Gallbladder Sludge and Stone Formation in Relation to Contractile Function After Gastrectomy

A Prospective Study

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In a prospective trial to determine whether gastric surgery induces gallbladder sludge and stone formation, 48 patients with gastric cancer were ultrasonographically examined with simultaneous observation on changes in gallbladder contractile function before and serially for 5 years after gastrectomy. Gallbladder sludge formation was induced with a high frequency of 42% 1 month after gastrectomy, with corresponding significant lowering of gallbladder contractile function. Most of gallbladder sludges, however, disappeared within 12 months in relation to the gradual recovery of gallbladder contractile function. Conversely, gallstone developed in nine patients (18.8%), mostly more than 6 months after gastrectomy. Interestingly, gallstone formation was induced in seven patients who were sludge negative. An evolvement of gallbladder sludge into stone was observed in only two patients, who were, however, treated with intravenous hyperalimentation. This study first provides evidence for the relationship between gastrectomy and a considerably high frequency of incidence of gallbladder sludge and stone in relation to changes in gallbladder kinetics after gastrectomy.

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SINCE MAJOOR AND SUREN first drew attention to the possible association of gallstones with gastric surgery, an increased incidence of gallstones has been widely reported in patients with gastrectomy.[2-9] There has been, however, very little information about the pathophysiologic mechanism for the occurrence of gallbladder disease after gastric surgery. Most of the studies on gallstone disease after gastrectomy have been retrospective.[1-9] No report has been available to carry out a prospective study on pathophysiology of gallbladder in relation to changes of gallbladder contractile function after gastrectomy.

In this study, we performed a prospective serial ultrasonographic study on changes of gallbladder volume and contractile function with special reference to sludge[10-13] formation and cholelithiasis in gastric cancer patients who have undergone gastrectomy.

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Patients and Methods

Adult patients with gastric cancer who were about to undergo gastric surgery were studied. Conditions necessary for the present prospective study include absence of gallbladder disease, as assessed by both preoperative ultrasonographic study and careful examination of the gallbladder at the time of surgery, no pyloric stenosis, no laboratory alterations in liver function test, and no injection of insulin, opiates, or anticholinergic drugs.

A total of 48 patients (33 men, 15 women; mean age of 56 years) were examined. All of them were patients with relatively early stage of gastric cancer.[14,15] Curative resection was performed on all of the patients based on the general rules for gastric cancer in Japan.[15] The surgical procedures carried out are as follows; subtotal gastrectomy with Billroth I anastomosis (30 patients), with Billroth II anastomosis (3 patients), total gastrectomy with interposition reconstruction (6 patients), and with Roux-en-Y reconstruction (9 patients).

Postoperative course was uneventful without any sign of cholecystitis in these patients, except in three cases with postoperative complications (leakage, pancreatitis, and passage disturbance), who were treated with intravenous hyperalimentation with postoperative fasting for 33 to 34 days. The period of postoperative fasting was about 3 to 5 days after subtotal gastrectomy (30 patients) and 8 to 13 days after total gastrectomy (15 patients).

By comparison, seven patients with colon cancer (five men, two women; mean age of 54) also were examined.

The operative procedures performed were partial colonic resection (five patients) and right hemicolectomy (two patients). The period of postoperative fasting for these patients was 3 to 5 days.

Ultrasonographic Study on Gallbladder

Ultrasonographic examination was prospectively carried out before (48 patients) and serially 1 week (36 patients), 2 weeks (38 patients), 1 month (40 patients), 3 months (29 patients), 6 months (31 patients), 12 months (44 patients), about 24 months (13 patients), and about 60 months (9 patients) after operation. For patients with colon cancer, ultrasonographic examination was carried out before (7 patients) and 1 week (5 patients), 2 weeks (6 patients), 1 month (7 patients), 3 months (6 patients), 6 months (7 patients), and 12 months (6 patients) after colonic surgery. Ultrasonographic examination was begun early in the morning (about 8:30 A.M.) after an overnight fast. Sonograms of the gallbladder were obtained by a real time ultrasound unit (Aloka, Tokyo, Japan) with a 3.5-MHz phased-array transducer.

Examination on Sludge and Stone Formation

In this study, we classified gallbladder sludges observed into four types (scattered type [S], tumefactive type [T], layering type [L], and precipitated type [P]) (Fig. 1) and gallstones into two types (strong echo without acoustic shadow [SE] and strong echo with acoustic shadow [ST]).

