Manometric Diagnosis of Sphincter of Oddi Spasm as a Cause of Postcholecystectomy Pain and the Treatment by Endoscopic Sphincterotomy

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Seventeen patients with postcholecystectomy pain and nine controls were studied by nonoperative biliary manometry with stimulation of sphincter of Oddi spasm by morphine. The controls remained asymptomatic despite an elevation of bile duct pressure after morphine. In 13 patients with postcholecystectomy pain, morphine induced pain paralleling a pressure rise. Three other patients had pain not paralleling a pressure change, and another showed a pressure rise without pain. None of the controls, four with the parallel pain-pressure change, and one with the discordant pain-pressure correlation were positive at the traditional morphine-Prostigmin® test. Endoscopic sphincterotomy provided complete (8), moderate (3), or slight (1) relief of pain to 12 patients with the parallel pain-pressure relationship. Postsphincterotomy manometry showed disappearance of both the pressure elevation and pain induction, and the morphine-Prostigmin test turned negative. It is concluded that (a) morphine-induced bile duct pressure elevation coinciding with pain is diagnostic of sphincter spasm as a cause of postcholecystectomy pain, (b) the morphine-Prostigmin test, although helpful, is less specific and less sensitive in diagnosing sphincter spasm than the manometry, and (c) endoscopic sphincterotomy relieves the pain due to this condition in most cases.

PERSISTENT OR RECURRENT PAIN after cholecystectomy remains a challenging problem in biliary tract surgery.[1] The advent of modern diagnostic modalities has allowed us to elucidate the exact cause of the symptom in most cases. However, there do exist some cases where no structural abnormality can be demonstrated even after exhaustive investigations. Diagnosis of so-called postcholecystectomy syndrome is made by exclusion. Although the symptom in such patients seems attributable to elevation of bile duct pressure due to spasm of the sphincter of Oddi (SO), there has been no definitive method available to demonstrate its presence. We evaluated diagnostic utility of a manometric method with a microtransducer in such cases. A microtransducer catheter was retained by duodenoscopy in the bile duct for continuous measurement of the bile duct pressure.[2] The SO contraction was induced by the administration of morphine with observation of symptomatic and pressure responses. For comparison, the traditional morphine-Prostigmin® test was also performed. Those with proven SO contraction with pain underwent endoscopic sphincterotomy (EST) with remarkable relief of pain.

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Materials and Methods

Subjects

Seventeen patients referred to us from April 1981 to September 1984 with persistent pain in the right upper quadrant (RUQ) after cholecystectomy were studied. Thirteen of these patients were female and four male, ranging from 25 to 60 years of age. Their clinical data are listed in Table 1. Cases 1 and 2 were reported previously in a preliminary note.[2] The pain often radiated to the right back and/or the right shoulder. All patients were evaluated by barium swallow study and/or endoscopy to exclude gastroduodenal diseases. All had intravenous cholangiography and endoscopic retrograde cholangiopancreatography (ERCP) to show an absence of any structural abnormalities in the biliary tract and the pancreas. Nine other patients after cholecystectomy without common bile duct exploration were studied 2–3 weeks after surgery and served as controls. The controls were subsequently followed up for at least 2 years, and none of them developed so-called postcholecystectomy syndrome.

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TABLE 1. *Clinical Data of 17 Patients with Postcholecystectomy Pain*

