pH Dependence of Acid Secretion and Gastrin Release in Normal and Ulcer Subjects

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ABSTRACT By use of a recently described method, which estimates the rate of gastric acid secretion by measuring the rate of sodium bicarbonate infusion needed to keep intragastric pH constant, gastric acid secretion rates and changes in serum gastrin were measured in five normal subjects while gastric pH was kept at 5.5, 4.0, 3.0, or 2.5. Preliminary experiments revealed that the method did not accurately measure acid secretion at a pH lower than 2.5. Stimulation of acid secretion was produced by gastric instillation of a solution of amino acids and cornstarch. The secretion rate with the amino acid meal was highest at pH 5.5 and was 60% of that produced by a steak meal at the same pH. As the pH of the amino acid meal was decreased, there was a stepwise reduction in acid secretion so that at pH 2.5 the rate was only half as great as at pH 5.5.

The amino acid meal produced increases in serum gastrin that were also less marked than those produced by a steak meal. With amino acid stimulation, serum gastrin responses were similar at pH 5.5, 4.0, and 3.0, but no increase in gastrin could be measured when the meal was maintained at pH 2.5.

A group of six patients with duodenal ulcers was compared with seven normal subjects at pH 5.5 and 2.5. Ulcer patients released more gastrin and secreted more acid at each time period at both pH values. More important, the degree of inhibition at pH 2.5 was significantly less in ulcer patients. For example, during the 2nd h after stimulation acid secretion was inhibited by only 30% in ulcer patients compared with 70% in normal subjects. These findings suggest a defect in autoregulation of gastrin release and gastric acid secretion at low pH in ulcer patients which may play a role in pathogenesis of this disease.

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INTRODUCTION

From experiments in laboratory animals, it is known that gastric acid secretion is autoregulated and that high levels of gastric acidity reduce the rate of further acid secretion. This is accomplished in at least two ways. First, antral acidification reduces or completely inhibits antral gastrin release. In the dog, for example, gastrin release in response to an amino acid meal is inhibited when antral pH falls below 3.0 (1). Second, acid in the small intestine causes the release of enterogastrones such as secretin, which reduce the rate of further acid secretion (2).

It has not been possible in the past to study autoregulation of acid secretion in man in response to physiologic stimuli, such as a meal, since there has been no way to measure acid secretion when food is present in the stomach. Consequently, it is not known what concentrations of acid inhibit gastrin release and acid secretion, and whether or not a defect in autoregulation plays a role in the gastric hypersecretion of acid characteristic of some patients with duodenal ulcers.

Recently, a method was developed that permits measurement of acid secretion in human subjects after they ingest food (3). In the present study we have used this technique to assess the effect of gastric acid concentration on the rate of gastric acid secretion and endogenous gastrin release in response to an amino acid meal. Studies were performed in both normal subjects and in patients with duodenal ulcer disease.

METHODS

Subjects. Seven normal and six duodenal ulcer patients were studied. The latter had well-documented chronic duodenal ulcer disease; none had any recent complication

TABLE I
Patients Studied

Subject	Sex	Age	Acid output		Basal gastrin
			Basal	Peak	
		yr	*meq/h*	*meq/h*	*pg/ml*
Normal					
J. T.	M	28	0.3	37	34
R. T.	M	22	0.0	25	20
A. C.	F	40	0.2	18	48
G. L.	M	33	0.6	30	16
D. N. W.	F	30	0.0	21	44
D. N. R.	M	25	2.6	32	23
B. L.	F	42	1.5	21	28
Mean		31.4	0.74	26.3	30.4
SE		2.8	0.37	2.6	4.6
Duodenal ulcer					
L. S.	F	32	14.5	55	32
V. S.	F	54	7.2	27	65
J. D.	M	56	2.5	49	26
T. L.	M	70	3.9	52	29
T. K.	M	39	8.6	81	23
C. B.	F	28	4.0	36	34
Mean		46.5	6.78	50.0	34.0
SE		6.6	1.80	7.6	6.2

such as bleeding or perforation; none had any evidence of gastric outlet obstruction or prior gastrointestinal surgery. The patients were not taking anticholinergic drugs. The ages and sex of the normal and duodenal ulcer subjects are given in Table I. Their rates of acid secretion in the resting state and after 0.04 mg/kg histamine are also given in the table. These were measured by standard methods. Informed consent was obtained from all subjects.

