

Acta Medica Okayama

Volume 52, Issue 1

1998

Article 10

FEBRUARY 1998

Gastrobiliary Dysmotility in Patients with Chronic Pancreatitis as Assessed by a Single Noninvasive Test

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Abstract

We simultaneously assessed gastric emptying and gallbladder contraction after oral administration of a liquid meal by noninvasive ultrasonography in 17 patients with chronic pancreatitis (CP) and in 17 healthy controls. Gastrointestinal (GI) transit was also assessed by a noninvasive radioopaque marker method. Exocrine pancreatic function was evaluated by analyzing pure pancreatic juice and by analyzing the autonomic nervous system by cardiovascular reflex tests. Patients with CP showed impaired gallbladder contraction at 15 min and hastened gastric emptying. The cause of the former is unclear, whereas the latter was closely related with decreased pancreatic lipase output, but not with autonomic dysfunction. GI transit time did not differ between controls and patients with CP. In conclusion, we succeeded in clearly demonstrating impaired gallbladder contraction and hastened gastric emptying in patients with CP by a single noninvasive test, ultrasonography. We also revealed for the first time that hastened gastric emptying is associated with insufficient pancreatic lipase output.

KEYWORDS: chronic pancreatitis, gastric emptying, gallbladder motility, colonic transit, lipase output

*PMID: 9548995 [PubMed - indexed for MEDLINE]

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We simultaneously assessed gastric emptying and gallbladder contraction after oral administration of a liquid meal by noninvasive ultrasonography in 17 patients with chronic pancreatitis (CP) and in 17 healthy controls. Gastrointestinal (GI) transit was also assessed by a noninvasive radioopaque marker method. Exocrine pancreatic function was evaluated by analyzing pure pancreatic juice and by analyzing the autonomic nervous system by cardiovascular reflex tests. Patients with CP showed impaired gallbladder contraction at 15 min and hastened gastric emptying. The cause of the former is unclear, whereas the latter was closely related with decreased pancreatic lipase output, but not with autonomic dysfunction. GI transit time did not differ between controls and patients with CP. In conclusion, we succeeded in clearly demonstrating impaired gallbladder contraction and hastened gastric emptying in patients with CP by a single noninvasive test, ultrasonography. We also revealed for the first time that hastened gastric emptying is associated with insufficient pancreatic lipase output.

Key words: chronic pancreatitis, gastric emptying, gallbladder motility, colonic transit, lipase output

Disordered gastric emptying (1-3) or gallbladder motility (4-6) has been reported in patients with chronic pancreatitis (CP). However, these previous studies assessed the motility of only a single organ (stomach or gallbladder). The nasogastric tube or radio-labeled meal methods employed in these studies are somewhat invasive and cumbersome. Furthermore, the results obtained and the pathogenetic mechanisms proposed to explain the results are conflicting. We, there-

fore, assessed postprandial gastric emptying and gallbladder contraction simultaneously using an abdominal ultrasonographic scan. Ultrasonography is easy, accurate and non-invasive, does not expose the subject to radiation, and permits a combined assessment of gastric emptying (7) and gallbladder motility (8). We further assessed exocrine pancreatic function, autonomic nerve function and gastrointestinal (GI) transit time of the patients in the present study to elucidate the mechanisms of disordered gastric emptying and gallbladder contraction.

Patients and Methods

We studied 17 CP patients and 17 healthy controls (Table 1) at our institute. Alcoholics were defined as having consumed more than 81 g of ethanol daily for more than 10 years. None of the CP patients had suffered weight loss or gross steatorrhea during the previous year. Patients taking such drugs as cisapride and butylscopolamine that would influence the present study were excluded. Diagnosis of CP was based on radiological findings of pancreatic calcification and/or moderate to marked irregular dilatation of the pancreatic duct on endoscopic retrograde pancreatograms equivalent to moderate or marked CP according to the Cambridge grading system (9). Before entering the present study, both controls and CP patients underwent ultrasonographic and endoscopic examinations of upper GI and colon to insure that none were suffering from organic diseases of the stomach, biliary tract or colon. None had a past history of abdominal surgery. Informed consent was obtained from all subjects.