Case	Age	Sex	Duration of Postcholecystectomy Pain	Asymptomatic Period Postop	Symptoms	Previous Operations/Age
1	45	F	7 years	1 year	RUQ + back pain nausea, vomiting	Appendectomy/24 Hysterectomy/36 Cholecystectomy, CBDE*/37
2	34	F	1.5 years	13 years	RUQ + back pain	Appendectomy/19 Cholecystectomy/19 Lysis of intraperitoneal adhesion/33
3	52	F	3 years	0	RUQ + back pain	Cholecystectomy/49
4	31	F	3 months	1 week	RUQ pain	Right adnexectomy/26 Cholecystectomy/31
5	47	F	18 years	5 years	RUQ pain	Cholecystectomy/25
6	37	F	6 months	0	RUQ + back pain	Cholecystectomy/36
7	45	F	2 years	0	RUQ + back pain	Appendectomy/19 Laparotomy as acute abdomen/30 Hysterectomy/42 Cholecystectomy/43
8	60	F	5 years	27 years	RUQ + back pain	Cholecystectomy/37
9	41	F	2.5 years	1 year	RUQ pain	Cholecystectomy/38
10	47	F	1 year	5 months	RUQ pain	Cholecystectomy/45
11	47	M	7 years	0	RUQ + back pain	Cholecystectomy/40
12	41	F	2 months	8 months	RUQ pain	Cholecystectomy/32
13	46	M	1 year	0	RUQ + back pain	Gastrectomy for duodenal ulcer/34 Cholecystectomy/45
14	55	M	12 years	3 years	RUQ + back pain	Cholecystectomy/41
15	41	F	4 years	2 years	Right backache	Appendectomy/12 Lysis of intraperitoneal adhesion/22 Cholecystectomy/34
16	25	M	1 year	0	RUQ + back pain, right shoulder pain	Cholecystostomy, appendectomy/20 Cholecystectomy/24
17	26	F	7 years	3 years	RUQ + back pain, right shoulder pain	Cholecystectomy, CBDE*/22

* CBDE = common bile duct exploration.

Morphine-Prostigmin Test

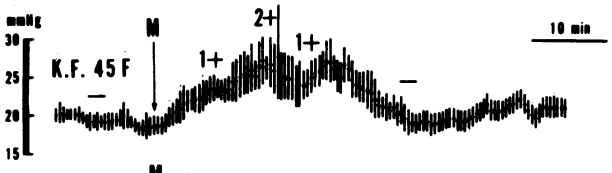
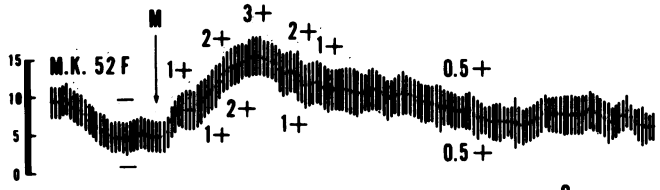
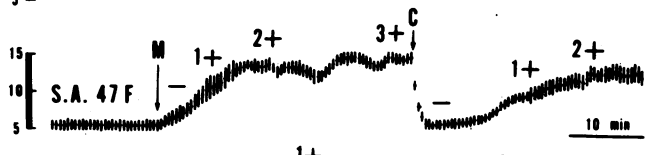
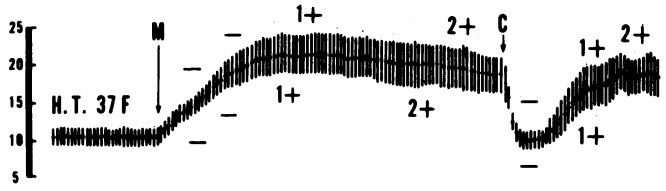
The morphine-Prostigmin test was carried out on the controls and all but one patient with postcholecystectomy pain. In a patient with moderately elevated liver function tests because of chronic active hepatitis (proven by biopsy), the test was not performed for fear of exacerbating the liver dysfunction. After overnight fast, morphine hydrochloride (10 mg) and Prostigmin (1 mg) were given intramuscularly, and blood samples were obtained before, at 1, 3, and 8 hours after the injections for determination of serum amylase, S-GOT, S-GPT, and total bilirubin. A fourfold rise above preinjection level of either one of these parameters was considered to be positive when it was associated with RUQ or epigastric pain.

Manometry with Provocation of SO Activity

The bile duct pressure was measured using a high-fidelity microtransducer catheter (model PC-340B, Miller Instruments Inc., Houston, Texas) placed in the common bile duct by duodenoscopy. After pharyngeal anesthesia with lidocaine spray, the papilla was identified with a side viewing duodenoscope (model JF-1T, Olympus Optical Co., Tokyo, Japan). Anticholinergic agents were not used to avoid possible effect on the SO function. Intravenous diazepam (5 mg) was given only in extremely nervous patients. The microtransducer catheter calibrated just before use at 38 C with atmospheric pressure as zero reference was introduced into the common bile duct. The position was confirmed under fluoroscopy in the prone position. The endoscope was withdrawn over the catheter completely while leaving the catheter in place. The posture of the patient was changed to the supine position and the location of the catheter was adjusted to the midportion of the common bile duct under fluoroscopy. Then pressure recording was started.

