaneous or endoscopic access) was performed in 37%, ranging from 30% to 44% per year ($P = 0\ 88$) Fourteen of the 27 patients treated with stenting had a common bile duct, common hepatic duct, or right hepatic duct leak The remaining 13 patients treated with stents has a cystic duct leak, 72% of all cystic duct leaks A total of 34 patients (47%) underwent biliary-enteric bypass, ranging from 40% to 55% per year ($P = 0\ 91$) Seven patients (20%) underwent preoperative stenting for at least 1 week, with a range of 4 to 100 weeks Twelve patients were not primarily treated with stenting or biliary bypass A variety of procedures were performed in this group including percutaneous drainage, laparoscopy/laparotomy for aspiration and drain placement, and in two patients no treatment When biliary-enteric anastomoses were performed, stenting of the anastomosis was used only for anastomoses considered tenuous, usually in the setting of proximal, nondilated bile ducts When employed, postoperative stents were used for 1 to 3 months

Complications occurred frequently in patients treated for bile duct injuries, regardless of the level of injury A total of 18 patients (25%) sustained complications at a mean follow-up of 31 months, two patients were lost to follow-up Four patients with complications (22%) had isolated cystic duct injuries A total of seven patients have evidence of stricture or recurrent clinical cholangitis following biliary-enteric bypass Three of these patients have been managed with percutaneous biliary dilatation and four with oral antibiotics, no biliary reoperations have been performed Three of these patients had Bismuth level III injuries—two with level IV, and one each with levels I and II

Table III. Laparoscopic bile duct injuries Management

Year	Bismuth injury level (No.) 0	I/II	III/IV	Stent No. (%)	Bypass No. (%)	Complications Stricture No.	Other	Months' follow-up Mean	Median
1991	2	6	1	3 (33)	4 (44)	1	Leak Small bowel obstruction	59 1	63 7
1992	6	5	6	7 (41)	8 (47)	2	Liver abscess	49 9	52 6
1993	2	3	5	3 (30)	5 (50)	1	Cirrhosis Pancreatitis	42 4	47 1
1994	4	7	5	7 (44)	7 (44)	2	3-ABD Abscesses	28 7	26 8
1995	2	3	5	3 (30)	4 (40)	1	Appendicitis	22 8	17 3
1996	2	3	6	4 (36)	6 (55)	0	Cystic bleed	14 1	10 9
TOTALS	18	27	28	27 (37)	34 (47)	7	11	36 2	37 8

DISCUSSION

A bile duct injury remains the major complication of LC, and data from our tertiary referral facility indicate that the number of injuries has not decreased with time Although the highest number of referrals was seen in 1992, as also found in a multi-institutional study,[8] the anticipated tapering in the number of injuries has not occurred Recent large population-based studies have documented a reduction in the incidence of injuries.[9,10] However, the incidence of injury is still not as low as is seen with open cholecystectomy. This has occurred despite increased application of the procedure and presumed plateauing of the learning curve, which may be achieved after as few as 30 laparoscopic cholecystectomies [11] Many factors may be responsible for the consistency in the number of referrals including complexity of the problems requiring referral to a tertiary center, delayed presentation of injuries or sequelae of prior intervention, or undiminished number of mishaps. We can only speculate as to the true denominator of LCs and injuries in our referral population, but if Connecticut is representative, then 89% of biliary tract injuries are being managed at the hospital where the LC is performed.[9]

The type and level of injury, including cystic duct leaks, have not changed with time This implies that the mechanisms of injury are likely the same. The time to diagnosis and time to referral in our population indicate that we are not identifying an increased number of delayed injuries but are continuing to see acute injuries Although patients with previously repaired injuries are frequently referred later, this appears not to be responsible for the persistent number of referrals Thus our data would suggest that the incidence of referrals for bile duct injuries has not diminished because acute injuries continue to occur

The occurrence of a bile duct injury during LC can be attributed to the misidentification of ductal structures.[12] Accurate identification of biliary anatomy is possible with correct performance of LC to minimize the incidence of injuries to the level seen with open cholecystectomy [13-15] Optimal performance of the operation should be possible even in cases of severe inflammation, aberrant anatomy, and poor visualization [10] Should an injury occur, it is important that it be recognized intraoperatively to reduce the severity of the injury and the overall treatment costs.[16,17] Only one third of our patients had an intraoperative diagnosis of an injury, and the intraoperative detection rate in other series does not exceed 50%.[10] Although intraoperative cholangiography may not prevent an injury, it can increase its recognition [8,18] Our data indicate that the value of routine cholangiography has not been accepted by the surgical community, where 28% overall had cholangiography attempted, and our findings are similar to those from other studies of patients with bile duct injuries.[13]

Management of biliary injuries depends on the type, presentation, and level of injury The high number of failed prior repairs reflects the complexity of some of these injuries and supports early referral to specialized centers.[19] This may include the more than one third of the injuries that may be recognized intraoperatively It may be advisable to simply drain a recognized injury and not convert to an open procedure where some type of repair will be required. If repair is attempted, it should be accomplished with minimal mobilization of the bile duct to decrease further proximal ischemia. In our experience the management of complex proximal injuries, Bismuth levels III and IV, require a multimodality approach This frequently will require a biliary-enteric anastomosis either as an immediate, staged, or reoperative procedure In our experience 20% of patients who require a biliary-enteric bypass are treated with a period of stenting. A delayed repair is nearly always preferred when the injury can be traversed to allow internal biliary drainage. This approach is not meant to be definitive, but a mechanism to permit proximal dilatation after the stent is removed, along with resolution of any associated bile peritonitis, and to define the ultimate proximal level of a stricture that may progress as a result of bile duct ischemia. Long-term success of operative repair of biliary strictures is excellent,[20] but long-term success in patients with more complex injuries has yet to be determined.

The persistent number of referrals for cystic duct leaks is surprising since the cystic duct remnant can be readily secured with Surgitie (United States Surgical Corp., Norwalk, Conn.) when necessary [21] Cystic duct leaks cannot be considered innocuous as they accounted for 36% of our morbidities Postoperatively they can usually be managed with a combination of percutaneous drainage and endobiliary stenting if necessary [22] In our experience an isolated leak from the cystic duct or bile duct can be successfully managed with endobiliary stenting

CONCLUSION

The incidence of bile duct injuries from LC is not decreasing with time The risk of an injury has not resulted in an increased use of operative cholangiography in the surgical community The time to referral indicates that injuries continue to occur The presentation and level of these injuries have not been altered, implying that the same mechanisms of injury

are responsible The management of these injuries remains difficult and is often associated with complications

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Contractile Activity of Circular Smooth Muscle in Rats One Year After Small Bowel Transplantation: Differing Adaptive Response of the Jejunum and Ileum to Denervation

Chikashi Shibata, M D, Michel M Murr, M D, Bruno Balsiger, M D, William J Anding, Michael G Sarr, M D

The aim of the present study was to determine the long-term effects of isogeneic small bowel transplantation (SBT) on jejunal and ileal circular smooth muscle contractile activity in the rat. Transmural strips of circular muscle were prepared from proximal jejunum and distal ileum of 1-year-old control rats and rats 1 year after SBT (SBT-1Y) to measure isometric force. Spontaneous contractile activity and the dose-responses to bethanechol and norepinephrine were studied Electrical field stimulation (EFS) at varying frequencies (1 to 20 Hz) was evaluated under adrenergic and cholinergic blockade to investigate inhibitory nerves Spontaneous activity both in the jejunum and ileum in SBT-1Y rats was not different compared to control rats Sensitivity to bethanechol did not differ between control and SBT-1Y rats in the jejunum or ileum Sensitivity to norepinephrine, however, was significantly increased after SBT in the ileum but not in the jejunum During EFS, inhibition was seen at low frequencies, and contractions were induced at high frequencies in all groups The degree of inhibition did not differ between control and SBT-1Y rats in the jejunum, however, it tended to be increased in the ileum after SBT The long-term adaptive response of smooth muscle to the extrinsic denervation accompanying SBT differs between the jejunum and the ileum (J GASTROINTEST SURG 1998,2 463-472)

Small bowel transplantation (SBT) represents the new frontier in the treatment of selected patients with intestinal failure. Yet, although significant progress has been made in its clinical application, many questions remain unresolved.[1,2] From a physiologic standpoint, long-term function of the small intestine after SBT, however, remains largely unknown. SBT necessitates a chronic and apparently permanent extrinsic denervation,[3] a temporary disruption of intrinsic neural continuity of the graft with the proximal gut, a perioperative ischemia/reperfusion injury, and a host of immune phenomena; all these obligate sequelae of the transplantation procedure affect intestinal motor function. Indeed, studies in dogs after models of intestinal autotransplantation have shown changes in global patterns of motility[4-7], abnormalities in motor patterns in humans after intestinal allotransplantation are less well defined.[8]

In previous work[9-12] we studied the contractile function of jejunal and ileal circular muscle early (1 week and 8 weeks) after SBT and found that SBT affects the contractile activity in the jejunum and ileum differently. In the jejunum spontaneous contractile activity was increased without any changes in the sensitivity to cholinergic and adrenergic agents, and the function of nonadrenergic, noncholinergic (NANC) inhibitory neurons activated during electrical field stimulation (EFS) appeared to be upregulated 1 week

From the Department of Surgery and the Gastroenterology Research Unit, Mayo Clinic and Mayo Foundation, Rochester, Minn
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Correspondence Michael G Sarr, M D, Professor of Surgery, Gastroenterology Research Unit, Mayo Clinic, 200 First Street SW, Rochester, MN 55905

after SBT but returned to control activity 8 weeks later In the ileum, however, neither spontaneous activity nor function of NANC neurons was altered after SBT, but the sensitivity to adrenergic agonists, but not to cholinergic agonists, was increased Because we used an isogeneic model of SBT, these changes were independent of immunologically mediated events and thus were related to the effects of complete extrinsic denervation, disruption of continuity of the enteric nervous system with the proximal gut, and potentially an ischemia/reperfusion injury necessitated by the (iso)transplantation procedure

Because the late or chronic effects of SBT on smooth muscle contractility are largely unknown, we studied rats 1 year after SBT to see if these differing changes in contractility in the jejunum and ileum persisted We hypothesized that changes in contractile mechanisms of the jejunum and ileum observed early after transplantation would persist 1 year later The aims of the present study were to determine separately in the jejunum and ileum the changes in spontaneous activity, sensitivities to the muscarinic cholinergic agonist bethanechol and to the adrenergic agonist norepinephrine, and the response to EFS in rats 1 year after isogeneic orthotopic SBT This approach would allow some insight into the adaptive response of the small bowel to SBT (chronic extrinsic denervation).

MATERIAL AND METHODS

Preparation of Animals

Procedures and subsequent animal care were undertaken according to the guidelines of the Animal Care and Use Committee of the Mayo Foundation in accordance with the guidelines of the National Institutes of Health and the United States Public Health Service Policy on the Humane Use and Care of Laboratory Animals All animals used were male inbred Lewis rats (Harlan Sprague-Dawley, Indianapolis, Ind) weighing 250 to 300 g at the time of arrival Animals were anesthetized by an intraperitoneal injection of 30 to 50 mg/kg sodium pentobarbital (Ampro Pharmacy, Arcadia, Calif)

Small Bowel Transplantation. SBT was performed using two isogeneic rats to avoid immunologic phenomenon or the need for immunosuppressive agents, each of which would introduce confounding variables One-stage orthotopic SBT was performed using standard microvascular techniques described previously [9] In brief, the jejunoileum was removed from the donor based on an aortic cuff, including the origin of the superior mesenteric artery, and on the portal vein Revascularization in the recipient was performed by end-to-side, aorta-aorta, and portal vein–inferior vena cava anastomoses Continuity of the alimentary tract was reestablished by immediate end-to-end jejunojejunostomy and ileoileostomy after the native jejunoileum was removed Five and eight rats maintained for 1 year after SBT were used for the jejunal and ileal experiments, respectively (SBT-1Y)

Controls. One-year-old rats (n = 5 for the jejunum and n = 8 for the ileum) were used as a control group because of some experimental evidence suggesting changes in control of contractile activity with age [13] We did not use a sham-operated control group because previous work from our laboratory showed that jejunal and ileal smooth muscle of sham-operated rats behaved similarly to that of nonoperated control rats [9,12]

Recording of Contractile Activity

After rats were anesthetized as previously described, a standardized segment of proximal jejunum 10 cm distal to the duodenojejunal junction (or jejunojejunostomy) and distal ileum 10 cm proximal to the ileocecal junction (or ileoileostomy) were removed and pinned in chilled modified Krebs-Ringer's bicarbonate solution (concentrations in mmol/L as follows NaCl = 118.3, KCl = 4 7, $CaCl_2$ = 2 5, $MgSO_4$ = 1 2, KH_2PO_4 = 1 2, $NaHCO_3$ = 25 0, calcium disodium edeate = 0 26, and glucose = 11 1) The mesentery was excised and the jejunum opened along the mesenteric border Eight full-thickness muscle strips (1 to 2 mm wide) cut in the direction of the circular muscle layer were suspended in eight temperature-controlled (37 5° C) 25 ml tissue chambers filled with modified Krebs-Ringer's bicarbonate solution continuously bubbled with 95% oxygen and 5% carbon dioxide The strips were suspended vertically between a fixed point at the bottom of the chamber and a noncompliant force transducer (Kulite Semiconductors Products Inc , Leonia, N J) to measure isometric force Contractile activity was monitored on an eight-channel recorder (Grass 7D Polygraph, Grass Instrument Co , Quincy, Mass) and simultaneously converted to digital signals by a computerized data acquisition system (Biopac Systems, Inc , Goleta, Calif) The digital signals were displayed and stored on a personal computer (Reason 486, Reason Technology, Inc , Minneapolis, Minn) for on-line analysis using specialized software (Acqknowledge, Biopac Systems, Inc , Goleta, Calif)

Tension-Length Experiment. After equilibration for 45 to 60 minutes with intervening washout every 15 minutes, each strip was incrementally stretched to its optimal length (L_o), which was defined as the length beyond which further stretch failed to increase

the amplitude or frequency of spontaneous contractile activity. Stretches were separated by intervals of 10 to 12 minutes. All subsequent experiments were performed at this L_o

Experimental Protocol

Spontaneous Contractile Activity. Baseline spontaneous activity was evaluated in all chambers at L_o Spontaneous activity was then recorded in two chambers after a 10-minute incubation with 10^{-6} mol/L tetrodotoxin (TTX) and in four other chambers under NANC conditions after a 35-minute incubation with atropine (10^{-6} mol/L), phentolamine (5×10^{-6} mol/L), and propranolol (10^{-5} mol/L).