Test meal. In selecting a meal for study at different pH levels, it was necessary to avoid any substance such as protein that would be digested at low pH levels. As pointed out previously (3), generation of buffer by peptic digestion would result in underestimation of the rate of acid secretion. The meal used in these studies ("amino acid meal") was composed of 10 g mixed amino acids (hydrolyzed casein + 1% DL-tryptophan, Stuart Pharmaceuticals, Wilmington, Del.), 120 g cornstarch, and sodium chloride sufficient to maintain a constant osmolality of 270 mosmol/kg in a final volume of 500 ml. Before infusion into the stomach, the pH of the meal was adjusted to either 5.5, 4.0, 3.0, or 2.5 by the addition of hydrochloric acid or sodium bicarbonate. The meal contained no fat. For comparison, a meal known to induce near maximal rates of acid secretion (3) was administered to five of the normal subjects. This meal consisted of 142 g chopped sirloin steak, 1 slice (17 g) toast, and 1 pat (4 g) margarine homogenized in a final volume of 600 ml and having an osmolality of 147 mosmol/kg and a pH of 5.5.

Measurement of acid secretion. The procedure for intragastric titration has been described previously (3). Subjects were fasted overnight. Test meals were instilled into the stomach via a nasogastric tube. Acid secretion was determined by titration with 0.3 N sodium bicarbonate to maintain the intragastric pH the same as the initial pH of the meal. The milliequivalents of bicarbonate required to keep the pH constant are equal to the milliequivalents of gastric acid secretion during a given period of time (3).

It was shown earlier that titration with alkali is an accurate method for measuring the rate of acid secretion at pH levels between 5.5 and 3.0 (3). Before undertaking tests at lower pH levels in vivo, we tested the reliability of titration with alkali at lower pH levels in vitro by methods that have been previously described in detail (3). As shown in Fig. 1, titration with sodium bicarbonate accurately measured the rate of acid addition to a test meal at pH 5.5 and 2.5. However, the rate of acid addition was overestimated when the pH was maintained at 6.0 or higher and was underestimated at pH 2.0 or lower. At pH 6.0 (and higher) titration is incomplete because of an artifact introduced by CO_2 (3). At pH 2.0 (and lower) the discrepancy is due to dilution by water. To the extent that acid is diluted rather than neutralized chemically, the method underestimates the rate of acid addition. The same artifact is present at higher pH ranges but produces a negligible discrepancy between the amount of acid added to the meal and the amount of sodium bicarbonate required to prevent a fall in pH. Thus, intragastric titration is accurate between pH 2.5 and 5.5 but not below 2.5 or above 5.5.

pH of gastric contents was measured with a Sargent pH meter (Sargent Welch Co., Skokie, Ill.) using standards of pH 1.07, 2.1, 4.0, and 7.0.

Serum gastrin. Blood samples were obtained during the basal period and then at 30-min intervals after the test meal.