After stable basal pressure was recorded for at least 20 minutes, 0.2 mg/kg of morphine hydrochloride was administered intramuscularly to induce SO spasm. While not informed of possible occurrence of pain to avoid emotional overlay on the study, the patient was told to report any symptom at its first appearance. The vital signs and location of the catheter were frequently checked during pressure recording after the morphine injection. If the

TABLE 2. *Morphine-Prostigmin Test and Manometric Study in 17 Patients with Postcholecystectomy Pain*

Case	Age	Sex	Morphine-Prostigmin Test: Pain	Morphine-Prostigmin Test: Enzyme	Manometric Record with Pain Score M: intramuscular morphine, 0.2 mg/kg, C: intravenous caerulein, 0.1 μg/kg
Parallel Pain-Pressure Change Group					
1	45	F	–	normal	
2	34	F	–	20×	
3	52	F	+	7×	
4	31	F	+	normal	
5	47	F	+	10×	
6	37	F	+	10×	

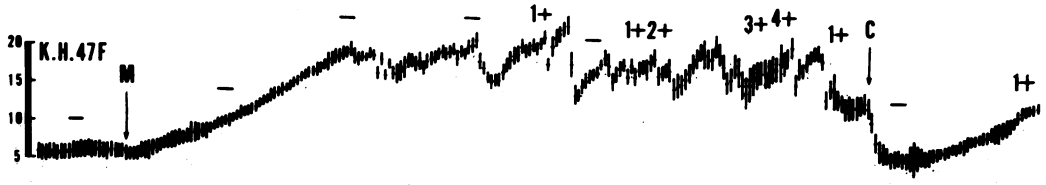
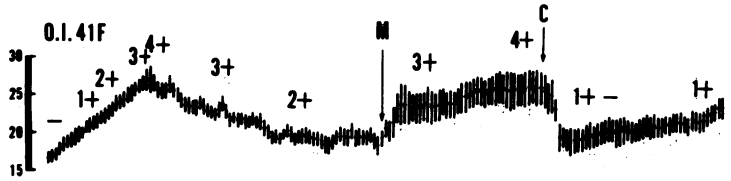
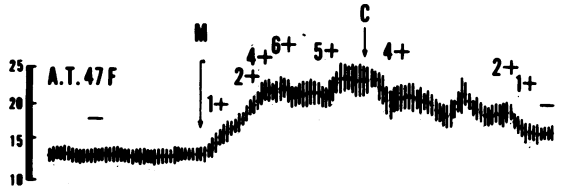
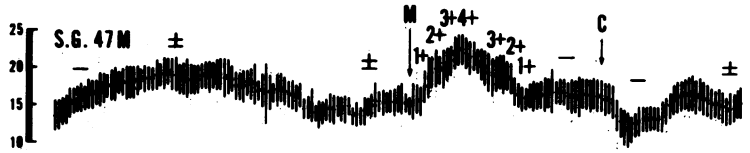
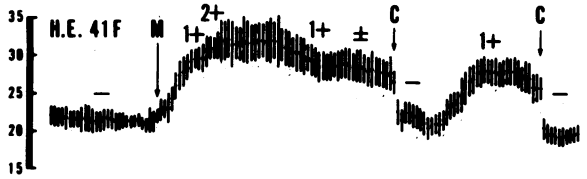
patient developed pain, its severity was graded by the patient himself and the "pain score" was recorded on the pressure chart. At the end of the study (usually 30–40 minutes after morphine), 0.1 μg/kg of caerulein (Farmitalia Laboratories, Milano, Italy), a decapeptide analogue of cholecystokinin, diluted in 5 ml of saline was given intravenously to relax the SO and confirm the SO origin of the morphine-induced manometric and symptomatic responses. Caerulein was given earlier if the pain was unbearable. Blood samples were drawn for amylase determination and liver function tests before and 1, 3, and 15 hours after the morphine administration.