Concentration-Response Experiment. Muscle strips were exposed to increasing concentrations of bethanechol (3×10^{-6}-10^{-4} mol/L) or norepinephrine (10^{-6} - 3×10^{-5} mol/L) for 6 minutes before the next dose was evaluated. After each dose of bethanechol was evaluated, the chamber was washed, and the strip was allowed to equilibrate for 10 minutes before adding the next higher dose. In the dose-response experiments to bethanechol in the ileum, 10^{-6} mol/L TTX was administered immediately after each wash In two other chambers, norepinephrine was added in a cumulative manner without intervening washes

Electrical Field Stimulation. The response of the muscle strips to EFS was studied under NANC conditions After determining optimal conditions in the jejunum and ileum separately, square wave currents (amplitude = 20 and 40 V, pulse width = 4 and 1 msec in the jejunum and ileum, respectively, stimulus duration = 10 seconds) were delivered every 3 minutes, and the responses to varying frequencies (1, 2, 5, 10, and 20 Hz) were studied

Measurement of Weight. At the conclusion of each experiment, all muscle strips were washed thoroughly, blotted on a No. 1 filter paper, and weighed

Drugs and Chemicals

Bethanechol chloride, norepinephrine bitartarate salt, DL-propranolol hydrochloride, phentolamine hydrochloride, atropine sulfate, and TTX were purchased from Sigma Chemical Company, St. Louis, Mo All concentrations are expressed as the final molar concentration in the tissue chamber

Data Analysis

Baseline total spontaneous contractile activity, as measured by the integral of the force (*g*) generated per 5 minutes (area under the contractile curve), was determined at L_o before any interventions were performed The frequency of contractions, analyzed visually by counting the number of phasic contractions per 5 minutes, was expressed as contractions per minute

Responses of muscle strips to bethanechol and norepinephrine were quantitated as the integral of force generated in the first 5 minutes after administration of the drug Dose-response curves were obtained for bethanechol by expressing contractile response as the percentage of the response to the highest dose evaluated (10^{-4} mol/L) and for the inhibitory effects of norepinephrine by expressing responses as the percentage of baseline spontaneous contractile activity. The negative log of the equieffective concentration that caused 50% of the maximal response (ED_{50} for bethanechol), or reduction in spontaneous activity to 50% of its basal activity (ED_{50} for norepinephrine) was calculated.

Contractile activity during EFS was quantitated by calculating the force generated during the 10-second stimulus and comparing this value to the force of baseline activity per 10 seconds determined for each strip for a 5-minute period immediately before beginning EFS The "off contraction" that occurs just after the EFS is stopped was specifically not included in the response, because this response represents a different phenomenon and is not necessarily a function of the NANC inhibitory neurons Because the response to EFS is biphasic (inhibitory at low frequencies and stimulatory at higher frequencies), the equieffective frequency (F_{100}) was calculated, F_{100} was defined as the frequency that produced a response equal to baseline activity, that is, the calculated frequency of EFS at which the response to EFS shifts from net inhibition to net stimulation

The force generated was standardized per wet weight of each strip Each parameter was calculated for each rat, and the group means ± standard error of the mean (SEM) were calculated. Mean values between groups were compared with Student's *t* test or with one-way analysis of variance, depending on the experiment, if significance was found with analysis of variance, means were compared using Student's *t* test with Bonferroni's correction for multiple comparisons. All data were expressed as mean ± SEM

RESULTS

Spontaneous Contractile Activity

Jejunum. Neither the integral of force (total contractile activity) nor the frequency of spontaneous contractile activity was different 1 year after SBT when compared to values in the 1-year control rats (Fig 1, Table I). Under NANC conditions, certain changes occurred. In control tissue the integral of

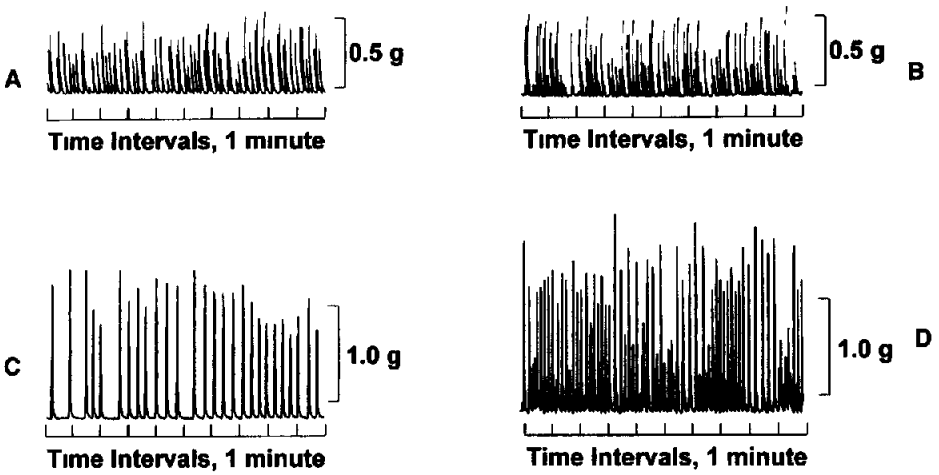

Fig. 1. Changes in spontaneous baseline contractile activity of rat circular muscle strips **A**, Jejunal control, **B**, jejunal muscle 1 year after SBT, **C**, ileal control, **D**, ileal muscle 1 year after SBT

Table I. Spontaneous contractile activity of jejunal and ileal circular muscle after small bowel transplantation*

	Baseline†		NANC conditions‡§		TTX (10^{-6}mol/L)§	
	Force	Frequency	Force	Frequency	Force	Frequency
Jejunum						
Control	3 2 ± 0 4	16 5 ± 1 1	2 2 ± 0 6‖	28 3 ± 2 4‖	3 0 ± 0 7	27 8 ± 1 5‖
(n = 5)			(3 2 ± 0 4)	(16 8 ± 1 8)	(3 3 ± 0 4)	(15 6 ± 1 6)
SBT-1Y	2 9 ± 0 3	13 7 ± 2 6	2 9 ± 0 4	15 7 ± 4 8	2 7 ± 0 6	20 6 ± 3 9‖
(n = 5)			(2 7 ± 0 4)	(12 2 ± 3 1)	(3 4 ± 0 5)	(13 8 ± 3 9)
Ileum						
Control	3 2 ± 0 5	2 4 ± 0 5	3 4 ± 0 6	2 2 ± 0 5	2 8 ± 0 5	2 9 ± 0 5
(n = 8)			(3 3 ± 0 6)	(2 5 ± 0 6)	(3 2 ± 0 6)	(2 9 ± 0 4)
SBT-1Y	3 8 ± 0 3	4 3 ± 0 5¶	4 0 ± 0 4	5 7 ± 0 9‖	4 1 ± 0 5	6 2 ± 0 8‖
(n = 8)			(3 6 ± 0 4)	(4 3 ± 0 5)	(4 3 ± 0 4)	(4 7 ± 0 6)

NANC = nonadrenergic, noncholinergic, TTX = tetrodotoxin, SBT-1Y = small bowel transplantation 1 year postoperatively, n = number of rats in each group

*Mean ± SEM, force = $g \cdot 5$ min/mg weight, frequency = contractions/min

†Eight muscle strips evaluated in each rat

‡Atropine (10^{-6}mol/L), phentolamine (5×10^{-6}mol/L), and propranolol (10^{-5}mol/L)

§Numbers in parentheses are values before drug administration, n = 2 muscle strips per rat

‖$P < 0.05$ compared to values in the same group before drug administration (baseline conditions)

¶$P < 0.05$ compared to control values under baseline conditions

force was significantly decreased, and the frequency was significantly increased, these parameters were not altered by NANC conditions 1 year after SBT (see Table I) Administration of TTX did not change the integral of force when compared to baseline conditions but did significantly increase the frequency of contractions in both control and SBT-1Y rats (see Table I).

Ileum. The frequency of contractions but not the total force was increased after SBT under baseline and NANC conditions as compared to control rats (4 3 ± 0 5 vs 2 4 ± 0 5 and 5 7 ± 0 9 vs 2 2 ± 0 5 contractions/min, $P < 0.05$ each, respectively) TTX induced similar changes, the integral of force was unchanged in both the control and SBT-1Y rats, but the frequency of contractions was increased in the SBT-1Y group

Response to Bethanechol and Norepinephrine

Jejunum. Bethanechol induced a dose-dependent increase in contractile activity in the jejunum in both control and SBT-1Y rats (Fig 2, *A*) The sensitivities to bethanechol were not different when the two groups were compared, the ED_{50} 1 year after SBT was not different from control values (Table II). Nor-

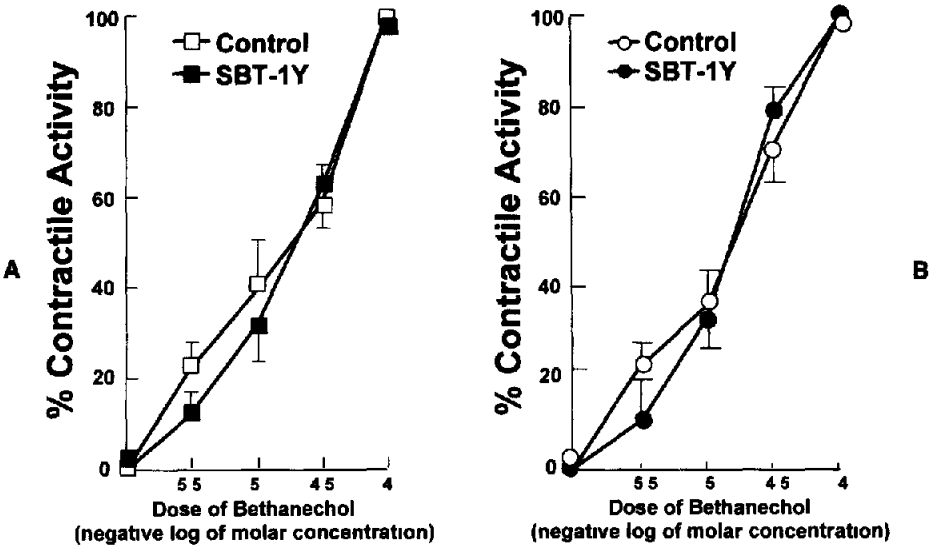

Fig. 2. Dose-response curves for bethanechol **A,** Response in jejunum (n = 5 rats/group) **B,** Response in ileum, TTX (10^{-6} mmol/L) was added to the ileal tissue chamber (n = 8 rats/group)

Table II. ED_{50} for bethanechol and norepinephrine in rat jejunal and ileal circular muscle*

	Bethanechol	Norepinephrine
Jejunum		
Control (n = 5)	4 7 ± 0 1	5 3 ± 0 1
SBT-1Y (n = 5)	4 8 ± 0 2	4 9 ± 0 3
Ileum		
Control (n = 8)	4 9 ± 0 1	5 2 ± 0 2
SBT-1Y (n = 8)	4 8 ± 0 2	5 9 ± 0 1†

ED_{50} = equieffective dose causing 50% of maximal response, SBT-1Y = small bowel transplantation 1 year postoperatively
*Mean ± SEM, values are negative log of drug concentrations that evoked 50% response, two muscle strips were evaluated per rat
†P <0 05 compared to control value under the same condition

epinephrine dose dependency inhibited contractile activity in the jejunum in a similar manner in both groups (Fig 3, *A*). The ED_{50} was not different in SBT-1Y rats when compared to control values (see Table II)

Ileum. Similar to the findings in the jejunum, bethanechol induced a dose-dependent increase in contractile activity in both groups (Fig. 2, *B*); the ED_{50} to bethanechol did not differ between groups (see Table II). In contrast to what occurred in the jejunum, the sensitivity to norepinephrine 1 year after SBT was markedly increased compared to control values (Fig 4), the dose-response curve in SBT-1Y rats was shifted to the left (Fig 3, *B*). ED_{50} 1 year after SBT was significantly greater than control values (5.9 ± 0.1 vs 5.2 ± 0.2, P <0.05) (see Table II), signifying a lesser concentration of norepinephrine to induce 50% inhibition of contractile activity and thus suggesting a hypersensitivity to norepinephrine in the ileum in SBT-1Y rats.