Observation on Changes in the Resting Gallbladder Area

Changes in the resting gallbladder area were observed before (48 patients) and serially 1 week (36 patients), 2 weeks (38 patients), 1 month (40 patients), 3 months (29 patients), 6 months (31 patients), 12 months (44 patients), and 60 months (9 patients) after gastrectomy. For patients with colon cancer, the same study was performed before (7 patients) and 1 week (5 patients), 2 weeks (6 patients), 1 month (7 patients), 3 months (6 patients), 6 months (7 patients), and 12 months (6 patients) after colonic surgery.

Study on Changes in Gallbladder Contractile Function

Prospective studies on changes of gallbladder contractile function were performed on 35 patients, employing cerulein as an exogenous stimulation of cholecystokinin (CCK).[16-19] Cerulein (0.2 μg/kg) was injected intramuscularly to each patient before (35 patients) and 1 month (27 patients), 3 months (25 patients), 6 months (26 patients), 12 months (30 patients), and 60 months (9 patients) after gastrectomy. Cerulein (0.2 μg/kg) also was injected into patients with colon cancer before (7 patients) and 1 month (7 patients), 3 months (5 patients), 6 months (6 patients), and 12 months (6 patients) after colonic sur-

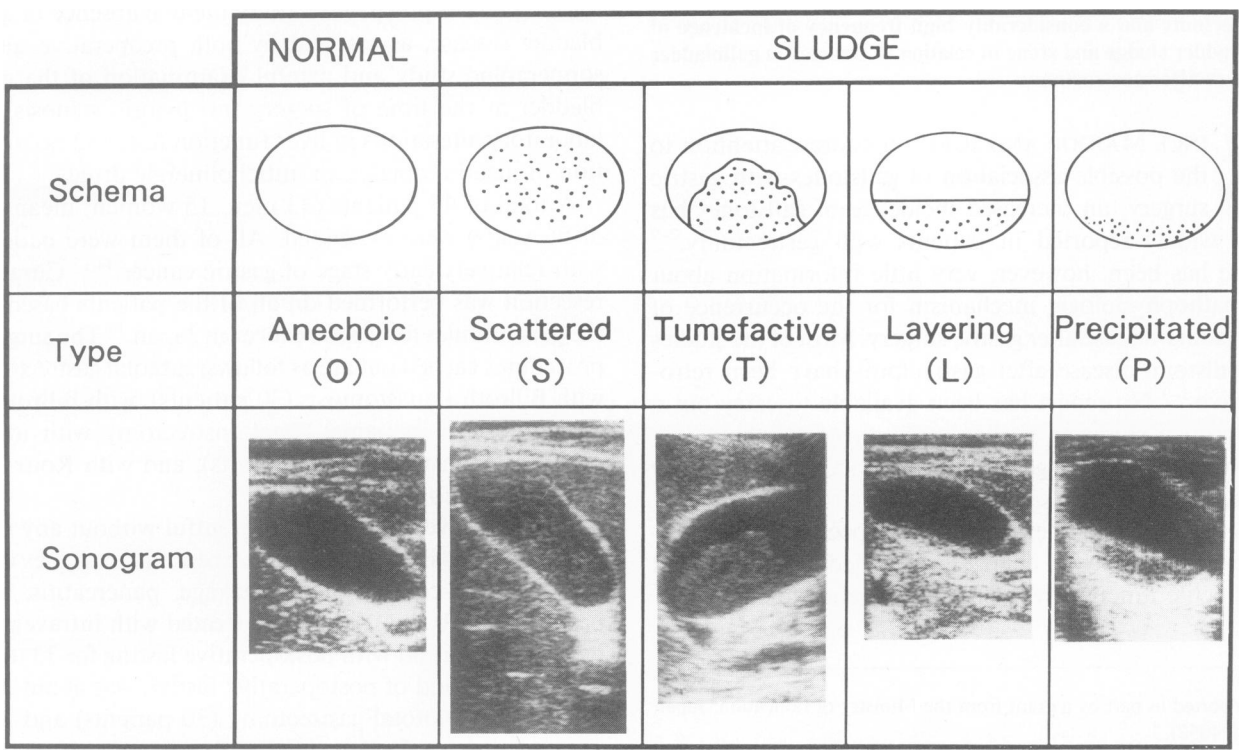

FIG. 1. Ultrasonographic classification of gallbladder sludge observed after gastrectomy.