A pressure tracing was divided into 30-second segments, and an area under the tracing line was measured by planimetry. A baseline drift of the microtransducer precalibrated at 38 C was −0.5 mmHg at 40 minutes and −1.0 mmHg at 80 minutes. An area beneath the drift curve was also measured by planimetry. The time of the introduction of the catheter into the duodenum was taken as time zero, and the mean pressure value at each time interval was calculated by subtraction of the area of the drift from the area of the pressure tracing.

Endoscopic Sphincterotomy

EST was performed when the patient with postcholecystectomy pain showed pressure elevation with pain during the manometric study with morphine provocation. After the papilla was identified in the usual manner, the bile duct was entered with a long-tipped sphincterotome.[3]

TABLE 2. (*Continued*)

Case	Age	Sex	Morphine-Prostigmin Test: Pain	Morphine-Prostigmin Test: Enzyme	Manometric Record with Pain Score M: intramuscular morphine, 0.2 mg/kg, C: intravenous caerulein, 0.1 μg/kg
7	47	F	+	16×	
8	60	F	–	normal	
9	41	F	–	normal	
10	47	F	–	normal	
11	47	M	not tested		
12	41	F	–	normal	

The cannulation into the bile duct was quickly confirmed by aspiration of bile with a syringe. Diathermy was applied to the wire portion of the cutting probe, and the oral prominence of the papilla was incised cephalad. The tip of the probe was kept within the bile duct during the procedure, allowing an easy control of the direction and speed of cutting.

Statistical Analysis

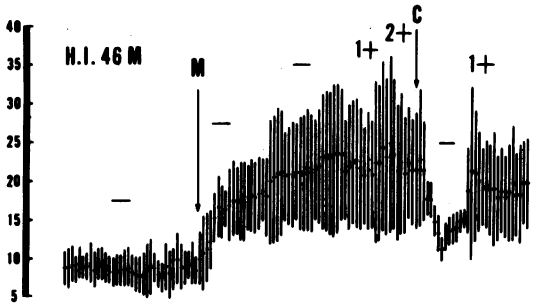
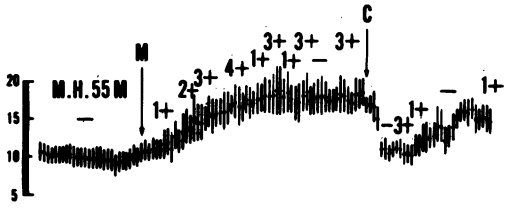
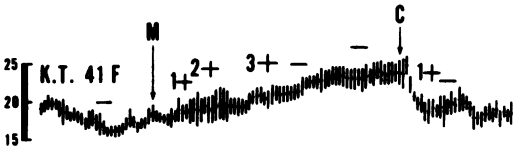
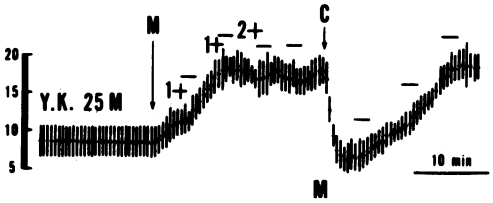
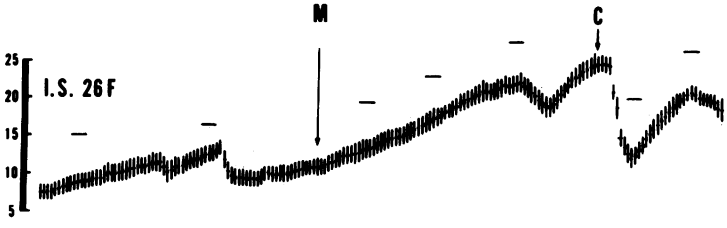
The Student's t-test for unpaired data was used for statistical evaluation of the mean pressure values. The difference was considered significant if p was <0.05.