Response to Electrical Field Stimulation

Jejunum. In control tissue, low-frequency EFS (1 to 2 Hz) induced a prominent relaxation in the muscle strip and inhibited phasic contractions, whereas higher frequencies (10 to 20 Hz) augmented contractile activity (Fig 5, *A*) Significant inhibition of contractile activity was obtained at 1 Hz, when compared to baseline activity immediately before EFS, and significant augmentation occurred at 10 Hz (Fig. 6, *A*). The calculated frequency at which the response was equal to spontaneous activity, F_{100}, was 5 ± 1 Hz In the SBT-1Y group, the responses to various frequencies were not markedly different from those of control tissue (Fig. 5, *B*). Significant inhibition and augmentation were obtained at 1 and 2 Hz, and 10 and 20 Hz, respectively (Fig. 6, *A*). The F_{100} (4 ± 1 Hz) did not differ from the 1-year control values

Ileum. In the control ileal circular muscle strips, inhibition was not apparent at lower frequencies (Fig 5, *C*), but augmentation was observed at the higher frequencies. When quantitated compared to baseline activity, no consistent inhibition was observed. Significant augmentation was noted only at 20 Hz (Fig. 6, *B*). The F_{100} value for the ileal control was 7 ± 2 3 Hz. In contrast, 1 year after SBT, an immediate, well-

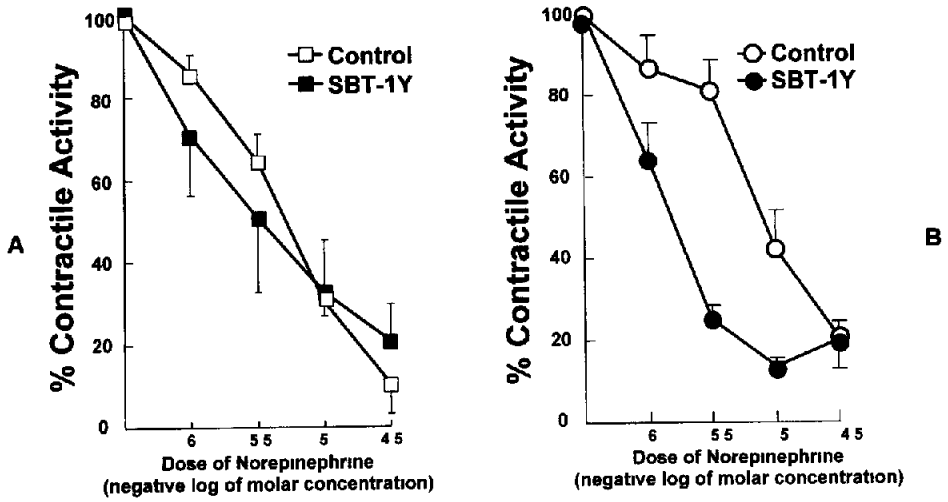

Fig. 3. Dose-response curves for norepinephrine **A,** Response in jejunum (n = 5 rats/group), **B,** Response in ileum (n = 8 rats/group)

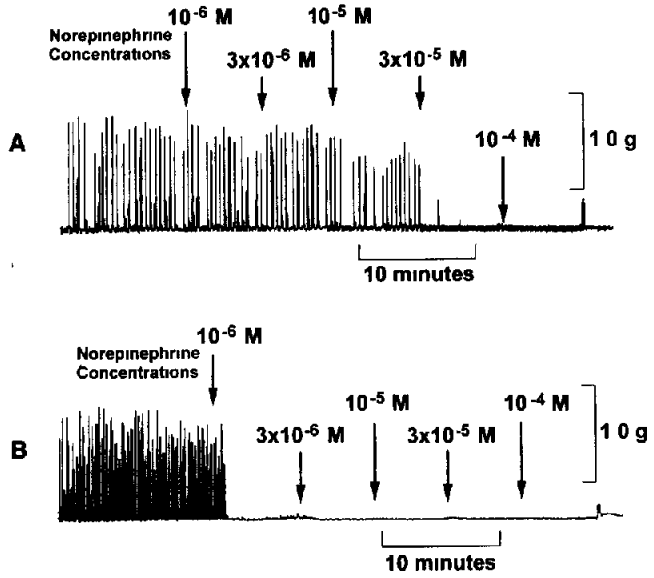

Fig. 4. Typical effect of norepinephrine on spontaneous activity of rat circular muscle strips **A,** Control ileum, **B,** ileum 1 year after SBT

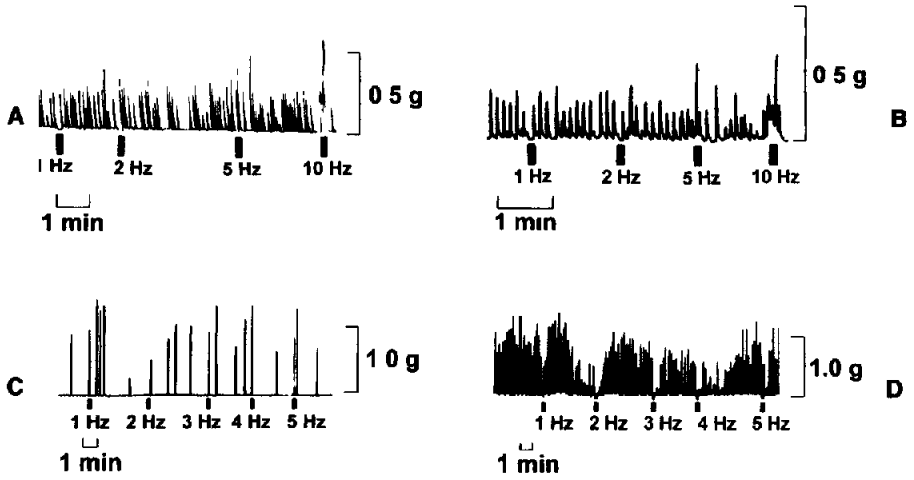

Fig. 5. Effect of varying frequencies of EFS on contractile activity of rat circular muscle strips under NANC conditions **A**, Jejunal control, **B**, jejunum SBT-1Y, **C**, ileal control, **D**, ileal SBT-1Y

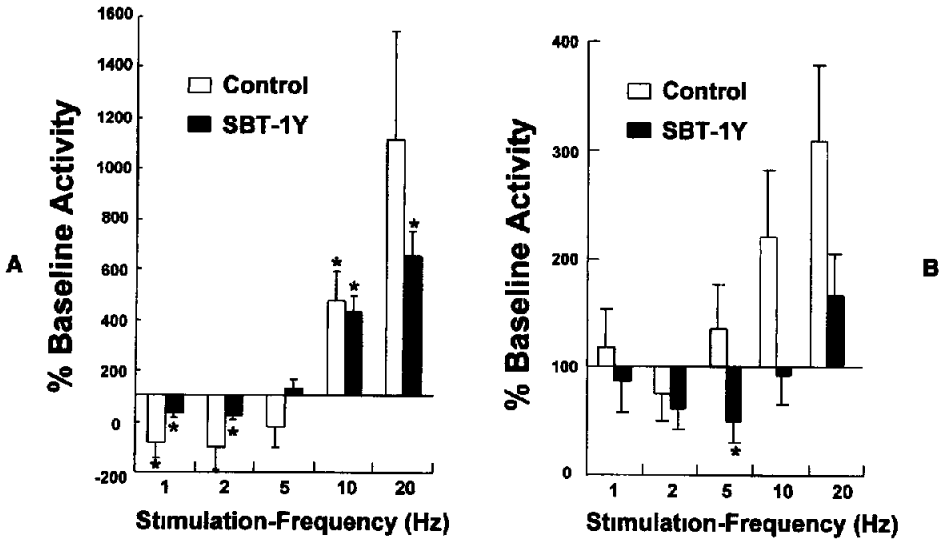

Fig. 6. Frequency-response curves of rat circular smooth muscle strips to EFS **A**, Jejunum (n = 5), **B**, ileum (n = 8) $^{*}P < 0.05$ compared to baseline contractile activity immediately before EFS

defined relaxation was seen at 1, 2, and 5 Hz (Fig 5, *D*), and augmentation was observed at 20 Hz The quantitated pattern of response also differed from control values (Fig 6, *B*) The F_{100} was increased compared to the control values (17 ± 5 Hz vs 7 ± 2 Hz, $P = 0.11$)

DISCUSSION

Our aim was to compare the adaptive changes in the contractility of rat jejunal and ileal circular smooth muscle 1 year after SBT with our previous observations early after SBT[9-11] In the current study we found that not all changes in the contractile responses observed early (1 week and 8 weeks after SBT) persisted 1 year later, but markedly different adaptive responses continued to be noted in the jejunum and ileum These observations demonstrate that small intestinal smooth muscle adaptation to chronic extrinsic denervation in the rat is region specific Such differing responses may have important implications in the clinical application of SBT, especially when considering region-specific segmental[14,15] SBT as suggested for living, related donors.

The increased activity that had been seen at both 1 and 8 weeks after SBT in jejunal circular muscle was no longer present 1 year after SBT Our previous work showed that the increased contractile activity early after SBT was not secondary to either increased sensitivity to a standard cholinergic muscarinic agonist or decreased sensitivity to adrenergic agonists [9] In contrast, no marked changes in spontaneous activity were noted early after SBT in ileal circular muscle,[11] and at 1 year only a small, albeit statistically significant, increase in the frequency of contractions was noted As with the jejunal muscle, no differences were noted either early or late after SBT in the sensitivity to the muscarinic cholinergic agonist but, unlike the jejunum, the ileal circular smooth muscle showed a marked hypersensitivity to the adrenergic agonist norepinephrine There was a marked shift to the left in the dose-response curve, signifying a hypersensitivity to the inhibitory effects of the adrenergic agonist The current experiments are not able to further define the mechanisms of this unexpected finding of adrenergic denervation hypersensitivity, but recent work in our laboratory suggests that this effect is mediated by changes in the response of the smooth muscle itself (i e , receptor density, signal transduction mechanism, and so forth) and not mediated via changes in the adrenergic neurons of the enteric nervous system [12]

We also investigated the effects of blocking selected aspects of tonic intrinsic (enteric) neural input This approach was designed in an attempt to allow insight into enteric neural control of contractile activity in response to chronic extrinsic denervation. Because all extrinsic neural input (vagal, sympathetic) to the muscularis of the small bowel is believed to synapse directly within the enteric nervous system and without direct input to the muscle, one might expect changes in the enteric nervous system in response to chronic extrinsic denervation similar in principle to the denervation hypersensitivity of skeletal muscle

In jejunal muscle strips 1 year after SBT, we detected no augmentation of contractile activity (either total force or frequency of contractions) under NANC conditions of adrenergic and cholinergic blockade. The addition of TTX, an agent that inhibits almost all enteric neural tone to the smooth muscle mediated through sodium channels,[16] also did not affect total contractile force but did increase the frequency of contractions 1 year after SBT in the jejunum These observations at 1 year after SBT differ in several respects from our previous observations[9] in which the response of jejunal muscle strips at 1 and 8 weeks after SBT demonstrated a marked augmentation of total contractile activity (to values greater than those in control tissue) without any increase in the number of contractions per minute The alterations in contractile response to selective neural blockade (NANC conditions) and to near-total enteric neural blockade (using TTX) 1 year after SBT suggests a type of adaptation within the wall of the small intestine to chronic extrinsic denervation involving a decrease in certain inhibitory input from the enteric nervous system or a change in the jejunal smooth muscle response to the presumed inhibitory neurotransmitters released by the enteric nerves. Whether this occurs through a change in inhibitory input or a reciprocal or transient change in excitatory input is unknown

The response of ileal circular smooth muscle to selective enteric neural blockade differed from the jejunal response Under NANC conditions, no significant change in total contractile activity or in frequency of contractions occurred either early after SBT[11] or in 1-year-old control tissue A similar lack of response was noted for TTX (near-complete neural blockade) In contrast, 1 year after SBT, both NANC conditions and TTX induced a slight but significant reproducible increase in the frequency of contractions These observations suggest that enteric neural tone may play a less prominent role in modulating baseline ileal contractility in normal tissue but after chronic, but not the more acute, extrinsic denervation, a tonic input to the muscle, which functions to partially suppress contractile frequency, may be uncovered, again reflecting

differing adaptive responses of the ileum and jejunum to the chronic extrinsic denervation necessitated by SBT.