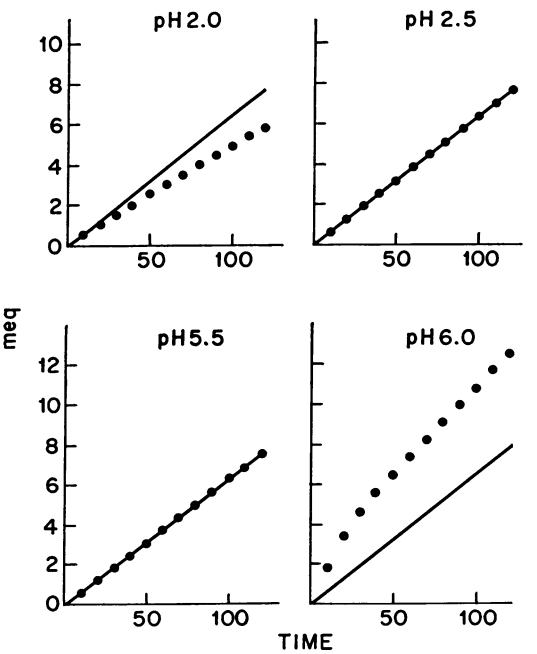

FIGURE 1 Correlation of milliequivalents of 0.1 N HCl added to a sample meal and the milliequivalents of $NaHCO_3$ required to maintain the pH at 2.0, 2.5, 5.5, and 6.0 in vitro. A fraction of the reaction mixture was discarded every 10 min to stimulate gastric emptying. The straight line represents the rate of acid addition, and the circles indicate the rate of bicarbonate addition required to maintain the pH at the indicated level.

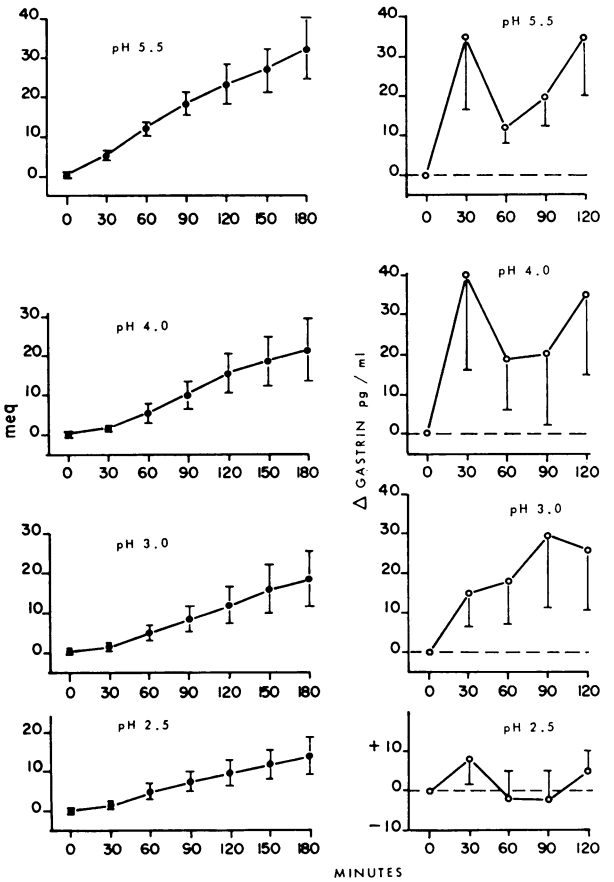

FIGURE 2 Mean changes in gastric acid secretion (closed circles) and in serum gastrin (open circles) at 30-min intervals in five subjects given an amino acid meal (see text) on 4 different days. The pH of the meal and intragastric pH were maintained at the indicated value throughout the study. Bars represent ±1 SE.

The serum was removed and stored frozen until serum gastrin was measured by radioimmunoassay (4). All samples were tested in duplicate in the same assay. Antibody 1296, rabbit antigastrin prepared by immunization with gastrin conjugated to bovine serum albumin, was used at a final dilution of 1:300,000 (5). Prior testing established that heptadecapeptide gastrin (G-17) and 34 amino acid "big gastrin" (G-34) were measured on a roughly equimolar basis in this system. The antibody was slightly more specific for G-17 than for G-34. Cross reactivity with cholecystokinin is less than 5% for antibody 1296 (5). Results were expressed as picograms per milliliter with natural human G-17-I used as standard.

Analysis of data. Significance of differences obtained in the same subjects was determined by use of the *t* test for paired values and between groups of different subjects by the *t* test for unpaired values (6).