Results

Morphine-Prostigmin Test

In all control patients, the test was negative for pain, whereas a threefold rise of S-GOT and S-GPT was noticed at 1 and 3 hours in one patient and also a threefold rise of S-GOT at 1 hour in another. In the patients with postcholecystectomy pain (Table 2), pain was reproducible in seven patients. The pain was associated with a more than fourfold elevation of one or more enzymes in five of the seven subjects. Thus, the morphine-Prostigmin test was positive in five of the 16 patients with postcholecystectomy pain studied, whereas it was negative in all

TABLE 2. (*Continued*)

Case	Age	Sex	Morphine-Prostigmin Test: Pain	Morphine-Prostigmin Test: Enzyme	Manometric Record with Pain Score M: intramuscular morphine, 0.2 mg/kg, C: intravenous caerulein, 0.1 μg/kg
13	46	M	–	6×	
Discordant Pain-Pressure Change Group					
14	55	M	+	13×	
15	41	F	+	normal	
16	25	M	–	normal	
17	26	F	–	normal	

control patients. Two other patients with postcholecystectomy pain had a twentyfold rise of S-GOT and S-GPT at 8 hours and a sixfold increase of S-GOT at 8 hours with a fourfold rise of serum amylase at 8 hours, respectively, but without pain.

Manometry

The administration of morphine invariably caused a pressure elevation but no pain in the controls. A baseline tracing was stable and the mean pressure value in nine control subjects just before morphine administration was 9.8 ± 1.4 (1 SD) mmHg. The pressure rose shortly after the injection, reaching maximum in 10–25 minutes (Fig. 1). The mean maximal pressure after morphine was 19.0 ± 3.0 mmHg. Associated with the pressure elevation, the tracing became high in amplitude and irregular in shape and height as described in detail in the earlier report from this department.[4] Caerulein given 60 minutes after the morphine injection produced an abrupt and transient fall of the pressure, which was not associated with pain.

There were two types of manometric and symptomatic responses in the patients with postcholecystectomy pain (Table 2). Thirteen of the 17 patients showed a pressure elevation associated with RUQ or epigastric pain after the administration of morphine. The intensity of the pain

paralleled the degree of the pressure elevation (parallel pain-pressure change group). The mean basal pressure in this group of patients was 12.0 ± 5.3 mmHg; the mean peak pressure after morphine was 22.0 ± 5.2 mmHg. Both basal and peak pressures were higher than those of the controls but not significant. When caerulein was injected, the pressure instantly fell and the pain disappeared or, where it was severe, diminished. Postcholecystectomy pain in this group seemed to originate with spasm of the SO because (a) the morphine-induced SO spasm caused pain only in these patients, not in the controls, (b) the occurrence and subsequent changes in intensity of the morphine-induced pain completely coincided with the alteration of the bile duct pressure, (c) an administration of caerulein, the most potent SO relaxant, produced an instant disappearance of the morphine-induced pain and the pressure rise, and (d) the nature of the morphine-provoked pain was quite similar to those experienced clinically. Therefore, those of the parallel pain-pressure change group were subjected to EST to relieve the symptom with the exception of one patient with no severe pain after the manometric investigation.

In four other patients with postcholecystectomy pain, we failed to demonstrate consistent relationship between pressure changes and symptomatic responses (discordant pain-pressure change group). Pain could be reproduced by the morphine injection in three patients but subsequent changes in its intensity did not parallel changes in bile duct pressure. In another patient, morphine raised the pressure but no pain at all. Their symptom was partially relieved by elimination of the patients' fears of having some serious disease.

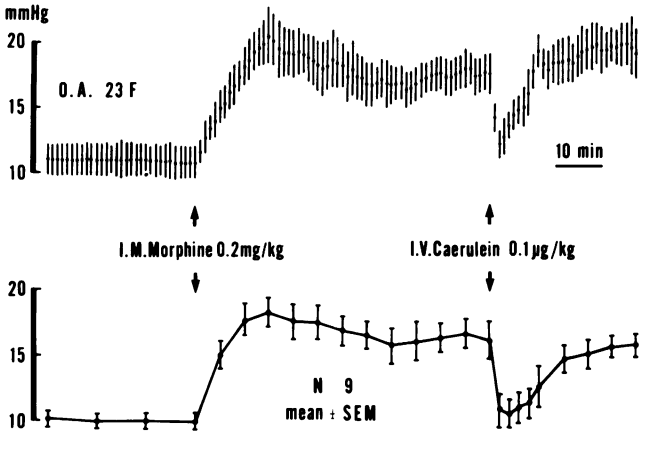


FIG. 1. Changes in common bile duct pressure after an administration of morphine followed by caerulein in control patients after cholecystectomy. Top demonstrates a representative tracing. The pressure level is expressed as the mean values in 30-second periods calculated by the method described in the text. Vertical bars represent maximal height of the pressure waves in each period. Bottom shows the mean value ± standard error of the mean in the nine control subjects.