The experiments with EFS were designed specifically to investigate one aspect of enteric neural modulation of contractile activity, that is, the NANC inhibitory neurotransmitters. Because TTX blocks EFS-induced contractile activity (unpublished observations), the EFS-induced response is presumably neurally mediated. Our past work[10] and that of others [17,18] suggest that SBT may upregulate the activity of NANC neurons and specifically neurons releasing nitric oxide or vasoactive intestinal polypeptide as inhibitory neurotransmitters. Under adrenergic and cholinergic blockade (NANC conditions) in normal small bowel circular smooth muscle, EFS at low frequencies activates inhibitory neurons (and possibly a subset of excitatory neurons) and causes a net relaxation via an inhibitory junction potential secondary to release of an inhibitory neurotransmitter(s), the primary neurotransmitters believed to mediate this response vary in different species.[19] The two prime candidates are nitric oxide and vasoactive intestinal polypeptide, but other candidate inhibitory neurotransmitters include carbon monoxide[20] and adenosine triphosphate.[21] We evaluated the NANC inhibitory neurons by studying frequency-response curves in circular muscle strips at various times after SBT Previously, in jejunum circular muscle, we showed that the F_{100} value, the calculated frequency at which the response to EFS was equal to spontaneous activity (frequency at which inhibition turned into augmentation), was significantly greater in rats at 1 week but not at 8 weeks after SBT compared to control tissue, suggesting a relative upregulation of NANC inhibitory neurons early after SBT[10] In contrast, in the ileum, we could demonstrate no changes in NANC inhibitory function during EFS early after SBT.[12] The current study showed that the F_{100} 1 year after SBT was not different from control values in the jejunum, whereas in the ileum net inhibitory function was more prominent, and the F_{100} in rats 1 year after SBT tended to be greater than control values. NANC inhibitory function exhibited a temporal variation in reference to the time after SBT and a region specificity (jejunum vs. ileum); NANC inhibitory function in the jejunum is increased 1 week after SBT but returns to normal levels thereafter, which persist for 1 year, whereas NANC inhibitory effects in the ileum may not be altered early after SBT but were apparently increased 1 year after SBT The increase in net inhibitory function is presumably secondary to an augmented release of inhibitory neurotransmitters but could also be the result of a decrease in release of excitatory neurotransmitters; our experimental design cannot differentiate these possibilities.

The temporal results of this study are presumably related to adaptive responses to complete extrinsic denervation. Previous work in the rat[22] has demonstrated the lack of extrinsic reinnervation of the transplanted small bowel 6 months postoperatively. However, at 1 year postoperatively there is a scant extrinsic reinnervation of both jejunum and ileum. This reinnervation may itself alter the measured "adaptive" response of the gut smooth muscle to chronic denervation, but of itself will not explain the ileal adrenergic hypersensitivity noted at 1 and 8 weeks after intestinal transplantation in our recent study.[12] Moreover, the lack of adrenergic hypersensitivity in the jejunum further contrasts the adaptive responses of the jejunum and the ileum to extrinsic denervation.

CONCLUSION

Spontaneous contractile activity, sensitivity to bethanechol and norepinephrine, or the effect of activating NANC inhibitory neurons by EFS did not change in rat jejunal circular smooth muscle strips 1 year after SBT. In the ileal circular muscle strips 1 year after SBT, however, a marked hypersensitivity to norepinephrine was observed, and NANC inhibitory function during EFS was upregulated, despite the fact that spontaneous activity was not largely changed. The responses of these circular muscle strips were different from those of similar strips evaluated at 1 and 8 weeks after SBT. These observations indicate a differential regulation/adaptation of enteric nerves depending on the duration of time after SBT and the anatomic site These changes may have important implications in the clinical application of small bowel transplantation in humans.

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Surgical Experience With Pancreatic and Peripancreatic Neuroendocrine Tumors: Review of 125 Patients

Giao Q Phan, M D , Charles J Yeo, M D., Ralph H Hruban, M D , Keith D Lillemoe, M D , Henry A Pitt, M D., John L Cameron, M D

Neuroendocrine tumors of the pancreas and peripancreatic area are rare entities with a wide spectrum of clinical presentation. This study retrospectively reviews the patients who underwent surgery for these tumors at The Johns Hopkins Hospital from 1949 to 1996, inclusive There were 125 patients (65 males and 60 females) whose mean age was 51 ± 1 years Fifty-eight patients (48%) had nonfunctional tumors, whereas 64 (52%) had functional tumors 35 (55%) insulinomas, 23 (36%) gastrinomas, three (5%) VIPomas, two (3%) glucagonomas, and one (1%) ACTHoma All patients with functional tumors presented with appropriate signs and symptoms of hormonal excess, 86% of patients with nonfunctional tumors presented with weight loss, abdominal pain, or jaundice Preoperative computed tomography (CT) correctly localized the tumor in 66 (76%) of 87 patients, angiography in 45 (58%) of 78 patients, and CT plus angiography in 54 (79%) of 68 patients Tumors were benign in 60 patients (48%), malignant in 65 patients (52%), and were located in the head, neck, or uncinate process of the pancreas in 54, body in 14, tail in 18, and duodenum in eight The most common operative procedures performed were 50 pancreaticoduodenectomies (40%), 39 distal pancreatectomies (31%), and 21 tumor enucleations (17%) Nine synchronous hepatic resections were performed for metastases Of the evaluable patients, 46 (43%) had postoperative complications, the most common of which were pancreatic fistula (16%), wound infection (15%), and delayed gastric emptying (8%) There were three in-hospital deaths (2 8%) With a mean follow-up of 55 ± 6 months, there have been 30 additional deaths, 23 of which were related to disease progression The overall 2-, 5-, and 10-year actuarial survival rates were 82%, 65%, and 47%, respectively The 5-year survival for patients with functional tumors was 77% compared to 52% for those with nonfunctional tumors ($P = 0.025$), the 5-year survival for patients with benign tumors was 91% compared to 49% for those with malignant tumors ($P = 0.0004$) By univariate analysis the most powerful predictor of poor outcome for patients with malignant tumors (n = 60) was positive surgical margins ($P = 0.006$) This single-institution experience documents low mortality and moderate morbidity for patients treated operatively for pancreatic and peripancreatic neuroendocrine tumors The most favorable outcomes are observed in patients with benign functional tumors and in those with completely resected malignant tumors (J GASTROINTEST SURG 1998,2 473-482)

Pancreatic and peripancreatic neuroendocrine tumors are uncommon neoplasms with an annual incidence of approximately five clinically recognized cases per million persons The first account of an islet cell tumor of the pancreas was published in 1902 by Nicholls,[1] who discovered an incidental adenoma at autopsy In 1927 Wilder et al.[2] reported the first malignant pancreatic endocrine tumor, an insulinoma that had infiltrated most of the pancreas and metastasized to the liver In 1929 Howland et al.[3] reported the first surgical cure of a functional pancreatic endocrine tumor via the enucleation of a benign insulinoma from the body of the pancreas. In 1940 Whipple[4] performed the first pancreaticoduodenectomy for an islet cell carcinoma of the pancreas, the patient lived for 10 years before dying of tumor progression

From the Departments of Surgery and Pathology (R H H), The Johns Hopkins Medical Institutions, Baltimore, Md
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Reprint requests Charles J Yeo, M D , Professor, Departments of Surgery and Oncology, The Johns Hopkins Hospital, Blalock 606, 600 North Wolfe St , Baltimore, MD 21287-4606

In addition to the classic presentation of hypoglycemia due to insulinoma, several other clinical syndromes have been described for tumors producing gastrin, vasoactive intestinal polypeptide (VIP), glucagon, and somatostatin In 1955 Zollinger and Ellison[5] proposed the triad of gastric hypersecretion, peptic ulceration, and non–beta cell islet tumors, thus defining the gastrinoma syndrome. Although Priest and Alexander[6] in 1957 first described the association of an islet cell tumor with severe watery diarrhea, Verner and Morrison[7] in 1958 further defined the syndrome now known to be related to excess circulating VIP. In 1942 Becker et al [8] described an unusual rash in a patient who had diabetes, weight loss, anemia, and a pancreatic endocrine tumor However, it was not until 1966 that McGavran et al [9] documented elevated glucagon levels in a patient with a similar clinical syndrome including the classic dermatologic manifestation of necrolytic migratory erythema. The somatostatinoma syndrome was first reported in 1977 by Ganda et al ,[10] who described a woman with diabetes, cholelithiasis, and a pancreatic tumor demonstrating abnormally high levels of somatostatin The somatostatin syndrome was further defined by Krejs et al [11] in 1979 Several other even rarer syndromes have been described for pancreatic tumors secreting adrenocorticotropic hormone (ACTH), parathyroid-like hormone, calcitonin, gastrin-releasing factor (GRF), and neurotensin [12]

For neuroendocrine tumors of the pancreas and periampullary region, the indications for surgical therapy are to relieve the symptoms of hormonal excess in patients with functional tumors and the obstructive and constitutional symptoms of patients with nonfunctional tumors Although enucleation and distal pancreatectomy are appropriate surgical options in many cases, a pancreaticoduodenectomy may be necessary for larger or malignant tumors involving the periampullary region. This article reviews the clinical presentation, preoperative evaluation, intraoperative and postoperative management, pathology, and survival of 125 consecutive patients undergoing surgery for pancreatic and peripancreatic neuroendocrine tumors at The Johns Hopkins Hospital

PATIENTS AND METHODS

Patient Selection and Follow-Up

The pathology records of The Johns Hopkins Hospital were examined retrospectively to 1949 to identify patients who had undergone surgery for pancreatic or peripancreatic neuroendocrine tumors A total of 125 patients were identified and their medical records were reviewed, follow-up was done by telephone or office visit during October and November 1996. Twenty-seven patients were lost to follow-up and were excluded from the survival analyses Previous publications from this institution have included some of these patients.[13-16]

Diagnostic Criteria

Patients presenting with appropriate signs, symptoms, and biochemical evidence of hormonal excess were classified into the corresponding clinical syndromes· insulinoma (Whipple's triad, neuroglycopenia, catecholamine surge), gastrinoma (peptic ulcer, diarrhea, esophagitis), VIPoma (watery diarrhea, hypokalemia, achlorhydria), glucagonoma (hyperglycemia, necrolytic migratory erythema, hypoproteinemia), and ACTHoma (Cushing's syndrome). No patients with the somatostatinoma syndrome were identified in this series Patients presenting without an apparent clinical syndrome and with normal serum hormone levels (with the exception of pancreatic polypeptide) were categorized as having nonfunctional tumors, independent of the outcome of the immunoperoxidase stains of the tumor specimen

Tumor Characteristics

The site of the primary tumor was determined by the operative note or pathology records. Malignancy was defined by evidence of nodal or hepatic metastases found at surgery, or by the development of such metastases during follow-up In cases in which the primary tumor was not found but pathologic examination showed lymph node involvement (as occurred in 6 patients), the tumor was classified as metastatic. Tumor size and surgical margin status were obtained from the pathology report

Postoperative Course

Complications were characterized according to the following published criteria[17] delayed gastric emptying = need for postoperative nasogastric decompression for more than 10 days, pancreatic fistula = daily drainage of ≥50 ml of amylase-rich fluid after postoperative day 7; intra-abdominal abscess = radiographically defined or surgically found fluid collection associated with clinical signs and symptoms of sepsis, and wound infection = need for the wound to be partially or wholly opened and packed Other complications were tabulated using standard accepted criteria.

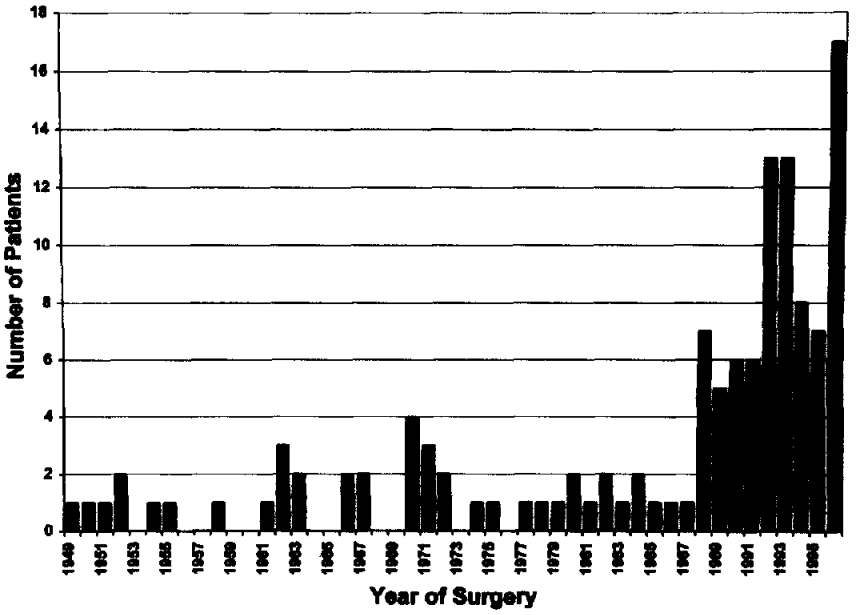

Fig. 1. Annual distribution of the 125 patients undergoing surgery for pancreatic and peripancreatic neuroendocrine tumors at The Johns Hopkins Hospital

Statistical Analyses

Survival and univariate analyses were calculated by the Kaplan-Meier method Differences among subsets were compared using the log-rank test. Significance was accepted at the 5% level Data are presented as the median or the mean ± standard error of the mean. Statistical computations were performed using either SPSS for Windows version 7.0 or Corel Quattro Pro 7.