Study design. The study was divided into three phases. First, gastric emptying and gallbladder contrac-

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Table 1 Distribution and characteristics of patients with chronic pancreatitis and healthy controls examined

	Distribution (number of patients)					Characteristics (mean $\pm$ SD)		
	Women	Men	Alc	DM	IDDM	Age (years)	Height (cm)	Weight (kg)
CP (n = 17)	3	14	13	8	2	52 $\pm$ 10	164 $\pm$ 7	59 $\pm$ 6
Controls (n = 17)	4	13	10	0	0	57 $\pm$ 8	167 $\pm$ 9	63 $\pm$ 6

Alc: Alcoholic; DM: Diabetic; IDDM: Insulin dependent diabetic; CP: Chronic pancreatitis patients. Subject characteristics were not significantly different between chronic pancreatitis patients and controls.

Table 2 Autonomic function tests and age-related normal values

Test	Unit	Age-related normal values	
		Age	Value
Electrocardiographic R-R variation at rest (150 heartbeats)	Standard deviation $\times$ 100, mean	20-29	≥ 3
		30-39	≥ 2.5
		40-59	≥ 2
		≥ 60	≥ 1.5
Immediate orthostatic heart rate response	R-R 30/R-R 15	20-39	≥ 1.07
		40-69	≥ 1.03
		≥ 70	≥ 1.00

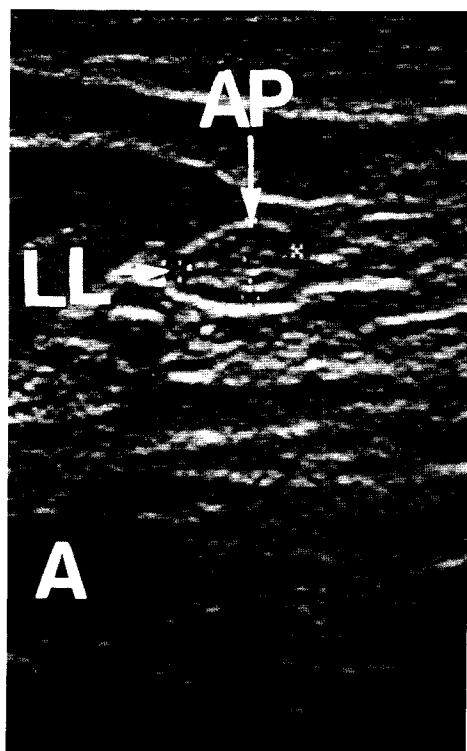


Fig. 1 Cross-sectional area of the gastric antrum in a subject visualized by a sagittal scan passing through the aorta. A: Aorta; AP: Anteroposterior diameter; LL: Laterolateral diameter.

tion were evaluated by ultrasonography after ingestion of skimmed milk. Second, GI transit time was evaluated after ingestion of radioopaque markers. Third, pancreatic exocrine function was measured by the intraductal secretin test (IDST) (10) in 8 of 17 CP patients. Each phase of the study was performed at about 2-week intervals. Studies of gastric emptying and gallbladder contraction were started at 9:00 a.m. after an overnight fast. Tests were performed with subjects in an upright sitting position, using an Aloca SSA 650 Sonolayer equipped with a 3.5-MHz linear probe. Before ingesting the test meal, anteroposterior (AP) and laterolateral (LL) gastric measurements of a single section of the stomach were done in the zone of transition between the corpus and antrum, using the superior mesenteric vein or aorta as a reference point to obtain a consistent scanning level (7) (Fig. 1). The gallbladder volume was calculated by the ellipsoid method ($V = \text{length} \times \text{width} \times \text{depth} \times 0.52$) (8) (Fig. 2). Then, the patients were asked to ingest 500 ml of skim milk (fat 9 g, protein 9.25 g, carbohydrate 28.25 g, caloric content of about 230 kcal per 500 ml, at a temperature of 37°C) within 2-3 min, using a straw (7). After baseline measurement, AP and LL dimension of the stomach and residual gallbladder volumes were measured at the end of meal ingestion and monitored every 15 min thereafter for a maximum of 210 min. Ultrasonography was performed by a impartial investigator who was unaware of the patients profile.

The value of $AP + LL/2$ was defined as gastric diameter. Gastric emptying was considered completed when the gastric diameter equaled or was less than the one computed before the ingestion (7).