TABLE 3. *Results of Endoscopic Sphincterotomy in 12 Patients with Postcholecystectomy Pain Showing Elevation of Bile Duct Pressure Paralleling Morphine-induced Pain*

Case	Age	Sex	Follow-up Period	Results
1	45	F	4 years, 2 months	Complete relief
2	34	F	3 years, 7 months	Complete relief
3	52	F	3 years	Complete relief
4	31	F	2 years, 1 month	Complete relief
5	47	F	1 year, 9 months	Complete relief
6	37	F	1 year, 7 months	Moderate relief
7	45	F	1 year, 6 months	Slight relief, return to pre-EST level in 6 months
8	60	F	1 year, 5 months	Complete relief
9	41	F	1 year, 3 months	Complete relief till recurrence of slight pain in 12 months
10	49	F	1 year, 3 months	Moderate relief
11	47	M	1 year, 2 months	Complete relief
13	46	M	2 months	Moderate relief

Endoscopic Sphincterotomy

EST was safely carried out in all 12 cases where indicated. Manometry with morphine stimulation was repeated 1–2 weeks after EST. No (3 patients) or only slight (9 patients) pressure elevation was noted. Mild and transient pain was elicited in two patients (cases 10 and 11). One of them (case 10) underwent EST again to enlarge the opening. This patient had no pain at the repeat provocational manometry after the second EST. A repeat morphine-Prostigmin test showed that the previously positive response turned negative after EST in all cases. EST resulted in complete relief of the symptom in eight patients, moderate relief in three, and slight relief in one (Table 3). All of them have been followed up for 2–50 months (average 23 months). Slight pain recurred in 12 months in one of the eight patients with complete relief, and the severity of the pain returned to the pre-EST level in one patient with slight relief.

Complications

There were no serious complications with the morphine-Prostigmin test, manometry, and EST. Some of both controls and those with postcholecystectomy pain had nausea with or without vomiting mostly several hours after the completion of the manometric investigation probably due to a side effect of morphine. Caerulein

sometimes caused slight nausea during intravenous administration. Two of the 17 patients with postcholecystectomy pain had a slight increase of serum amylase with or without elevation of transaminases after the manometry. Two other patients showed only slight elevation of transaminases. Elevation of transaminase levels was also noted in two of the nine control patients. One of them reached sixfold levels of the preprocedure values. EST was associated with transient elevation of serum amylase in one patient, who developed no clinical symptom of pancreatitis. Three patients showed transient exacerbation of pain probably due to edema at the sphincterotomy site. It lasted only for a day or two.

Discussion

Postcholecystectomy pain often poses an embarrassing problem for both the patient and surgeon. There certainly exists a population, although small, in which thorough examination of pancreatobiliary systems is unremarkable but their pain still seems to be of biliary origin. This study addressed the importance of the endoscopic manometry in evaluating such patients. Organic stenosis of the SO characterized by bile duct dilatation and, although ill defined at present, delayed drainage were excluded from this study. A possibility of pain having been caused by passage of small stones through the ampulla into the duodenum was also excluded by careful follow-up after ERCP that confirmed an absence of common bile duct stone.

Since the recent development of endoscopic manometry of the SO, this modality has been used to diagnose SO dysfunction. Toouli et al. evaluated a sequence of contractions within the SO segment and an effect of intravenous administration of cholecystokinin-octapeptide (CCK-OP) using a triple lumen infusion catheter.[5] CCK-OP did not alter the sequence pattern of SO phasic waves but reduced basal SO pressure and inhibited the phasic contractions. They stated that an inappropriate response to CCK-OP, *i.e.*, an increase in the basal pressure instead of the decrease, might occur in patients with suspected SO dysfunction, suggesting the diagnostic value of SO manometry with CCK-OP administration in this entity. In the present study, we studied a change of intraductal pressure in response to morphine to investigate if the pressure rise caused by SO spasm actually leads to abdominal pain. If endoscopic manometry should aid the diagnosis, direct assessment of the bile duct pressure would be a more direct and reliable approach.