gery. In each study, changes of gallbladder areas in response to cerulein were observed for 120 minutes at 10-minute intervals for the first 60 minutes and at 20-minute intervals thereafter. Gallbladder areas were measured by planimeter from photographs and expressed as percentages of the original resting areas. Each value was expressed as mean ± standard error of the mean (SEM). Student's t test was used to analyze the data obtained from the study on gallbladder contractile function for statistical difference. Values of $p < 0.05$ were considered significant. In-

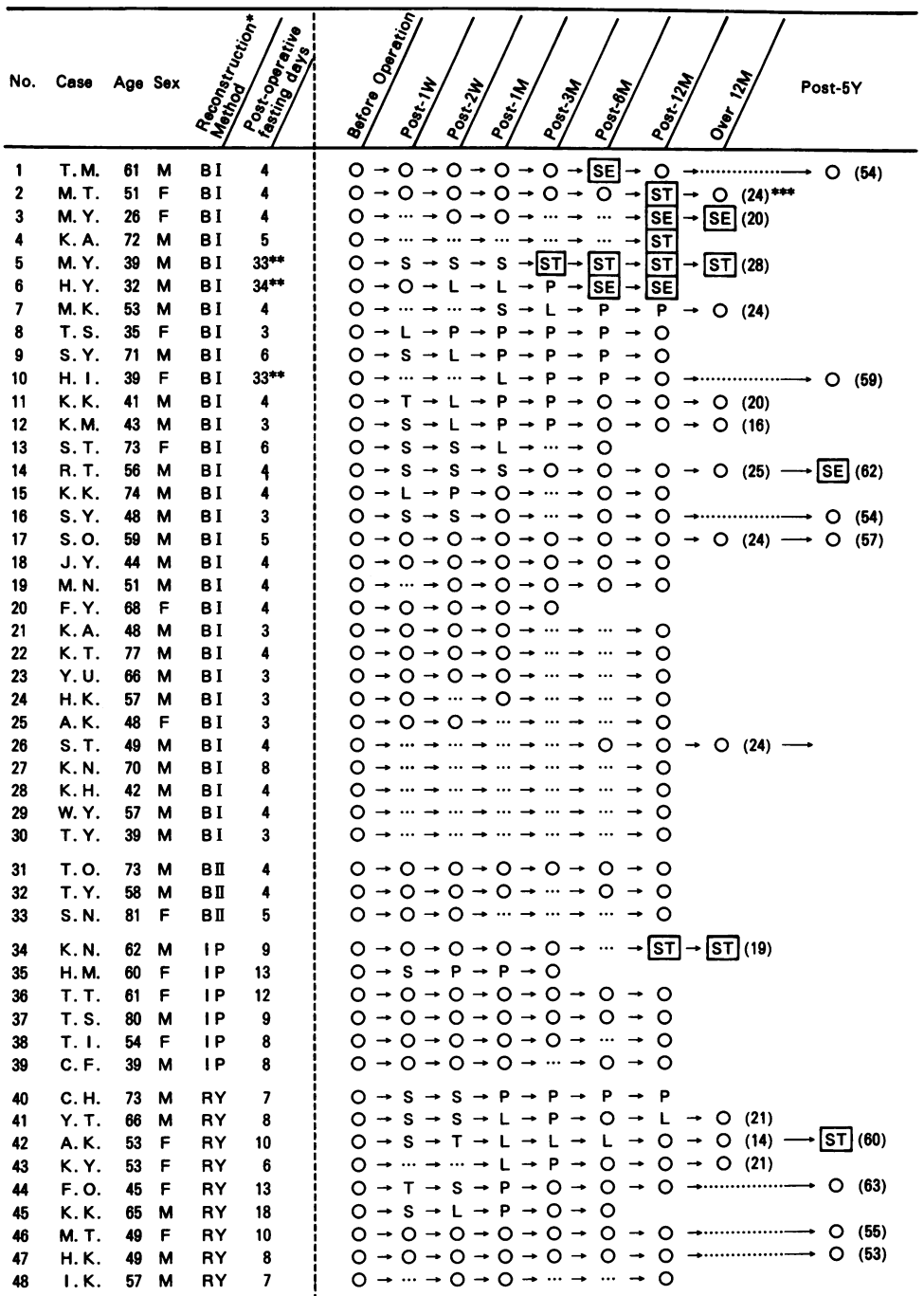

FIG. 2. Serial changes in types of gallbladder sludge and stone in each of 48 patients with gastric cancer after gastrectomy.