RESULTS

Meal-stimulated acid secretion and serum gastrin in normal subjects at pH 5.5, 4.0, 3.0, and 2.5. Mean cumulative acid secretory responses for 3 h after the test meal in five normal subjects are shown in Fig. 2. Highest rates of acid secretion were observed at pH 5.5, and progressive lowering of intragastric pH was associated with lowering of acid secretion. At pH 2.5 acid secretion was only half as great as at pH 5.5. During the first 30 min at pH 4.0, 3.0, and 2.5, only minimal secretion could be detected. These data for acid secretion over the 3-h period after instillation of the meal were analyzed by use of the *t* test for paired data. Acid secretion at pH 5.5 was significantly higher than at pH 2.5 ($P < 0.05$). Secretion at 2.5 was significantly higher than basal secretion rates shown in Table I ($P < 0.05$).

Increase in serum gastrin over basal concentrations was similar at pH levels of 5.5, 4.0, and 3.0. At pH 3.0 there was no peak at 30 min, and the greatest increment in gastrin was obtained 90 min after the meal, whereas at pH 5.5 and 4.0, a definite peak was found at 30 min. Measurable increase in serum gastrin was not obtained when the meal was maintained at pH 2.5.

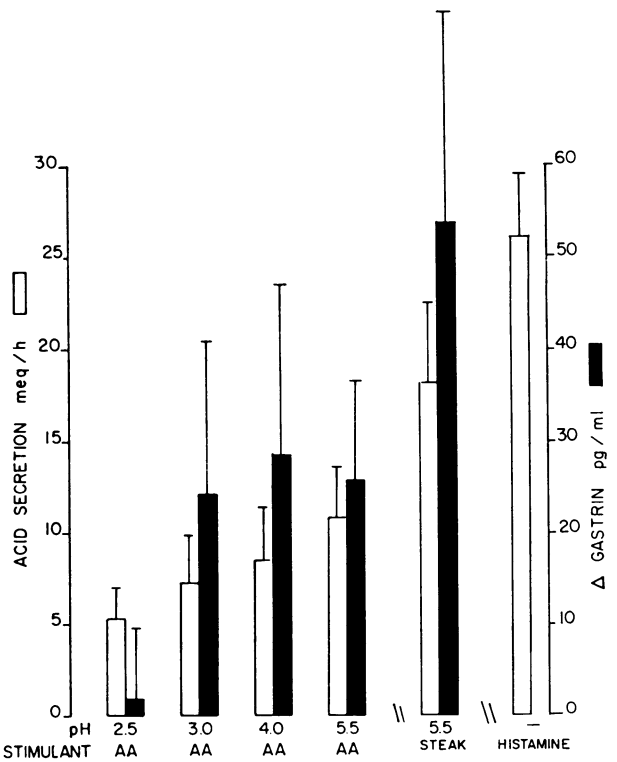

FIGURE 3 Average rate of acid secretion (mean±SE) expressed as milliequivalents per hour for the time period 30–150 min after onset of stimulation with amino acid or steak meals at the indicated pH. Maximal rate of acid secretion also is shown for stimulation with histamine. Acid results are shown as open bars. Solid bars indicate mean increment in serum gastrin (±SE) at 30, 60, 90, and 120 min compared with basal.

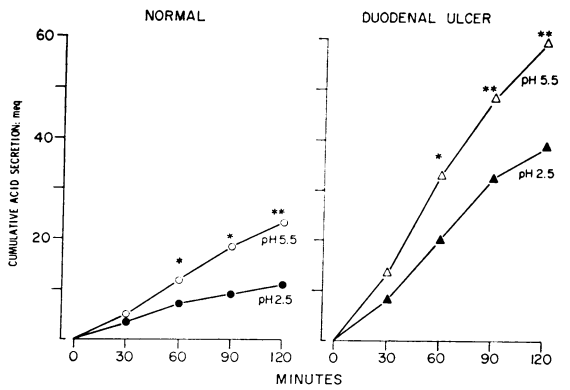

FIGURE 4 Cumulative acid secretion for 2 h after gastric instillation of amino acids and cornstarch. Seven normal subjects were studied at pH 5.5 (open circles) and 2.5 (closed circles). Six duodenal ulcer patients were studied under identical conditions (pH 5.5, open triangles; pH 2.5, closed triangles). Significance of differences in secretion rates at the two pH levels is indicated by * ($P < 0.05$) or ** ($P < 0.01$).