Morphine is well known to produce SO spasm and is used in the morphine-Prostigmin test to evaluate SO dysfunction.[6,7] It induces SO spasm and, in turn, pressure elevation in the pancreatic and/or the bile duct. When the pressure rise elicits pain associated with an increase in serum amylase, lipase, and/or transaminases, the test is positive. However, there has been much debate as to the specificity and reproducibility of the test in diagnosing SO dysfunction.[8,9] Morphine may cause a painful spasm of bowels as well as the SO in some cases but may produce an SO spasm without accompanying pain yet vigorous enough to cause an elevation of the enzyme levels in some cases, causing the lack of specificity. Furthermore, the presence of a functioning gallbladder may contribute to the nonspecificity of the test because the gallbladder acts as a pressure reservoir in the face of morphine-induced SO spasm, and this may lead to false-negative results.[4] Selection of subjects to be tested should be strict before any conclusion is made about the specificity of this diagnostic test. In the present study, therefore, we chose asymptomatic postcholecystectomy patients as controls. The test was negative in all controls, whereas it was positive in five of the 16 patients with postcholecystectomy pain tested. All patients with a positive test had an elevation of the bile duct pressure associated with pain paralleling (4) or not paralleling (1) the pressure change after morphine, as measured by the microtransducer manometry. In view of these results, we believe that the test is still helpful in making the diagnosis of SO dysfunction, but, if the diagnosis is based solely on this test, about two thirds of patients with this entity may well be missed.

The dose of morphine used in this study caused no biliary pain in control patients after cholecystectomy despite a marked rise of bile duct pressure. In contrast, the response was quite different in patients with suspected postcholecystectomy SO spasm. Morphine-induced SO spasm well documented by the pressure rise did elicit the symptom in most of the patients. The elevation of the bile duct pressure after morphine administration coincided exactly with the intensity of morphine-induced pain. Both were completely or partly abolished by an injection of caerulein, the most potent SO relaxant. It would therefore be judicious to consider that a bile duct pressure elevation coincident with the change of intensity of morphine-provoked pain might be pathognomonic to SO spasm as a cause of postcholecystectomy pain. The peak pressure after morphine as well as the basal pressure, however, was not significantly greater than that in controls. Rather, some of the patients developed the pain at even lower pressure levels. This may indicate that an individual difference in the pain threshold at a given degree of SO spasm is an important factor in the development of postcholecystectomy pain. Three patients with postcholecystectomy pain showed no correlation between morphine-induced pain and pressure changes, suggesting that the pain was unlikely to have arisen from SO spasm. An additional patient had no pain in spite of a pressure rise, similar to controls. The pain in these patients might have originated from bowel spasm or some other causes. Biliary manometry in combination with morphine provocation

has proved to be useful in demonstrating the extrabiliary origin of the postcholecystectomy pain. Since EST was considered not to be effective but only harmful in such cases, we did not perform the procedure on this group of patients.

The medical treatment of postcholecystectomy pain due to SO spasm has not been established yet. Various sedative and/or spasmolytic agents have been used with little benefit. Since the effect of medical treatments has been uncertain, the patients tend to become more and more dependent on narcotics. The pain sometimes disturbs the activity of the patients seriously, and some incline for a relaparotomy for lysis of real or imagined intraperitoneal adhesion, yet with no benefit. If it is definitely demonstrated that the SO spasm is the cause of the pain by bile duct manometry with morphine challenge as described here, EST appears to be a reasonable choice to relieve the pain. In this series, EST provided a complete (8), moderate (3), or slight (1) relief to 12 patients who had pain paralleling pressure elevation on the morphine-stimulated manometry and thus underwent the procedure. They have been well for 2–50 months (average 23 months) except for case 7. The pain-pressure relationship in this case had been somewhat discordant particularly in the earlier section of the pressure tracing. We attributed this discordance to the analgesic effect of morphine. However, in retrospect, the delayed pain response may have been caused by some difference in the pain-producing mechanism. Her residual symptom seemed to be due to bowel spasm, and in all probability the patient had initially the pain from both origins—biliary and intestinal. One should be well aware of such overlapping causes. In general, from our experience, the more severe the patient's symptom and the morphine-induced pain are, the more effective EST tends to be.

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