* BI; Subtotal Gastrectomy With Billroth I Reconstruction
BII; Subtotal Gastrectomy With Billroth II Reconstruction
IP; Total Gastrectomy With Interposition Reconstruction
RY; Total Gastrectomy With Roux-enY Reconstruction
(W : Weeks, M : Months, Y : Years)
** With Intravenous Hyperalimentation
*** ( ); Post-Operative Months

TABLE 1. *Frequency of Sludge and Stone Formation in the Gallbladder After Gastrectomy*

	Post-1 wk (n = 36)	Post-2 wk (n = 38)	Post-1 mo (n = 40)	Post-3 mo (n = 29)	Post-6 mo (n = 31)	Post-12 mo (n = 44)	Post-60 mo (n = 9)
Sludge	42% (n = 15)	42% (n = 16)	43% (n = 17)	38% (n = 11)	19% (n = 6)	7% (n = 3)	0% (n = 0)
Stone	0% (n = 0)	0% (n = 0)	0% (n = 1)	3% (n = 1)	10% (n = 3)	14% (n = 6)	22% (n = 2)

formed consent was obtained from each patient. All investigations were carried out in accordance with the World Medical Association Declaration of Helsinki, adopted in 1964 and amended in 1975, 1983, and 1989.

Results

Sludge Formation in the Gallbladder

Gallbladder sludge formation was frequently induced in the very early postoperative period after gastrectomy (Fig. 2, Table 1). The frequencies of gallbladder sludge formation 1 month after gastrectomy were 100% in subtotal gastrectomized patients with intravenous hyperalimentation (3/3), 47% in patients with total gastrectomy (7/15), and 38% in patients with subtotal gastrectomy (7/22) (Fig. 2). Sludge positivity thereafter was gradually decreased to 19% at 6 months and prominently decreased to only 7% at 12 months (Fig. 2, Table 2). Furthermore, two of the 3 patients who were sludge positive at 12 months after gastrectomy were later found to be sludge negative at 21 months (case 41, Fig. 2) and at 24 months (case 7, Fig. 2), respectively.

Regarding the type of gallbladder sludges, the most frequent pattern of changes during the follow-up course is as follows; scattered type (S) → layering type (L) → precipitated type (P) → anechoic type (O) (Fig. 1, Fig. 2, Table 2). Patients with colon cancer showed no development of sludges at any observation period after colonic surgery.

Stone Formation in the Gallbladder

Gallstone formation was observed in nine of 48 patients with gastrectomy (18.8%) during the follow-up period of approximately 5 years. In four cases with development of gallstone (cases 1, 2, 3, and 34), no presence of sludge has been found until the formation of the stone (Fig. 2). In cases 14 and 42, although gallbladder sludge had been induced once after gastrectomy, sludge had completely disappeared within 3 months and 12 months, respectively. Gallstone formation occurred, however, 5 years after gastrectomy. In cases 1 and 2, spontaneous disappearance of gallstone was observed at 12 months and 24 months, respectively (Fig. 2). In two gastrectomized patients with intravenous hyperalimentation, changes of gallbladder sludge to the strong echo were demonstrated at 3 months (case 5) and 6 months (case 6), respectively, indicating the direct evolvement of the sludge into the stone (Fig. 3). The echotomograms of gallstones induced in another seven cases after gastrectomy are represented also in Figure 4. Of 9 cases with gallstone, a single stone was found in six cases, whereas multiple stones were found in three cases, smaller than 9 mm in all cases. All of the patients with either gallbladder sludge formation or gallstone formation were asymptomatic, and no alterations of the gallbladder wall suggestive of cholecystitis were seen.

One patient (case 4) required cholecystectomy on the 13th month after gastrectomy because of multiple stones. Cholecystectomy showed that there were five pigment stones 3 to 9 mm in diameter in the gallbladder of this

TABLE 2. *Serial Changes in Types of Gallbladder Sludge and Stone After Gastrectomy*

	Post-1 wk	Post-2 wk	Post-1 mo	Post-3 mo	Post-6 mo	Post-12 mo	Post-60 mo
Sludge							
S	11	7	3	0	0	0	0
T	2	1	0	0	0	0	0
L	2	5	6	2	1	1	0
P	0	3	8	9	5	2	0
Stone							
SE	—	—	—	—	2	2	1
ST	—	—	—	1	1	4	1

Each value represents the number of patients with either ultrasonographic sludge or strong echo.

S, scattered type; T, tumefactive type; L, layering type; P, precipitated type; SE, strong echo without acoustic shadow; ST, strong echo with acoustic shadow.