RESULTS

Patient Demographics

From September 1949 to November 1996, 125 patients underwent surgery for pathologically proved pancreatic or peripancreatic neuroendocrine tumors at The Johns Hopkins Hospital; 83 of these patients (66%) were treated in or after 1987. The series was comprised of 65 men (52%) and 60 women (48%), with ages ranging from 3 months to 80 years with a mean of 51 ± 1 years. One hundred six patients (85%) were white, 16 (13%) were black, and three (2%) were of another race The year of operation of these patients is depicted in Fig 1

Clinical Presentation

Nonfunctional tumors were seen in 58 patients (48%), whereas functional tumors were found in 64

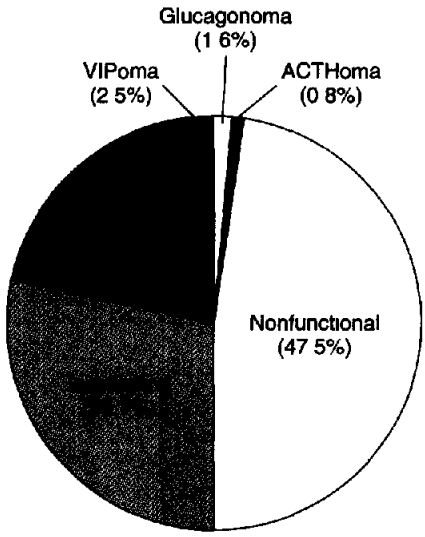

Fig. 2. Distribution of types of tumor in the present series (N = 122) based on the presence or absence of specific clinical syndromes of hormonal excess

(52%), with 35 insulinomas, 23 gastrinomas, three VIPomas, two glucagonomas, and one ACTHoma (Fig. 2). All patients with functional tumors presented with appropriate signs and symptoms of hormonal excess. The majority (86%) of patients with nonfunctional tumors presented with either abdominal pain,

weight loss, or jaundice (Table I) The functional status of three patients' tumors could not be determined. Seven patients had the MEN-1 syndrome (four gastrinoma, one insulinoma, one VIPoma, and one glucagonoma)

Preoperative Imaging Studies (Fig 3)

Ninety-eight patients (78%) underwent at least one of the following preoperative studies to localize the tumor computed tomography (CT), magnetic resonance imaging (MRI), selective celiac and mesenteric angiography, endoscopic ultrasound, portal venous hormonal sampling, and somatostatin receptor imaging. The results of the imaging studies are depicted in Fig 3

Table I. Clinical presentation Nonfunctional tumors (N = 58)

Symptoms/signs	Patients	%
Abdominal pain	32	56
Weight loss	26	46
Jaundice	20	35
Nausea/vomiting	12	21
Pruritus	8	14
Anorexia	8	14
Diarrhea	8	14
Lethargy	5	9
Weakness	4	7

Intraoperative Factors

The most common operative procedures performed were 50 pancreaticoduodenectomies (40%), 39 distal pancreatectomies (31%), and 21 tumor enucleations (17%) (Fig 4). In 18 patients whose primary operation was not a pancreatic resection, other procedures performed included gastrectomy, local duodenal resection, palliative gastric or biliary bypass, liver or pancreatic biopsy, and retroperitoneal mass resection Among the 11 patients in whom a gastrectomy was performed, seven had the Zollinger-Ellison syndrome and four had nonfunctional (carcinoid) tumors with gastric involvement

Nine patients underwent synchronous hepatic resection for liver metastases Six of these patients had nonfunctional tumors and three had functional tumors (one insulinoma, one gastrinoma, and one VIPoma) One patient underwent a transverse colectomy plus a pylorus-preserving pancreaticoduodenectomy for a malignant insulinoma adherent to the colon Resection of the superior mesenteric vein and a left renal vein was performed in two separate patients for nonfunctional tumors infiltrating the vein

Estimated intraoperative blood loss ranged from 20 to 28,000 ml (in a patient with a portal vein injury),

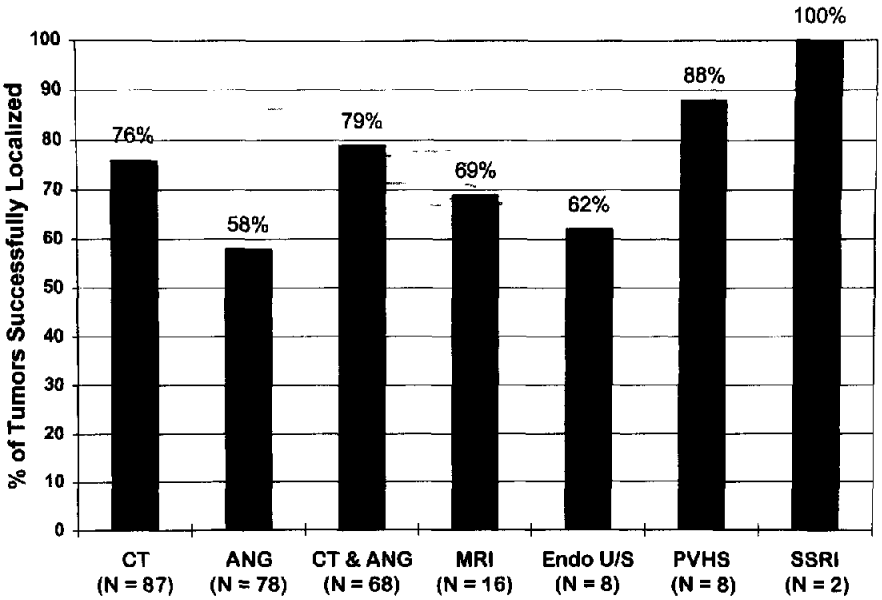

Fig 3 Percentage of neuroendocrine tumors successfully localized preoperatively using the following studies computed tomography *(CT)*, selective celiac and mesenteric angiography *(ANG)*, magnetic resonance imaging *(MRI)*, endoscopic ultrasound *(Endo U/S)*, portal venous hormonal sampling *(PVHS)*, and somatostatin receptor imaging *(SSRI)* Numbers in parentheses indicate the number of patients undergoing each imaging study

with a median of 600 ml and a mean of 1285 ± 302 ml. The number of units of red blood cells transfused ranged from 0 to 35 (in the same patient with the portal vein injury), with a median of zero units and a mean of 1 4 ± 0.4 units The operative time ranged from 1 3 to 13.4 hours, with a median of 5.2 hours and a mean of 5 3 ± 0.2 hours

Tumor Characteristics (Table II)

Malignant tumors were found in 65 patients (52%), whereas benign neoplasms were found in 60 (48%). Thirty (47%) of the 64 functional tumors were malignant, whereas 35 (60%) of the 58 nonfunctional tumors were malignant. Of the 64 functional tumors, the majority (74%) of the insulinomas were benign, whereas the majority of the gastrinomas (69%) and VIPomas (67%) were malignant. both glucagonomas and the ACTHoma were malignant Tumor diameter data are presented in Table II

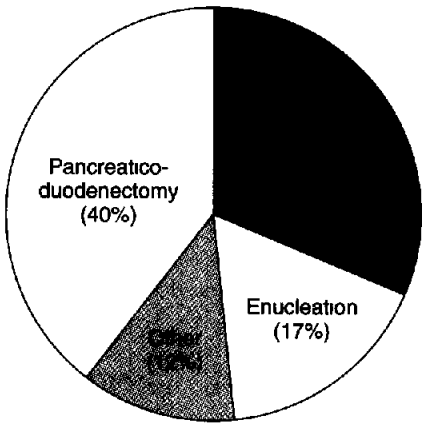

Fig. 4. Types of surgery performed in the management of the 125 patients Other operations included gastrectomy, local duodenal resection, palliative gastric or biliary bypass, and biopsy of the pancreas or liver

The primary tumor was located in the head, neck, or uncinate process of the pancreas in 54 patients (53%), the body of the pancreas in 14 (14%), the tail of the pancreas in 18 (18%), the duodenum in eight (8%), the distal common bile duct in one (1%), the stomach in one (1%), the retroperitoneum in one (1%), and was multicentered in four (4%). The site of the primary tumor could not be determined in 24 patients in 13 because the tumor was too large (up to 18 cm), in six because tumor was found only in peripancreatic lymph nodes, and in five because the site was not identified in the operative note or the pathology report

Postoperative Course

Postoperative length of stay ranged from 1 to 86 days, with a median of 12 days and a mean of 16 ± 1 days. Sixty patients (57%) were discharged home without in-hospital complications, whereas 46 (43%) had some type of complication (Table III). Complications could not be assessed in 19 patients because of inadequate clinical information. The most common complications were pancreatic fistula (16%), wound infection (15%), and delayed gastric emptying (8%). Five patients (5%) required reoperation during the index hospital stay· one for completion pancreatectomy required for a persistent pancreaticojejunostomy

Table II. Tumor characteristics

Tumor function	Total No.	Malignant
Functional	64 (52%)	30 (47%)
Nonfunctional	58 (48%)	35 (60%)
TOTAL		65 (52%)

		Diameter of primary tumor (cm)		
	No.	Mean	Median	Range
Entire group	98	3 8 ± 0 3	3 0	0 3-18 0
Functional	49	2 6 ± 0 3	1 9	0 3-9 0
Nonfunctional	47	5 1 ± 0 5*	4 0	0 6-18 0
Benign	53	3 5 ± 0 5	2 0	0 5-18 0
Malignant	45	4 1 ± 0 3	3 7	0 3-12 5
Tumors requiring pancreatico-duodenectomy	46	3 8 ± 0 5	3 0	0 3-18 0

*P <0 001 compared to functional tumors by analysis of variance

Table III. Postoperative complications

Complication	No. of patients	%
None	60	57
Any complication	46	43
Pancreatic fistula (1 reoperation)	17	16
Wound infection	16	15
Delayed gastric emptying	8	8
Intra-abdominal abscess (1 reoperation)	6	6
Biliary fistula	4	4
Sepsis (2 deaths*)	4	4
Pleural effusion	3	3
Adult respiratory distress syndrome*	1	1
Perioperative myocardial infarction	1	1
Fascial dehiscence (reoperation)	1	1
Gastrocutaneous fistula (reoperation)	1	1
Small bowel obstruction (reoperation)	1	1
Postoperative hemorrhage (death)	1	1

*The patient who was reoperated on for an intra-abdominal abscess also developed adult respiratory distress syndrome and eventually died on postoperative day 35 from sepsis

leak, one for drainage of an intra-abdominal abscess, one for repair of a fascial dehiscence, one for repair of a gastrocutaneous fistula, and one for small bowel obstruction There were three in-hospital deaths (2 8%) one secondary to postoperative hemorrhage on the first postoperative day after a classic pancreaticoduodenectomy performed in 1967 in a patient with a benign insulinoma, one secondary to sepsis in a patient who underwent a distal pancreatectomy in 1970 for a malignant ACTHoma, and one secondary to sepsis (after reoperation for evacuation of an intra-abdominal abscess) in a patient after a subtotal gastrectomy in 1980 for a benign nonfunctional distal gastric tumor

Postdischarge follow-up of the 98 evaluable patients revealed that 19 patients (19%) had late complications, eight of which required surgery three for small bowel obstruction, four for incisional hernia, and one for gastric outlet obstruction Other late complications included six patients with small bowel obstruction managed medically, five patients with late-identified wound infection, two patients with intra-abdominal abscess managed percutaneously, and two patients with symptomatic pancreatic pseudocyst managed percutaneously

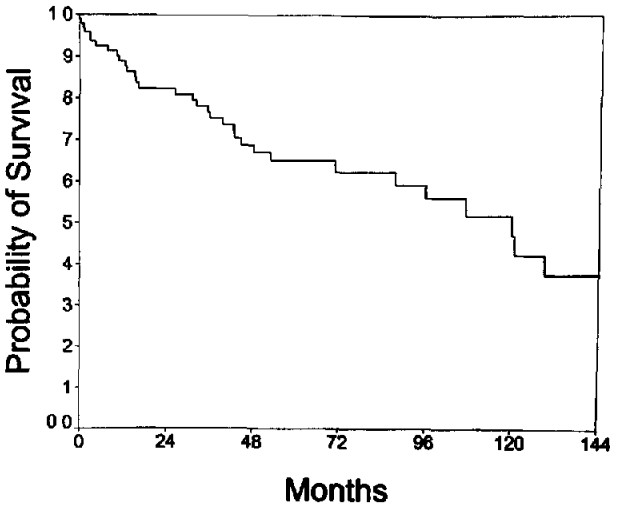

Fig 5. Actuarial survival curve following surgery for the entire cohort (N = 98 evaluable patients) The 2-, 5-, and 10-year survival rates are 82%, 65%, and 47%, respectively