Acid secretion rate and changes in serum gastrin in response to the amino acid meals were compared with the responses obtained during stimulation with a steak meal at pH 5.5 (Fig. 3). In these normal subjects the acid secretion between 30 and 150 min after the steak meal averaged 70% of the peak response obtained by maximal stimulation with histamine. Compared with the steak meal at pH 5.5, secretion induced by the amino acid-cornstarch meal was 29% at pH 2.5, 40% at pH 3.0, 47% at pH 4.0, and 60% at pH 5.5.

The average increment in serum gastrin concentrations (30, 60, 90, 120 min compared with basal) was only 48% as great with the amino acid meal at pH 5.5 as with the steak meal.

Comparison of normal and ulcer subjects. The ulcer patients were older than the normal subjects and had significantly higher rates of basal acid secretion ($P < 0.01$) and peak histamine-stimulated acid secretion ($P < 0.01$) as indicated in Table I.

At both pH 5.5 and 2.5, ulcer patients secreted more acid throughout the 2-h period after instillation of the amino acid-cornstarch meal than the normal subjects (Fig. 4). In fact, the ulcer patients secreted more acid at pH 2.5 than the normal subjects secreted at pH 5.5 ($0.1 > P > 0.05$).

When rates of acid secretion were normalized by expression of the rate of meal-stimulated acid secretion as percent of maximal histamine-stimulated acid secretion rate for individual subjects, the differences between normal and ulcer subjects persisted (Fig. 5, top). For example, at pH 5.5, ulcer subjects secreted at nearly 80% of maximal histamine-stimulated rates during the second 30-min period, whereas normal subjects secreted

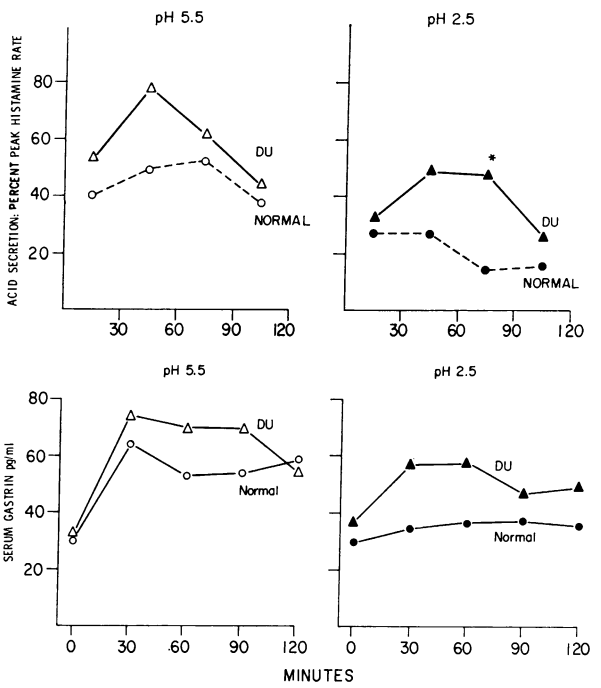

FIGURE 5 (Top) Normalized acid secretion rates expressed as percent maximal secretion rate in response to histamine. * $P < 0.05$. (Bottom) Serum gastrin concentrations in the same normal and ulcer subjects in the fasting state and at 30-min intervals after the amino acid-cornstarch meal. Comparison of pH 5.5 and 2.5.

at less than 50% of maximal. Differences in normalized secretion were more apparent at pH 2.5; normal subjects had significantly lower normalized acid secretion during the third 30-min period ($P < 0.05$).