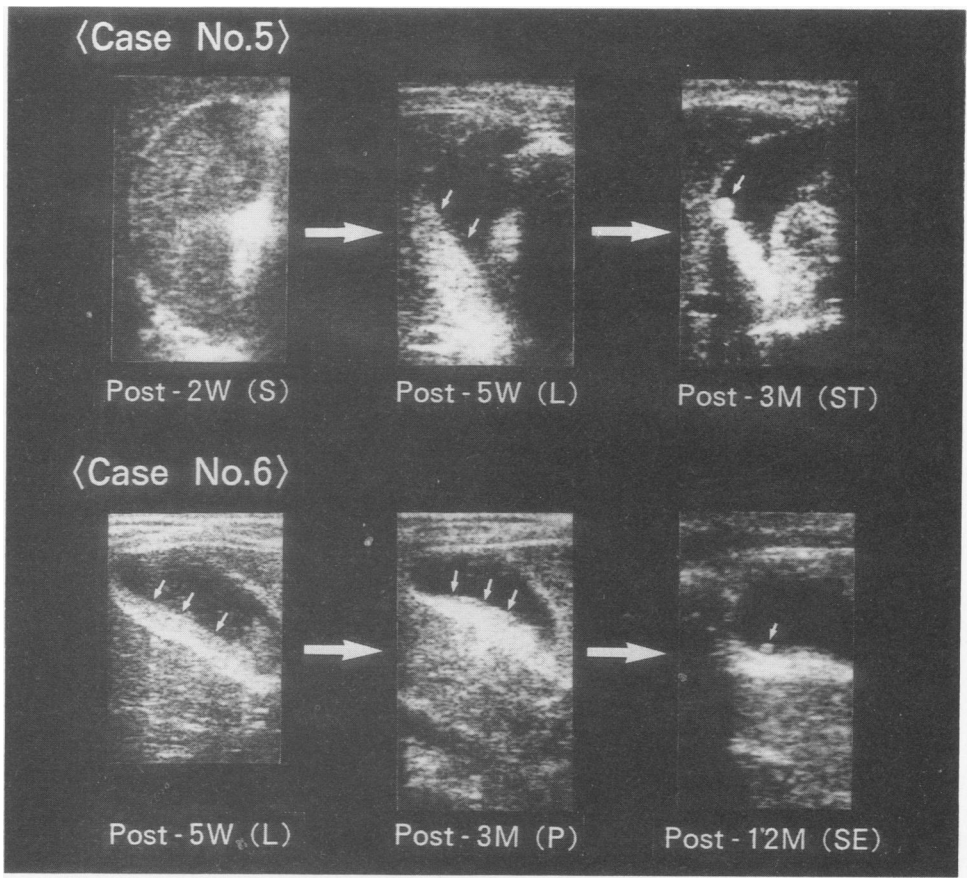

FIG. 3. Ultrasonographic observation on time course of evolvement of gallbladder sludge into the stone in gastrectomized patients with intravenous hyperalimentation. SE, strong echo without acoustic shadow; ST, strong echo with acoustic shadow; W, week; M, month.

patient. No formation of gallstone has been observed in patients with colonic surgery.

Changes in the Resting Gallbladder Area

The resting gallbladder area (Fig. 5) was significantly enlarged to 154% ± 9% of the original area (pregastrectomy) 1 week after gastrectomy, remaining significantly enlarged up to 12 months after gastrectomy. This dilatation of gallbladder, however, returned to pregastrectomy levels 60 months after gastrectomy. No significant changes in the resting gallbladder area were induced by colonic surgery.

Changes in Gallbladder Contractile Function

Gallbladder contractile function was significantly suppressed 1 month after gastrectomy, showing the decreased maximal gallbladder contraction rate of 55.2% ± 5.8% at 30 minutes (calculated as the percentage of that observed before gastrectomy) after cerulein stimulation. Although this significant suppression of gallbladder contractile function has lasted for 6 months after gastrectomy, the contractile function showed a gradual recovery thereafter, attaining the maximal gallbladder contraction rate of 91.7% ± 7.4% at 12 months (Fig. 6). Gallbladder contractile function in patients with colon cancer showed no significant changes at any observation period after colonic surgery compared with that before operation.