Survival and Outcome

Follow-up ranged from 1 to 316 months, with a mean of 55 ± 6 months. Sixty-five patients (66%) were alive at last follow-up, whereas 33 patients (34%) have died (including the three in-hospital deaths), 27 patients were lost to follow-up Of the 30 postdischarge deaths, 23 were secondary to tumor progression, two were from unknown causes, three were cardiac in origin, one was from colon cancer, and one was from sepsis

The overall actuarial survival rates at 2, 5, and 10 years were 82%, 65%, and 47%, respectively (Fig 5) The 2-, 5-, and 10-year survival rates for patients with functional tumors were 86%, 77%, and 56%, respectively, which are significantly better than the 2-, 5-, and 10-year survival rates for patients with nonfunctional tumors (79%, 52%, and 42%, respectively, $P = 0.025$) (Fig. 6) The 2-, 5-, and 10-year survival rates for patients with benign tumors (95%, 91%, and 70%, respectively) were significantly better than the rates for those with malignant tumors (75%, 49%, and 32%, respectively, $P = 0.0004$) (Fig 7)

Univariate analysis of the 60 evaluable patients with malignant tumors was performed to assess possible factors influencing long-term survival In this analysis the type of surgery performed, estimated intraoperative blood loss, operative time, tumor diameter, postoperative complication status, and postoperative length of stay did not affect long-term survival However, red blood cell transfusion status and the functional status of the tumor correlated with survival and approached statistical significance (both $P = 0$ 14)

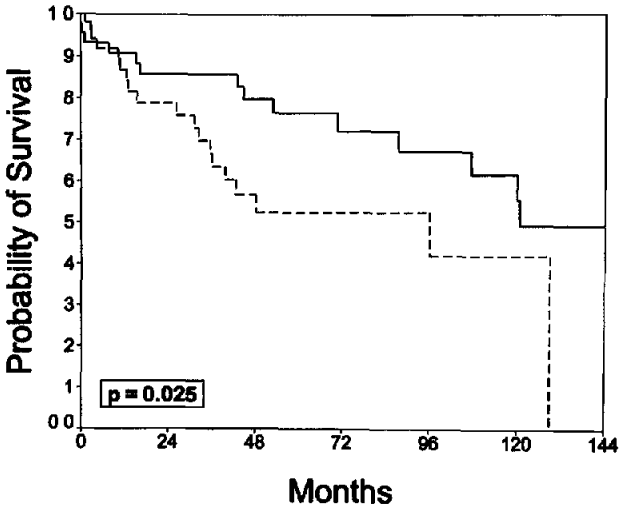

Fig. 6. Actuarial survival curves following surgery comparing patients with functional tumors (solid line, N = 46, median survival = 121 months) to those with nonfunctional tumors (broken line, N = 52, median survival = 96 months) (P = 0.025)

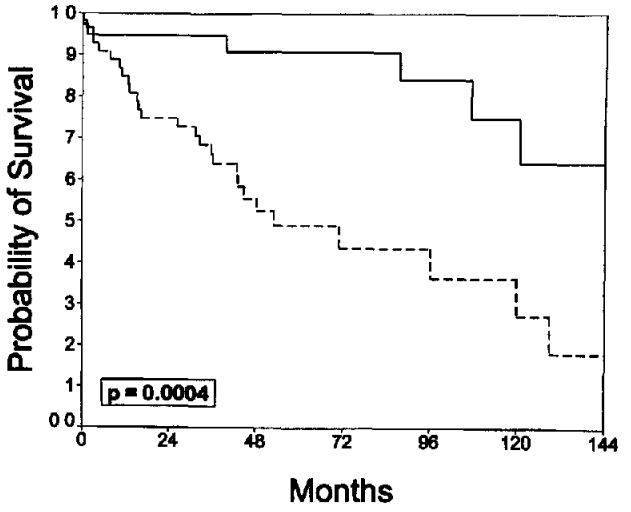

Fig. 7. Actuarial survival curves following surgery comparing patients with benign tumors (solid line, N = 38, median survival not reached) to those with malignant tumors (broken line, N = 60, median survival = 53 months) (P = 0.0004)

(Table IV). Patients who received a blood transfusion had a median survival of 43 months, whereas for those who did not receive a transfusion, the median survival was not reached. Patients with nonfunctional tumors had a median survival of 43 months, whereas those with functional tumors had a median survival of 71 months. Surgical margin status was the only significant predictor of survival. Patients with positive surgical margins had a median survival of only 36 months, whereas those with negative margins had a significantly longer median survival of 129 months (P = 0.006).

Table IV. Univariate survival analysis of malignant tumors (N = 60)

Parameter	Survival (mo)		P value
	Median	Mean	
Transfusion			
Yes	43	64 ± 14	0.14
No	NR	55 ± 6	
Tumor function			
Nonfunctional	43	62 ± 11	0.14
Functional	71	93 ± 18	
Surgical margins			
Positive	36	33 ± 6	0.006
Negative	129	118 ± 17	

NR = median survival not reached

DISCUSSION

Rienhoff and Lewis[18] reported the first operation for an islet cell tumor at The Johns Hopkins Hospital. This operation was a noncurative "blind" distal pancreatectomy performed in 1929 for a presumed insulinoma in a patient with frequent attacks of severe hypoglycemia, autopsy showed the tumor to be in the head of the pancreas.[18] As shown in Fig. 1, the number of operations performed for pancreatic and peripancreatic neuroendocrine tumors has increased appreciably during the past 10 years. Of the 83 operations performed since 1987, 42 (51%) have been pancreaticoduodenectomies[16] for a total of 50 pancreaticoduodenal resections in the present series. This large proportion of pancreaticoduodenal resections is due partly to a referral bias, as The Johns Hopkins Hospital is a tertiary care institution that for the past decade has served as a center for pancreatic surgery, with high volume and low mortality with pancreaticoduodenectomy.[19] The observations that the primary tumor was located in the periampullary region in 63 patients (head, neck, or uncinate process of the pancreas in 54, duodenum in 8, and distal common bile duct in 1) and that the average tumor size for the 50 patients requiring pancreaticoduodenectomy was 3.8 ± 0.5 cm (see Table II) further support the role of pancreaticoduodenectomy to allow for complete tumor resection and potential cure in these selected patients.

As this series encompasses a span of 48 years, available preoperative imaging modalities have changed dramatically. Thin-sliced, dynamic contrast-enhanced spiral CT is currently the initial modality of choice for imaging the hypervascular "blush" of neuroen-

docrine tumors and for assessing liver metastases Our experience with CT in 87 patients has shown it to be relatively sensitive (76% success) in detecting these tumors, as has been reported in other series.[20-22] MRI has been used increasingly based on the assumption that it may have improved sensitivity in imaging smaller hypervascular tumors, however, most studies have not shown it to be better than CT[23,24] Selective mesenteric and celiac angiography has long been used for localizing the primary tumor, reported sensitivities have generally ranged from 59% to 91% [21,25] Angiography combined with CT has been shown to provide little additional information on preoperative tumor localization [23] Endoscopic ultrasound, although invasive, in skilled hands can provide invaluable information, with reported sensitivities and specificities of 80% to 100%, it is generally considered to be more sensitive than CT and MRI in detecting tumors smaller than 3 cm [26,27] Transhepatic portal venous hormonal sampling is not routinely used but is often reserved for localization of functional tumors after an unsuccessful first attempt at resection or when all other localization modalities have failed Venous sampling can guide surgical therapy by defining the general location of venous drainage of the tumor.[28] Somatostatin receptor imaging (SSRI) is a new and exciting modality that has shown great promise in localizing neuroendocrine tumors.[29,30] Our successful albeit limited experience with SSRI has been with two patients with gastrinomas. With the ability to localize not only small primary lesions but also intra-abdominal and extra-abdominal metastases, SSRI may become the test of choice in the future

In the current series, postoperative mortality was an acceptable 2 8% The two patients who died in the hospital from sepsis were highly debilitated preoperatively The patient with the ACTHoma was in the hospital for 30 days preoperatively secondary to systemic complications of Cushing's syndrome before her neoplasm was diagnosed, the patient with the gastric tumor had a long history of alcoholism and severe anemia from multiple gastrointestinal bleeding sites There have been no postoperative deaths in the 92 patients resected since 1980 Postoperative morbidity has continued to be high (43%), although most of the complications were self-limited and not life threatening Eleven of the 17 patients with pancreatic fistula, seven of the eight with delayed gastric emptying, and all four patients with biliary fistula underwent pancreaticoduodenectomy Despite these complications, the mortality rate among those who underwent pancreaticoduodenectomy was only 2%.

Although neuroendocrine tumors are more indolent and slow growing than pancreatic adenocarcinoma, they can still cause significant morbidity and mortality The majority (52%) of the patients in the entire cohort had malignant tumors, with either lymph node involvement or distant metastases The majority of the nonfunctional tumors caused significant obstructive and constitutional symptoms, as evidenced by the fact that 86% of the patients presented with either abdominal pain, weight loss, or jaundice (see Table I). All patients with functional tumors were symptomatic of the corresponding hormone at presentation Our survival analysis confirms that pancreatic and peripancreatic neuroendocrine tumors have a relatively high survival rate, being 65% at 5 years for the entire cohort and 49% at 5 years for the subgroup with malignant tumors Since patients with functional tumors generally present earlier than those with nonfunctional tumors (secondary to effects of hormonal excess), functional tumors have smaller median size at surgery (1 9 cm vs. 4 0 cm, $P < 0$ 001) and a lower malignancy rate (47% vs 60%) Patients with functional tumors have a significantly better 5-year survival (77%) as compared to those with nonfunctional tumors (52%, $P = 0$ 025), as has been shown in other series [21,22] Additional details concerning our patients with nonfunctional tumors are given in Table V, with comparison to other series of nonfunctional tumors. In summary, nonfunctional tumors tend to present during the sixth decade of life, 60% are malignant, the majority occur in the head of the pancreas, and the 5-year survival rate following resection approximates 50%

Univariate analysis of malignant tumors indicated that functional tumors tend to correlate with a better prognosis (see Table IV) Furthermore, blood transfusion was also shown to correlate with a poorer prognosis, transfusion-induced immunosuppression has been suggested as a mechanism [31] However, surgical margin status was the only significant indicator of long-term survival, with those having positive margins having a median survival of only 36 months compared to 129 months for those with negative margins ($P = 0$ 006) Other studies have concluded similarly that aggressive resection of malignant neuroendocrine tumors improves long-term survival [32-34]

This report serves as a retrospective review of the surgical therapy for pancreatic and peripancreatic neuroendocrine tumors at one institution, encompassing the years 1949 to 1996, inclusive Two previous reports have focused on pancreaticoduodenectomy for these tumors,[14,16] whereas another report provided an analysis of only 37 patients treated surgically between 1979 and 1990 [13] The current series updates our previous reports, includes patients with all forms of surgical intervention, and covers a 48-year time span In conclusion, surgical management of pancreatic and peripancreatic neuroendocrine tumors

Table V. Case series of nonfunctional tumors

	JHH (N = 58)	M.D. Anderson[34] (N = 73)	Mayo Clinic[22] (N = 27)	Cleveland Clinic[21] (N = 21)
Male	35 (60%)	41 (56%)	NS	10 (48%)
Female	23 (40%)	32 (44%)	NS	11 (52%)
Median age (yr)	57	54	NS	58
Tumor				
Malignancy	35 (60%)	≥ 44 (≥ 60%)	NS	12 (60%)
Mean diameter (cm)	5 1 ± 0 5	NS	NS	NS
Site				
Head of pancreas/ neck/uncinate	29 (50%)	43 (59%)	"Predominantly"	9 (43%)
Body	6 (10%)	30 (41%)*	NS	3 (14%)
Tail	4 (7%)	NS	NS	4 (19%)
Duodenum	3 (5%)	0	0	0
Extends ≥2 regions	10 (17%)	0	0	0
Multicentered	1 (2%)	0	0	3 (14%)
Other†	4 (7%)	0	0	1 (5%)
Undeterminable	1 (2%)	0	0	1 (5%)
Surgery				
Pancreaticoduodenectomy	32 (55%)	13 (18%)	4 (15%)	3 (14%)
Distal pancreatectomy	14 (24%)	18 (25%)	8 (30%)	5 (24%)
Palliative bypass	6 (11%)	0	NS	5 (24%)
Biopsy and/or other	6 (11%)	42 (58%)‡	15 (55%)§	11 (52%)
Five-year survival rate (%)	52	50	58 (3-year)	63

JHH = The Johns Hopkins Hospital, NS = not stated
*Includes body and tail of pancreas
†Includes retroperitoneum, distal common bile duct, pancreatic duct, stomach, and other periampullary but nonpancreatic sites
‡Includes nonoperative management
§Two procedures were enucleations, whereas 13 were nonspecified "palliative" procedures

entails early recognition of clinical syndromes of hormonal excess, appropriate preoperative localization, and thorough consideration of surgical options. Aggressive resection, including pancreaticoduodenectomy if necessary, appears indicated in appropriately selected patients with large or malignant tumors, to allow for complete tumor resection and the potential for long-term survival

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Practice Guidelines for Patients With Gastrointestinal Surgical Diseases

*The Society for Surgery of the Alimentary Tract Patient Care Committee**

Practice guidelines have been written for a variety of medical and surgical disorders, as well as for antibiotic and other drug usage. It is the aim of such guidelines to improve and standardize the quality of care. Historically there has been significant variation in clinical practice patterns, and clinical guidelines are designed to set limits for these variations. In addition, procedures and tests may be administered inappropriately because of a lack of familiarity with rapidly changing technology or with diseases not frequently encountered. The Society for Surgery of the Alimentary Tract (SSAT) Patient Care Guidelines were formulated in an effort to disseminate useful and up-to-date information designed to assist practitioners and patients in choosing appropriate health care for specific clinical problems.