Fasting blood samples were taken from cubital veins before ingesting the test meal. Blood samples were analyzed for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and creatinine. Aliquots of sera were stored at -20°C before pepsinogen I (PG I) levels were assayed by the modified method of Ichinose

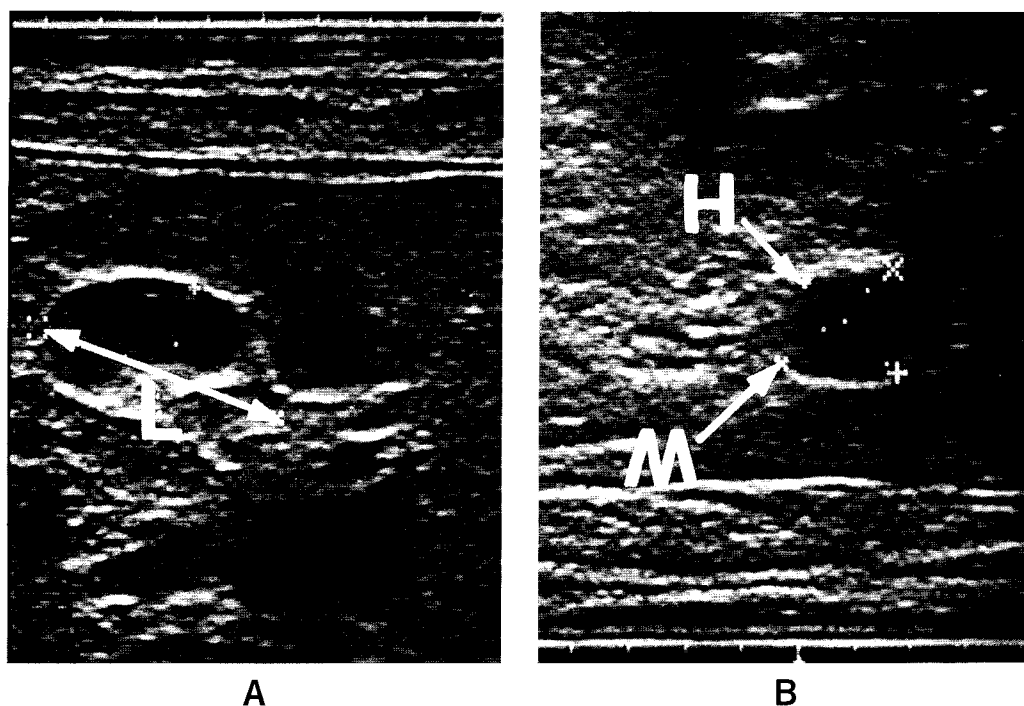


Fig. 2 Sonograms of gallbladder. **A:** Sagittal section through the central axis of the gallbladder yields measurement of length (L); **B:** Axial section through the middle of the gallbladder yields measurements of width (W) and height (H).

(11) (all assays were performed within two months of drawing the sample).

GI transit was determined by the following method as discussed in detail by Amanda *et al.* (12, 13): patients ingested 20 each of three different kinds of markers (for a total of 60 pieces ingested) at 12, 24 and 48 h, respectively, before plain abdominal radiographs were taken using a high-kilovoltage fast-film technique to reduce radiation exposure. These markers come in three shapes (rings, rods and blocks), are fashioned from radiologically distinguishable barium-impregnated polyvinylchloride and are 3 to 4 mm in length or diameter. The numbers of markers were counted by a impartial investigator who was unaware of the patient's profile. All patients were asked to maintain their usual diet avoiding alcohol for the duration of the study. Diet contents estimated by a dietician on the basis of direct questionnaire given to study subjects were not significantly different between CP patients (1780 ± 170 kcal/day) and controls (1870 ± 160 kcal).

The autonomic nervous system was assessed by two noninvasive cardiovascular reflex tests: a) electrocardiographic R-R variation at rest (from the first 150 R-R intervals, the coefficients of variation as well as the root

mean square of successive difference were computed), and b) immediate orthostatic heart rate response (the ratio between the length of the R-R intervals at beats number 30 and 15 after standing (R-R 30/R-R 15) were calculated). The results were assessed on the basis of age-related normal ranges as reported previously by Wedmann *et al.* (14) (Table 2). When at least one of the two tests was abnormal, a diagnosis of autonomic neuropathy was made.