Discussion

The present prospective study first provides evidence for the relationship between gastrectomy and a considerably high frequency of incidence of gallbladder sludge and stone, with simultaneous serial observation on changes in gallbladder contractile function. Since the widespread use of the ultrasonography in the assessment of the biliary tract, the presence of sludge in the gallbladder has been observed frequently.[10–12] The relationship between prolonged total parenteral nutrition and gallbladder sludge formation has been reported, suggesting that bowel rest and bile stasis during parenteral nutrition lead to production of sludge.[13] Bolondi et al[14] have observed gallbladder sludge formation during prolonged fasting after gastrointestinal surgery, indicating that the formation of gallbladder sludge was induced in 15% of patients with postoperative fasting for 7 days and in 32% of patients with postoperative fasting for 10 days, respectively, after gastrointestinal surgery.

The present serial and prospective study with postoperative fasting for 3 to 5 days for subtotal gastrectomy

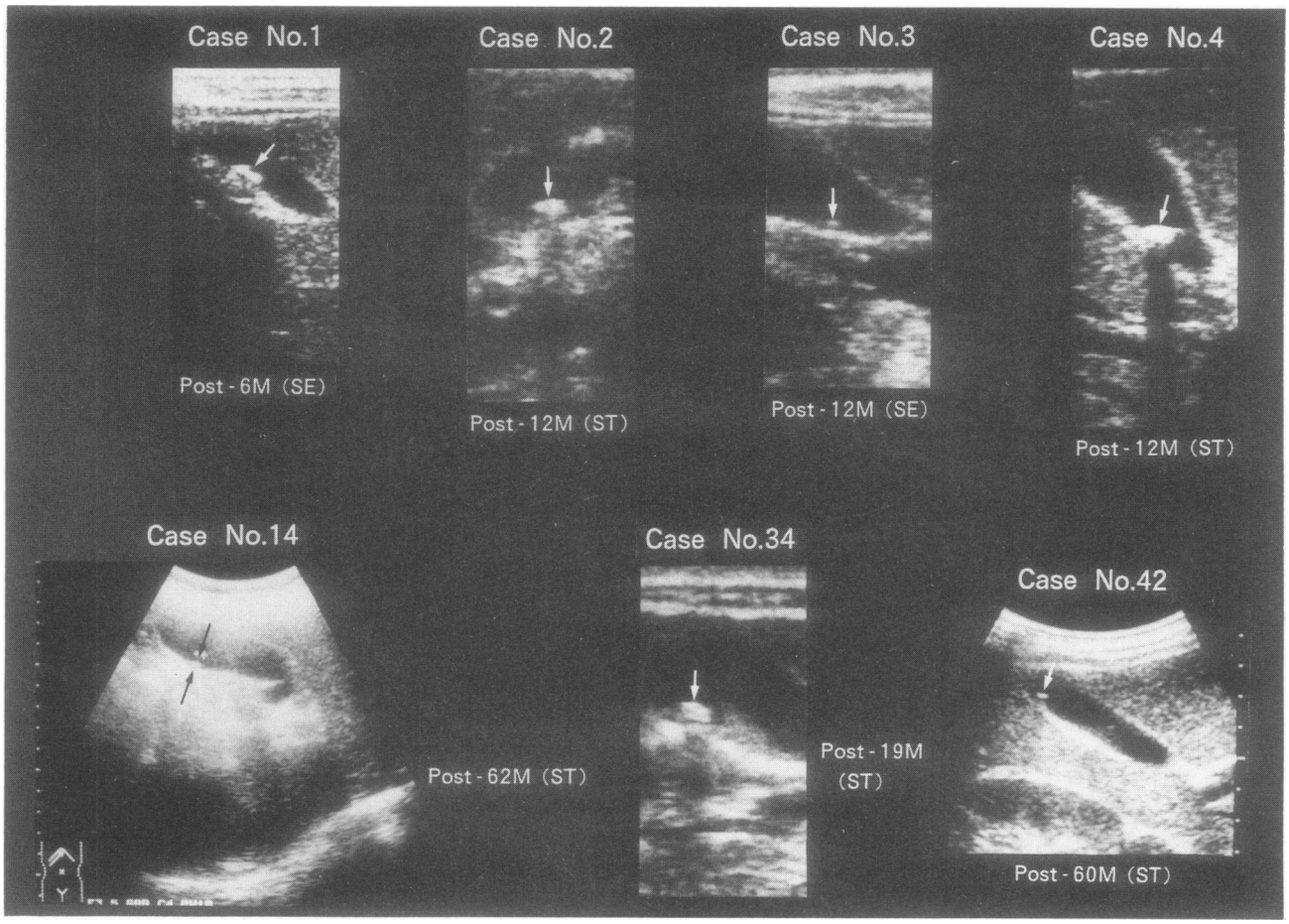

FIG. 4. Ultrasonographic observation of gallstones induced after gastrectomy. SE, strong echo without acoustic shadow; ST, strong echo with acoustic shadow; W, week; M, month.

and for 8 to 13 days for total gastrectomy demonstrated a high frequency of gallbladder sludge formation of 38% in patients with subtotal gastrectomy and of 47% in patients with total gastrectomy, respectively, with corresponding significant lowering of the gallbladder contractile function (Fig. 6).