In 1995, the SSAT established the Patient Care Committee to develop a set of practice guidelines for evaluating and treating patients with common gastrointestinal surgical diseases. The committee members identified 10 diseases or procedures and established an outline that could be followed for each practice guideline. SSAT members with recognized expertise in specific areas were asked to participate in the development of these practice guidelines The guidelines were reviewed numerous times and approved by the Board of Trustees of the SSAT. They are published with the intent of providing information and direction for evaluating and treating common gastrointestinal surgical disorders. They will be periodically reviewed and revised to reflect the current state-of-the-art practice for each disease.

OBJECTIVES

The SSAT Patient Care Guidelines are intended to provide information regarding the evaluation of gastrointestinal surgical diseases and to describe the operative treatment and expected outcome for these diseases. The guidelines should be of value to general practitioners, specialists, health maintenance organizations, and patients, all of whom share an interest in ensuring quality and improving outcome for gastrointestinal surgical disorders. These guidelines should help practitioners make consistent and appropriate decisions. The information contained in the guidelines is based on expert opinion and sound scientific data, all of which should aide in defining the boundaries of acceptable clinical care.

In addition to concerns about the quality of care and patient outcome, the cost of maintaining this quality was also given careful consideration. The SSAT reasoned that establishing guidelines for improving patient care would lead to a decrease in the cost of this care The cost of evaluation and treatment of a disease can be reduced provided that tests are utilized appropriately and needless procedures are avoided. Along with improved care comes a decrease in the incidence of complications, which also leads to a reduction of costs. In due course, implementation of these guidelines should result in less need to treat problems arising as a result of inappropriate management, and neglected and advanced disease.

GOALS FOR EVALUATION AND TREATMENT

In developing each guideline, the committee carefully reviewed all clinical data justifying tests and procedures. The patient's overall condition needs to be considered in the evaluation of any disease, and additional studies may be justified In order for these guidelines to be as meaningful as possible, they had to be based on the assumption that no other significant and concomitant diseases were present. However, the guidelines can also be applied to all good risk

Reprint requests Thomas R Gadacz, M D , Department of Surgery, Medical College of Georgia, 1120 Fifteenth St , Augusta, GA 30912-4000 E-mail deptsurg tgadacz@mail mcg edu

*SSAT Patient Care Committee Members Thomas R Gadacz, M D , Chairman, L William Traverso, M D , Gerald M Fried, M D , Bruce Stabile, M D , Barry A. Levine, M D

The SSAT Patient Care Guidelines were formulated by the Committee in 1997 Three of these guidelines appear in this issue of the JOURNAL Additional guidelines will appear in future issues

patients with other diseases that are minimal or stable It is recognized that complications may arise in association with a procedure, which might not be under the direct control of the surgeon It would be impossible to write meaningful guidelines that would take into account every conceivable complication that could occur during and following an operative procedure The current guidelines are based on the expected and common outcomes for most patients Of course, there may be exceptions

The guidelines also provide information regarding the timing of referral for operation However, it is recognized that concomitant diseases or a change in the status of a disease may require more immediate referral and treatment

The expectations of operative treatment are given to provide the referring physician, patient, and/or health care organization with information regarding the expected outcome following surgery. This information is based on data published in the surgical literature as well as the experience of the experts who helped develop these guidelines Unforeseen problems can arise the may alter the course of recovery

METHODS

Ten common gastrointestinal surgical diseases and procedures were identified The diseases and/or procedures chosen along with an outline for developing guidelines were sent to members of the SSAT with recognized expertise in specific areas The guidelines they developed were reviewed by several committee members and then by the entire committee on several occasions. Each guideline was then sent back to the original author for final comment and reviewed again by the committee Each guideline was approved by the Board of Trustees of the SSAT and final comments were reviewed by the committee These guidelines are based on statements and recommendations that were overwhelmingly supported by clinical evidence Each represents a consensus of opinion and is considered a reasonable plan for a specific clinical condition Relevant references are also provided for most of the guidelines

CONCLUSIONS

The rationale for practice guidelines has been elucidated It is hoped that these guidelines will result in changes in clinical care Perhaps the origin of these guidelines may be a critical factor in whether they become widely accepted. Our purpose in developing guidelines for gastrointestinal surgical disorders is to promulgate information that is needed to evaluate patients with diseases that require surgery and to provide information concerning expected outcomes following specific operative procedures As practice patterns and technology evolve, these guidelines will need to be changed accordingly.

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Treatment of Gallstone and Gallbladder Disease Using Cholecystectomy

Gallstone disease is a major national health care problem and results in more than 500,000 cholecystectomies per year. The vast majority of operations are for symptomatic gallstone disease and more than 80% of cholecystectomies are performed laparoscopically. Alternative forms of treatment are palliative rather than curative.

SYMPTOMS AND DIAGNOSIS

What is gallbladder pain or biliary colic? Patients with gallbladder stones may have transient postprandial right upper or epigastric abdominal pain or pressure discomfort that lasts from 1 to 24 hours This is considered the typical biliary colic of gallstone disease, and removal of the gallbladder and its stones (cholecystectomy) is the best treatment for most patients Sometimes the pain may radiate to the back between the scapulae In some patients the symptoms are mild and consist of only vague indigestion or dyspepsia.

The diagnosis of gallstones is usually established by ultrasonography or oral cholecystography. Other ultrasound findings, such as a thickened gallbladder wall or fluid around the gallbladder, suggest the presence of acute cholecystitis

TREATMENT

Gallstones without any abdominal symptoms are not an indication for cholecystectomy, except if the wall of the gallbladder is calcified or the gallstones are greater than 3 cm in diameter. Once a patient with gallstones begins to have pain in the upper abdomen for which there is no more likely explanation, elective cholecystectomy is indicated There are other indications for more urgent cholecystectomy such as acute cholecystitis, gallstone pancreatitis, choledocholithiasis (common duct stones), and cholangitis.

The patient should be seen by a surgeon within a few weeks if the acute episode has resolved or symptoms are mild Those patients with marked right upper quadrant tenderness, fever, or an elevated white blood cell count should be seen by a surgeon the same day Alternatives such as the dissolution of gallstones with oral agents, extracorporeal shock wave lithotripsy, and dissolution by instilling solvents directly into the gallbladder are not standard forms of treatment and are reserved for very unusual cases Oral dissolution therapy has very low efficacy and is expensive. Shock wave lithotripsy and contact dissolution are not approved by the Food and Drug Administration

Cholecystectomy may occasionally be indicated for patients with gallbladder pain who do not have gallstones (acalculous cholecystitis)

Cholecystectomy may be performed using laparoscopic techniques or through an abdominal incision The advantages of the laparoscopic approach are a shorter hospital stay, faster return to normal activities, and minimal scarring. The disadvantages are the superficial view of the abdominal contents and the inability to palpate the bile duct and other abdominal organs

RISKS

In patients undergoing elective cholecystectomy, the risks are exceedingly low. Risks related specifically to cholecystectomy include injury to the bile ducts, retained stones in the bile ducts, and injury to surrounding organs. The bile duct injury rate is approximately 0.5% for laparoscopic cholecystectomy and is slightly higher than the rate for open cholecystectomy. The chance of death in a good-risk patient undergoing elective operation is less than 1% The mortality rate for acute cholecystitis is similarly low unless the patient requires an emergency operation The risks are usually from comorbid conditions such as cardiac or pulmonary disease

CONVERSION OF LAPAROSCOPIC CHOLECYSTECTOMY TO AN OPEN PROCEDURE

Although a laparoscopic approach is feasible in most patients, conversion to an open procedure is occasionally required. Conversion to an open procedure should not be viewed as a complication, per se, but is an appropriate decision because of the presence of adhesions, difficulty in delineating the anatomy, or a suspected injury. Thus conversion to an open procedure may avoid complications

Conversion is more often necessary in elderly patients and those with prior upper abdominal operations, a thickened gallbladder wall, or acute cholecystitis The incidence of conversion to an open procedure is 5% to 10%, depending on the patient population

EXPECTED OUTCOMES

In the majority of good-risk patients (ASA I and II), elective laparoscopic cholecystectomy requires no more than an overnight hospital stay Emergency operations and high-risk patients (ASA III and IV) may require longer postoperative stays Following open cholecystectomy, patients are usually discharged after two or three nights in the hospital. Hospitalization may be prolonged in patients requiring placement of abdominal drains or exploration of the bile duct and in those with complicated biliary tract disease.

After undergoing cholecystectomy for biliary pain, 95% of patients are relieved of the pain The 5% failure rate represents the inability to be certain that the pain did not have an origin other than gallstones. Some patients may have abdominal cramps, bloating, excessive gas, diarrhea, or heartburn before the operation. These symptoms are less reliably related to gallbladder disease and may not be relieved following cholecystectomy They can usually be controlled by dietary manipulation or, if some other abdominal disease is present, treatment of that condition As an example, patients with heartburn would require treatment of reflux esophagitis.

TREATMENT OF COMMON DUCT STONES

Options for removal of common duct stones include endoscopic and surgical approaches. An endoscopic approach is indicated for patients with cholangitis, severe pancreatitis, or obstructive jaundice. Endoscopic clearance of common bile duct stones is an effective treatment but is associated with a small risk of pancreatitis, bleeding, or perforation Surgical removal of common bile duct stones can be performed by laparoscopic techniques if appropriate equipment is available and the surgeon has expertise. Open cholecystectomy with common bile duct exploration is a safe and effective treatment, especially if the patient is acutely ill Nonoperative treatment of common bile duct stones in patients who still have their gallbladders should only be performed after appropriate surgical consultation Since most common duct stones come from the gallbladder, cholecystectomy is also indicated unless the patient is not considered a suitable operative risk

COSTS

Cholecystectomy is cost-effective when compared to alternative treatments since it definitively treats the disease and reliably alleviates the symptoms. There may be no significant cost savings between laparoscopic cholecystectomy and open cholecystectomy The savings from the short hospital stay for laparoscopic cholecystectomy may be offset by the higher operating room costs for the laparoscopic procedure.

QUALIFICATIONS FOR PERFORMING SURGERY ON THE GALLBLADDER

The qualifications of a surgeon performing any operative procedure should be based on standard residency training (education), experience, and outcomes At a minimum, laparoscopic and open cholecystectomy should be performed by surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent

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Treatment of Acute Pancreatitis

Acute pancreatitis has a range of severity from edema to necrosis of the gland The edematous form of the disease occurs in approximately 80% to 85% of patients and is self-limited with recovery within a few days In the 15% to 20% of patients with the most severe form of pancreatitis, hospitalization is prolonged. Infection and other complications including multiple organ failure are common. Operative intervention may be required and survival is not assured. The incidence of acute pancreatitis is between 17 and 28 per 100,000 population The patient with severe pancreatitis should be identified as early as possible (within 7 days) and managed by a team experienced in preventing and treating its complications.