Exocrine pancreatic function was measured as described previously (10). No anticholinergic agents or glucagon were administered because these are known to inhibit exocrine pancreatic secretion (15). After pharyngeal anesthesia with 4 % xylocaine, the main pancreatic duct was cannulated to a depth of 1.5 to 3.0 cm, utilizing an Olympus model JF-200 duodenoscope. Pure pancreatic juice was collected by manual suction at 2-min intervals for 10 min after a bolus intravenous injection of secretin (100 U of Secrepan, Eisai, Tokyo, Japan). All specimens were collected in ice-cooled tubes and analyzed as soon as the collection was completed. Amylase activity was assayed by an amylolytic method (Amylase-Test, Wako Co., Osaka, Japan) and expressed as Caraway

units. Lipase activity was assayed with a Marupi Lipase Kit (IU) (Marupi Co., Osaka, Japan) using BAL tributyrates as a substrate (10).

Statistical analysis was done with the Student's *t* test. A simple linear regression (least-squares regression) was used to summarize the relationship (regression line) between two variables and Pearson's correlation coefficient was used to determine the strength of the correlation. Values with a *P* less than 0.05 were considered significant.

Results

Serum levels of PG I were not different between the CP patients (51.2 ± 11.2 ng/ml) and the controls ($46.4 \pm$

11.4 ng/ml). Blood biochemistries showed no evidence of hepatocellular damage, cholestasis, or renal impairment.

Fasting gastric diameters were not significantly different between the CP patients (2.8 ± 0.5 cm) and the controls (2.9 ± 0.4 cm) (Table 3). Likewise, postprandial gastric diameters were not significantly different between the CP patients (8.2 ± 2.3 cm) and the controls (7.8 ± 2.4 cm) (Table 3). However, gastric emptying time was significantly shorter in the CP patients (91.4 ± 24.2 min) than in the controls (128.6 ± 23.4 min) ($P < 0.05$) (Table 3). Similar results were obtained when gastric emptying time was compared for 14 alcoholic CP patients (87.3 ± 23.5 min) and 10 alcoholic controls (133.6 ± 20.9 min) ($P < 0.05$).

Fasting gallbladder volumes were not different be-

Table 3 Gastric diameter and emptying time in CP patients and controls

	Variables (mean $\pm$ SD)		
	FGD (cm)	MGD (cm)	MGET (min)
CP patients (n = 17)	2.8 ± 0.3	8.2 ± 2.3	91.4 ± 24.2
Controls (n = 17)	2.9 ± 0.4	7.8 ± 2.4	128.6 ± 23.4

FGD: Fasting gastric diameter; MGD: Maximal gastric diameter; MGET: Mean gastric emptying time; CP: Chronic pancreatitis.

*: Significantly different from the corresponding value in controls ($P < 0.05$).

Table 4 Gallbladder volume and contraction in CP patients and controls

	Variables (mean $\pm$ SD)		
	FGV (ml)	MGRV (%)	TMRGV (min)
CP patients (n = 17)	17.3 ± 5.1	37.7 ± 17.2	43.0 ± 15.9
Controls (n = 17)	19.8 ± 7.7	25.0 ± 9.1	45.0 ± 8.0

FGV: Fasting gallbladder volume; MGRV: Minimal gallbladder volume (% of fasting volume); TMRGV: Time required to reach the minimal residual gallbladder volume; CP: Chronic pancreatitis. There was no significant difference between CP patients and controls.

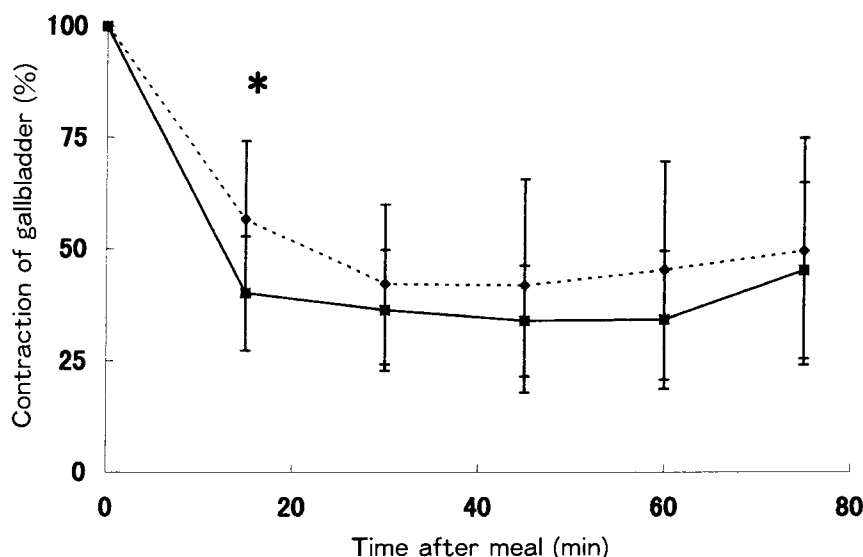


Fig. 3 Gallbladder residual volume (percent of fasting volume) in chronic pancreatitis patients (CP) and in controls following test meal stimulation.