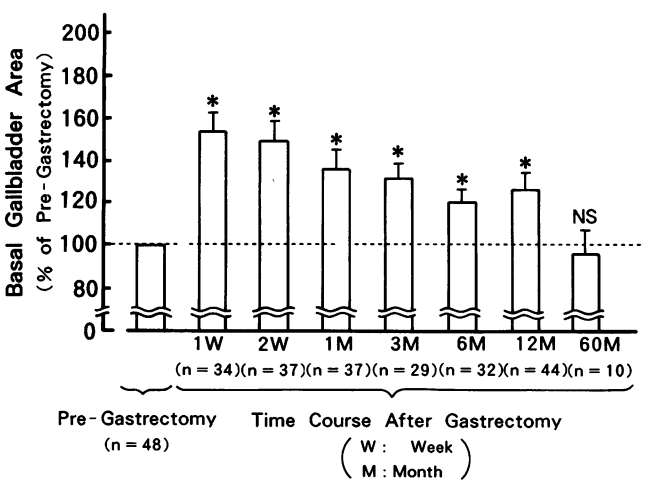

FIG. 5. Serial changes in the basal (resting) gallbladder area after gastrectomy. *$p < 0.05$.

The time course of the gradual disappearance of the gallbladder sludge (Fig. 2, Table 1) was closely related to that of the gradual recovery of gallbladder contractile function (Fig. 6), suggesting that the gradual disappearance of gallbladder sludges could be, at least partly, attributed to the corresponding recovery of the gallbladder contractile function after gastrectomy.

The present study also demonstrated that gallbladder sludges observed after gastrectomy showed an unique pattern of changes during the follow-up course: scattered type → layering type → precipitated type (Fig. 1, Fig. 2, Table 2). Most of these gallbladder sludges, however, disappeared within 12 months after gastrectomy, except two cases with intravenous hyperalimentation in which evolvement of gallbladder sludge into the stone was observed (Fig. 3). It has been clarified that patients who receive long-term total parenteral nutrition are at increased risk for the development of cholelithiasis.[13,20] Messing et al.[13] observed the prevalence of gallbladder sludge for-

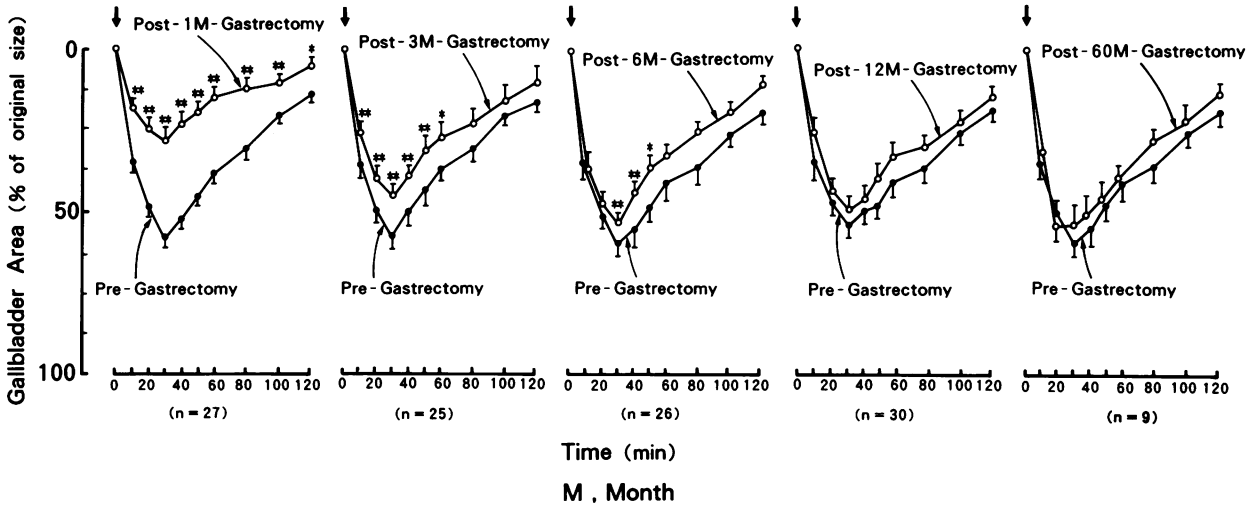

FIG. 6. Time course of changes in the gallbladder contractile function in response to cerulein (0.2 μg/kg intramuscularly) after gastrectomy. M, month. *$p < 0.05$; **$p < 0.01$.