SYMPTOMS AND DIAGNOSIS

Patients often complain of severe upper abdominal pain radiating straight through to the back with associated nausea and vomiting Abdominal findings may vary from epigastric tenderness on deep palpation to acute abdominal pain with distention. The serum amylase and lipase levels are usually elevated but they correlate poorly with the severity of the disease It is important to establish the etiology of the pancreatitis In some cases treatment of a specific cause of pancreatitis is indicated, such as cholecystectomy for patients with gallstone pancreatitis

Distinguishing patients who are severely ill from those with mild disease may be difficult initially If the patient has clinically severe pancreatitis and is adequately resuscitated, a CT scan with oral and intravenous contrast should be obtained, provided the patient's renal function is adequate. The CT scan can confirm the diagnosis and serve as a useful indicator of severity. The presence or absence of cholelithiasis should be determined as early as possible, usually with ultrasonography Other tests that are helpful in establishing the severity of pancreatitis include arterial blood gases, complete blood count, and serum chemical values for calcium, glucose, and creatinine among others

TREATMENT

Patients with mild pancreatitis usually respond to a regimen of nothing by mouth, narcotics for pain relief, and intravenous fluids, with resolution of pain within 24 to 48 hours If oral intake is tolerated, they can be discharged from the hospital. Patients with pancreatitis secondary to gallstones should undergo cholecystectomy during the same hospitalization Patients who have common bile duct obstruction from a stone at the ampulla should undergo urgent removal of the stone (preferably by endoscopic papillotomy) if they have evidence of cholangitis. Patients with a history of alcoholism should be counseled and encouraged to participate in a detoxification and rehabilitation program Patients with hyperlipidemia should be placed on an appropriate diet and given drug therapy.

Characteristically, severe pancreatitis is associated with a marked increase in microvascular permeability leading to large volume losses of intravascular fluid into the tissues, thereby decreasing perfusion of the lungs, kidneys and other organs Probably the single most important element in preventing multiple organ failure is vigorous fluid resuscitation with electrolyte solutions to optimize the cardiac index and maintain hemodynamic stability. Swan-Ganz monitoring is helpful in such patients. Few patients develop multiple organ failure in the absence of infection if fluid resuscitation is vigorous

Patients with *severe* pancreatitis should be treated in an intensive care unit If no improvement occurs within 7 days, the patient should be referred to a medical center with a team experienced in caring for patients with severe pancreatitis. The rationale for this recommendation is based on the high mortality and morbidity associated with severe pancreatitis

Infection early after the onset of pancreatitis (within 1 to 2 weeks) carries an ominous prognosis. When infection supervenes 2 weeks or more after the onset of symptoms, the infected pancreatic and peripancreatic tissue is more readily defined and removed at operation, and consequently the mortality is decreased Preventing or delaying infection with appropriate antibiotics reduces morbidity, length and cost of hospitalization, and the need for operative intervention, and may reduce mortality. Treatment of infected fluid and/or necrotic tissue may include endoscopic, radiologic, and operative procedures. Aggressive nutritional support is also essential for these patients

EXPECTED OUTCOMES

The overall mortality rate for severe pancreatitis is reported to average approximately 15%. The average length of hospital stay varies from 40 to 65 days These outcomes should improve with adequate early resuscitation and the use of less invasive procedures.

QUALIFICATIONS

Ideally these patients should be treated by a team of physicians qualified to care for critically ill patients and with experience in treating patients with severe pancreatitis Operations should be performed by surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent

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Surgical Treatment of Chronic Pancreatitis

Chronic pancreatitis has an incidence of 5 to 10 per 100,000 in the United States and is most commonly associated with chronic alcohol abuse (75%). The most common reason for patient presentation is chronic pain, either persistent continuous pain or pain related to eating. Patients selected for surgical treatment of pain should have some demonstrable pancreatic anatomic abnormality Patients with chronic pancreatitis have an increased risk of developing pancreatic cancer compared to the general population.

SYMPTOMS AND DIAGNOSIS

The major disabling symptom in patients with chronic pancreatitis is pain. There is often associated weight loss, and many patients develop narcotic dependency. Diabetes, maldigestion, and jaundice are also frequently seen.

The diagnosis of chronic pancreatitis and its complications is usually made by CT scan, ultrasonography, or endoscopic retrograde cholangiopancreatography (ERCP) Typical findings include a dilated pancreatic duct or "chain of lakes," pancreatic calcifications, and pseudocysts Biliary or duodenal obstruction or evidence of portal hypertension may also be found Distinguishing between chronic pancreatitis and pancreatic cancer may be difficult, particularly in patients without pancreatic calcification Marked elevation of the serum CA 19-9 level in a nonjaundiced patient is highly suggestive of pancreatic cancer

ERCP delineates the pancreatic and biliary ductal anatomy and is important in determining which patients might benefit from surgery and for planning the most appropriate operation. In patients with atypical gastrointestinal bleeding and pancreatitis, angiography of the celiac and superior mesenteric arteries is indicated to detect and embolize pseudoaneurysms.

In addition to assessing the pathologic anatomy of the pancreas, it is important to establish a baseline for pancreatic exocrine and endocrine function, nutritional status, pain severity, analgesia usage, employment status, and quality of life. Any problems involving continued alcohol or narcotic use need to be addressed as part of both surgical or nonsurgical management programs

TREATMENT

Patients with disabling abdominal pain and evidence of chronic pancreatitis who have pancreatic ductal disruption or obstruction with upstream dilatation are most likely to benefit from operative intervention. Such patients are best managed by surgical cyst or ductal decompression or resection. Patients with chronic pancreatitis and bile duct obstruction require biliary-enteric decompression Although preservation of pancreatic tissue is desirable to maintain both exocrine and endocrine function, there are situations in which pancreatic resection is the preferred treatment. Alternative procedures such as endoscopic sphincterotomy, short-term stent placement in the major pancreatic duct or pancreatic pseudocyst, and extracorporeal shock wave lithotripsy for stones may provide relief of symptoms on a short-term basis, but are less effective in the long term

RISKS

The risks associated with operations for chronic pancreatitis and its complications include infection, bleeding, biliary and pancreatic anastomic leaks, and acute pancreatitis The frequency of these complications ranges from 0.5% to 5% The mortality rate for pancreatic surgery varies with the procedure and is generally less than 5% for major resections and lower for nonresective operations

EXPECTED OUTCOMES

Good pain relief can be expected in 75% to 80% of patients initially and will be sustained in most patients for 3 to 5 years. The incidence of postoperative diabetes and steatorrhea is a reflection of the amount of parenchyma resected and the disease status of the residual gland The natural progression of exocrine and endocrine insufficiency associated with chronic pancreatitis exacts an additional toll of 10% to 15% of nondiabetic patients becoming diabetic within a decade. Abstinence from alcohol and decompression of an obstructed main ductal system may slow the progression of exocrine and endocrine insufficiency in some patients but will not prevent their occurrence. After surgery most patients experience weight gain The best outcomes occur in patients who abstain from alcohol and narcotics and are compliant with pancreatic enzyme replacement regimens

The average length of stay after major pancreatic surgical procedures is 12 to 16 days, and tends to be longer after pancreaticoduodenectomy than after dis-

tal pancreatectomy or ductal decompression operations

QUALIFICATIONS

Pancreatic surgery should be performed only by surgeons who are certified or eligible for certification by the American Board of Surgery, the Royal College of Physicians and Surgeons of Canada, or their equivalent. These surgeons have undergone at least 5 years of surgical training after medical school graduation

Pancreatic surgery should preferably be performed by surgeons who have special knowledge, training, and experience in pancreatic disease.

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Importance of Preoperative and Postoperative pH Monitoring in Patients With Esophageal Achalasia

To the Editors

I greatly enjoy the new Journal of Gastrointestinal Surgery but I am disappointed that the published versions of the papers presented at the annual meetings of The Society for Surgery of the Alimentary Tract (SSAT) do not always include the discussions that took place at the meetings I refer in particular to a paper by Patti et al (J GASTROINTEST SURG 1997,1 505-510)

The authors of this paper conclude that symptoms are an unreliable index of postmyotomy abnormal esophageal reflux in patients with achalasia, and they also conclude that pH monitoring should be performed in order to make this diagnosis and therefore to prevent the onset of complications such as a stricture or Barrett esophagus

Ulcerative esophagitis invariably precedes stricture formation, and the diagnosis of this and Barrett's esophagus is fundamentally endoscopic, yet their paper completely omits any reference to endoscopic findings One might ask, if there are no symptoms of reflux, and no endoscopic evidence of ulcerative esophagitis, what is the clinical significance of abnormal pH studies? Are the authors justified, in the absence of symptoms or endoscopically visible ulcerative esophagitis, in recommending the incorporation of an antireflux procedure in laparoscopic myotomy? When reflux occurs after myotomy, it is usually easily controlled by medication, whereas there is evidence that the addition of an antireflux procedure to myotomy, especially if it is done laparoscopically, may actually cause worsening of dysphagia in a significant number of patients

The authors describe pH findings indicative of "pseudo–gastroesophageal reflux (GER)" Did they consider the possibility that this might be an artifact resulting from "electrode drift?"

I was unable to attend the SSAT meeting at which some of these issues presumably were discussed In any case, how did this paper, with its notable defects, slip past the journal referees?

Thomas B Hugh, FRCS, FRACS
St Vincent's Clinic
Darlinghurst, New South Wales

Reply

We appreciate the opportunity to clarify the issues raised by Dr Hugh The statement Dr Hugh referred to concerning the value of pH monitoring in relation to the risks of stricture formation and Barrett's esophagus reads "The identification of patients with GER *after dilatation* " (italics added) We did not recommend routine pH monitoring after a Heller myotomy, and we do not ourselves perform routine postoperative pH monitoring for clinical purposes Nevertheless, Dr Hugh is probably correct in believing that surgeons who embrace his management strategy are being challenged to defend it via postoperative testing

More important, however, Dr Hugh's remarks contain the incorrect assumption that stricture formation and Barrett's changes can be prevented because they are regularly preceded by erosive esophagitis, which would be detected clinically and endoscopically and treated If that were the case, we would not encounter strictures, Barrett's disease, and esophageal neoplasms arising from Barrett's mucosa in clinical practice In fact, experience shows that previous symptoms of reflux are often so mild (or absent) that the patient does not report for care until late in the process

Our point in regard to postoperative testing was that validation of the results of these and similar operations should include pH studies, since one cannot say much about the presence or absence of reflux based on the clinical findings alone Clearly, when reflux produces clinical manifestations, clinical assessment is indicated and useful However, we do not at this point know the natural history of the subclinical reflux uncovered in this study Perhaps it is trivial, as Dr Hugh believes, but we think this is improbable and an unwise, unwarranted assumption

The postoperative pH monitoring was of principal value when comparing the two operations The older practice of assessing reflux clinically is now known to be insensitive, and even previous champions of that approach have reported data to that effect We might counter Dr Hugh's criticism of the editorial process by recommending that without postoperative pH monitoring, claims about reflux in papers on this subject are incompletely substantiated

pH drift, also known as pseudoreflux, can be seen in patients with achalasia as a result of esophageal stasis of food [1] This subject was discussed in the manuscript under Methodology, where we defined the distinction between bona fide reflux and pseudoreflux, and mentioned that we did not confuse the two when compiling the data

The principal observations in the study were as follows (1) reflux is often subclinical, (2) subclinical reflux may be substantial, (3) in certain instances knowing about the presence of reflux will change a plan of management, (4) postdilatation reflux is relatively common, (5) it is useful to know about the reflux before undertaking a Heller myotomy, since the myotomy is certainly not going to improve reflux, and one does not want the operation to ultimately get blamed for preexisting reflux, and (6) reflux was much less common when a Dor fundoplication was performed (even though the myotomy was longer in those cases) than when it was not

Dr Hugh noted that a fundoplication might cause worsening of dysphagia, and he implied, therefore, that a fundoplication should not be performed in conjunction with a Heller myotomy However, fundoplications did not produce dysphagia in these patients, while they did prevent reflux This is not a new idea, for Perrachia and Skinner have been recommending fundoplication in conjunction with a

Heller myotomy for many years Thus the question is, if a Heller myotomy is indicated, and subclinical reflux is common after myotomy alone, and a fundoplication can be done without worsening dysphagia while sharply decreasing the frequency of reflux, which operation should be chosen?

Lawrence W Way, M D
Marco G Patti, M D
Department of Surgery
University of California, San Francisco
San Francisco, California 94143-0475

REFERENCE

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Esophagectomy Volume and Operative Mortality

To the Editors

I read with interest the article by Patti et al [1] Their paper convincingly shows that patient outcome after esophagectomy is better in high-volume hospitals An inverse correlation between hospital surgical volume and operative mortality has also been documented for other complex operations [2] The three major factors responsible for this relationship are the skill of the surgeon, the experience of the "supporting cast" (i e , anesthesiologists, intensivists, and nurses), and the resources of the hospital

Skilled surgeons often develop high-volume practices at tertiary care hospitals, so it is difficult to study the various factors in isolation However, studies examining the role of the surgeon in esophagectomy outcome have consistently shown better results for surgeons with high-volume practices [3,4] In addition, specific complications, such as anastomotic leakage, are more a function of surgical expertise than the exact anastomotic technique used [5] For other complex surgical procedures, such as pancreatic resection, the size or nature (community or academic) of the hospital is not critical as long as the surgeon is skilled and experienced [6]

Although both hospital and surgeon volume are important in esophagectomy outcome, the surgeon may be a more important variable than the hospital I agree with the suggestion made by Patti et al that esophagectomy be performed in centers with sufficient volume Within these centers, esophagectomies should only be undertaken by surgeons with skill and experience in this particular operation

John D Urschel, M D
Department of Thoracic Surgical Oncology
Roswell Park Institute
Buffalo, New York

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