Gallbladder residual volumes at 15 min after meal were significantly larger in the CP patients than in the controls. (*: $P < 0.05$)

—■— control; ---◆--- CP.

Table 5 Number of three types of ingested markers observed on abdominal X-ray films in CP patients and controls

	Markers ingested 48 h before X-ray	Markers ingested 24 h before X-ray	Markers ingested 12 h before X-ray
CP patients (n = 17)	4.6 ± 3.2	14.9 ± 4.7	15.2 ± 3.7
Controls (n = 17)	7.0 ± 4.8	16.2 ± 3.1	19.0 ± 1.0

CP: Chronic pancreatitis

There was no significant difference between chronic pancreatitis patients and controls. (mean ± SD)

Table 6 Relationship of autonomic nerve function to gastrointestinal and gallbladder motility in CP patients

	GET (min)	RGV (%)	CTMI2
CP patients with autonomic neuropathy (n = 5)	96.0 ± 26.6	58.5 ± 20.5	16.3 ± 5.3
CP patients without autonomic neuropathy (n = 12)	90.0 ± 10.6	53.4 ± 23.6	14.0 ± 9.5

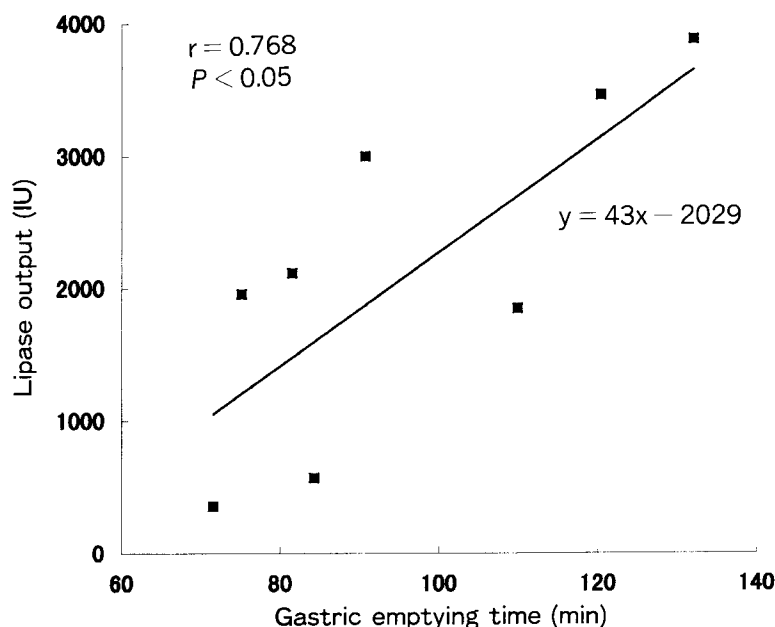
GET: Gastric emptying time; RGV: Residual gallbladder volume (% of fasting volume) at 15 min after meal; CP: Chronic pancreatitis; CTMI2: Numbers of markers ingested 12h before abdominal X-ray. There was no significant difference between CP patients with autonomic neuropathy and those without neuropathy. (mean ± SD).

tween the CP patients ($17.3 \pm 5.1 \text{ cm}^3$) and the controls ($19.8 \pm 7.7 \text{ cm}^3$) (Table 4). Gallbladder residual volumes (expressed as a percentage of the respective fasting volume) at 15 min after meal were significantly higher in the CP patients ($56.7 \pm 12.8 \%$) than in the controls ($40.0 \pm 17.4 \%$) ($P < 0.05$), as shown in Fig. 3. However, the minimal gallbladder residual volumes and the time required to reach the minimal residual gallbladder volumes were not different between the CP patients and the controls (Table 4).

The number of ingested markers observed on abdominal X-rays were not significantly different between the CP patients and the controls (Table 5).

Five of the 17 CP patients and none of the controls had autonomic neuropathy as elicited by the cardiovascular reflex tests. Gastrobiliary motility and GI transit were not related to the presence or absence of autonomic neuropathy (Table 6).