mation during total parenteral nutrition and further found that gallstone formation was induced in sludge-forming patients, but not in patients who were sludge negative. Their observation is consistent with above-mentioned two gastrectomized cases with intravenous hyperalimentation in our study (Fig. 3). On the contrary, all of the other patients who developed gallbladder sludges in our study did not show any evolvement of gallbladder sludge into gallstone, but showed complete disappearance of gallbladder sludges during the follow-up course after gastrectomy. Thus, the present study first demonstrated that development of gallstone was induced mostly in patients who had shown no formation of gallbladder sludges and slightly in patients who were sludge negative, but had been sludge positive before, suggesting that development of gallstone observed after gastrectomy has very little to do with formation of gallbladder sludges. This phenomenon leads us to presume that the pathophysiology of gallstone formation after gastrectomy could be, to some extent, different from that observed during total parenteral nutrition, which is capable of evolving gallbladder sludge into gallstone.[13]

Observations on the function as well as on the volume of the gallbladder after gastric surgery have been controversial.[2,21-24] The present study first performed consecutive and prospective observation on these subjects. A possible explanation for a dilatation of the gallbladder after gastrectomy could be sectioning of the hepatic branch of the vagus nerve,[2,7,8,9,21,22] which plays an important role in regulating the tonicity of the gallbladder.[25] In our study, to perform curative resection, lymph nodes of both the first and second group[15,16] were removed so that the anterior hepatic branch of the vagus nerve was inevitably dissected in each patient. No dilatation of the gallbladder was observed during the follow-up course after colonic surgery, leading us to realize the importance of the hepatic branch of the vagus nerve for retaining the tonicity of the gallbladder.

With regard to the humoral factor that affects gallbladder contractile function, CCK is supposed to play a physiologically important role in the modulation of gallbladder contraction.[17-19] We cannot deny a possibility that significant dilatation of the gallbladder, which was observed even 12 months after gastrectomy, might cause bile stasis, leading to the formation of gallstones. It may be, however, more likely that changes in the release of CCK, followed by changes in the gallbladder kinetics, in response to the physiologic endogenous stimulation, could be deeply involved in the incidence of gallstones after gastrectomy.[1-9,21] In 1958, Cox et al.[2] speculated that an excessive amount of CCK is liberated after gastrectomy. This hypothesis was confirmed later by several studies[19,26] that demonstrated a significantly augmented plasma CCK response to oral ingestion of fat after gastrectomy. An augmented plasma CCK response to the ingestion of a fatty meal[19,26] could be at least partly due to the rapid gastric emptying after gastretomy.[27] Masclee et al.[28] have investigated the intestinal phase of CCK release and gallbladder emptying in patients with partial gastrectomy by precluding the effect of gastric emptying and the effect of cephalic and gastric phases of gallbladder contraction, in which CCK is not involved,[29] finding the delayed plasma CCK and gallbladder responses to intestinal fat. The impaired vagal-cholinergic stimulation of pancreatic enzyme after gastrectomy may result in reduced fat digestion, followed by subsequent and delayed plasma CCK and gallbladder responses to intestinal fat. We have observed that CCK showed a rapid and greater response to oral fatty meal 1

month after gastrectomy, but refilling of the gallbladder was induced much earlier, with corresponding earlier reduction of plasma CCK, without showing any consistent gallbladder contraction phase before gastrectomy.[19] We also have observed similar phenomena 12 months after gastrectomy (unpublished observation). The incidence of gallstones after gastrectomy may be due at least partly to the changes of endogenously released CCK, followed by the changes in gallbladder kinetics, leading to the bile stasis, which could result in eventual gallstone formation, especially when accompanied by the retrograde biliary infection or reduction of the total bile acid pool.[30] The pathophysiologic mechanism for the incidence of gallstones after gastrectomy needs further investigation.

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