Gastric emptying time was significantly correlated with lipase output ($r = 0.768$, $P < 0.05$) (Fig. 4), but not with amylase output ($r = 0.252$, $P > 0.05$). Gallbladder contraction at 15 min tended to correlate with lipase output, but the correlation did not reach the level of statistical significance. ($r = 0.686$, $P > 0.05$). GI transit was not significantly correlated with lipase output ($r = -0.322$, $P > 0.05$).

**Fig. 4** Relationship between gastric emptying time and lipase output in chronic pancreatitis patients. The two variables exhibit a strong and statistically significant correlation.

Discussion

In the present study, we performed a combined study on the motility of the gastrointestinal tract and gallbladder in patients with CP, and obtained the following results: In CP patients, a) gastric emptying of a liquid meal was completed much faster than in healthy controls; b) gastric emptying was closely correlated with pancreatic lipase output; c) gallbladder contraction was suppressed in the early postprandial phase as compared with the controls; d) GI transit was not different between the CP patients and the controls.

The question to be raised here is whether the shorter gastric emptying time really reflects accelerated motility (3) or whether it merely reflects reduced gastric secretion (2). Our results support the former possibility. There are two reasons for this: firstly, because the gastric diameters before and after the test meal were not different between the CP patients and the controls and secondly, because serum PG I levels, which are known to be closely correlate with gastric secretions (11) were not different between the CP patients and the controls. Indeed, gastric secretion is reported by some investigators to be rather enhanced by suppression of fat-induced gastric inhibition (16–18).

The next question concerns what mechanisms are responsible for the accelerated gastric emptying. Our results reveal for the first time that the accelerated gastric emptying is most likely caused by reduced pancreatic lipase output. A previous report (3) focused on the relationship between exocrine pancreatic function and gastric emptying using supplemental desiccated porcine pancreas in patients with far-advanced CP. However, the investigators failed to demonstrate a specific relationship between lipase output and gastric emptying, although they could identify insufficient pancreatic enzyme secretion as a cause of the rapid gastric emptying. Reportedly, a deficiency in intraduodenal fatty acids suppresses antral contraction (19) and perfusion of specific lipase inhibitors into the duodenum hastens gastric emptying (20).

It is unlikely that accelerated gastric emptying is caused by CP-associated diabetic autonomic neuropathy (21) or chronic consumption of large amounts of alcohol. There are two reasons for this: firstly, no relation was found between these three variables, and secondly, chronic alcohol consumption is reported to suppress gastric emptying (22–24). It is also unlikely from the

ultrasonographic and endoscopic examinations that accelerated gastric emptying is caused by impaired receptive relaxation of the stomach secondary to blood congestion, edema, fibrosis or amyloid deposition in the gastric wall (25).

Our results in this study of gallbladder motility were different from those of Meguro *et al.* (4) and Glasbrenner *et al.* (6). We found no significant difference in fasting gallbladder volumes between the CP patients and the controls, although the above two groups found significantly larger fasting volumes in CP patients. This disparity may be due to less frequent and less severe involvement of the autonomic nervous system in the patients we studied versus those studied by Glasbrenner *et al.* (6). Alternately, it may be due to the lack of intra-pancreatic bile duct stenosis in our CP patients in contrast to those studied by Glasbrenner *et al.* (6).

Postprandial gallbladder contraction was significantly reduced in our CP patients only at the 15-min. In contrast, Meguro *et al.* (4) found significantly reduced contraction in CP patients throughout the observation period, whereas Glasbrenner *et al.* (6) found no significant difference between the CP patients and the controls. These differences are most probably related to the different fat contents of the test meals employed (0.5 g fat with 41 kcal by Meguro *et al.*, 9 g fat with 230 kcal in our study, and 12 g fat with 347 kcal by Glasbrenner *et al.*). All in all, the reduced gallbladder responsiveness in CP patients is probably so subtle that only minimal differences in the amounts of fat ingested can give rise to significant differences in contraction.

In the present study, GI transit was not different between the CP patients and the controls despite the fact that gastric emptying was more rapid in the former. This finding results most probably from compensatory retardation of intestinal transit, as documented by Johansson *et al.* (26).

In conclusion, we confirmed by a simple and non-invasive ultrasonographic method that patients with CP show reduced gallbladder responsiveness to liquid test meals as well as accelerated gastric emptying. We also revealed for the first time that the latter abnormality was associated with insufficient pancreatic lipase output.

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Received September 25, 1997; accepted October 7, 1997.