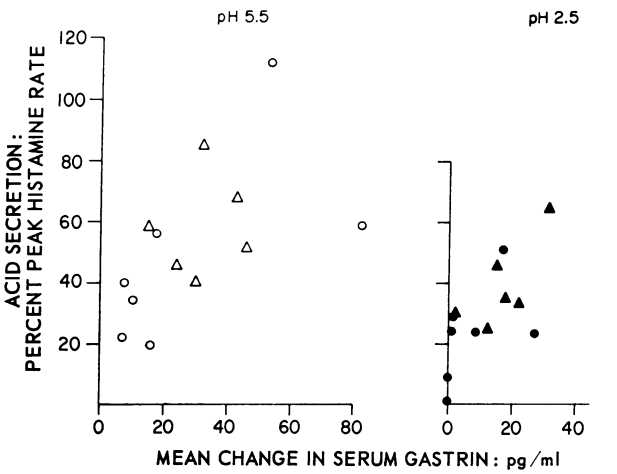

FIGURE 6 Percent of peak histamine acid secretion of 2 h plotted against mean increment in serum gastrin during the same period. (Normal subjects shown as circles, ulcer patients as triangles.) Left: pH 5.5, $r = 0.55$; Right: pH 2.5, $r = 0.64$.

Serum gastrin results at pH 5.5 and 2.5 are shown in Figs. 5 and 6. There was no significant difference in basal gastrin concentrations. Mean gastrin responses were significantly diminished in both normal and in ulcer subjects at pH 2.5 ($P < 0.05$), and responses at pH 5.5 did not differ significantly.

The ratios of response at pH 2.5 vs. 5.5 were calculated to determine the degree to which acid and gastrin responses were suppressed at lower pH. Normal and ulcer subjects' acid responses both decreased by approximately 40% during the 1st h at pH 2.5, but ulcer patients' responses were diminished only 30% during the 2nd postprandial h, compared with a 70% inhibition of acid secretion in the normals. Serum gastrin responses were suppressed by approximately 75% in normal subjects and 50% in ulcer subjects during both hours.

Differences also were found when four normal subjects (J. T., R. T., G. L., D. N. R.) and two ulcer subjects (V. S., C. B.) with similar peak rates of acid secretion (25–37 meq/h) were compared. For the 2-h period, ratios of responses at pH 2.5–5.5 were 0.42 vs. 0.71 for acid and 0.21 vs. 0.41 for gastrin. This finding suggests that differences between normal and ulcer subjects were not due simply to higher basal and maximal secretion rates in the ulcer patients.

Correlation of acid secretion and serum gastrin response. Average increment in serum gastrin over 2 h was plotted against acid secretion rates (0–2 h) in individual subjects. Acid secretion rates were normalized by expressing them as percent of maximal histamine-stimulated secretion rates. Results from normal and ulcer subjects were plotted together (Fig. 6). It was found that changes in serum gastrin were correlated significantly with acid secretion rates at both pH 5.5 ($r = 0.55$, $P = 0.05$) and 2.5 ($r = 0.64$, $P < 0.05$).

DISCUSSION

The present investigation demonstrated a defect in autoregulation of acid secretion and gastrin release in patients with chronic duodenal ulcer disease. This defect was manifest by failure to achieve normal suppression at pH 2.5, a level of acidity commonly found in the stomach of both normal subjects and patients with duodenal ulcers.

Two limitations were imposed by the meal and by the intragastric titration method. First, at pH levels lower than 2.5, the intragastric titration method under-estimates the rate of acid secretion. Therefore, acid secretion in response to food cannot be studied at higher levels of acidity by this technique. Second, at low pH, the action of pepsin on whole protein and polypeptides generates additional buffer from a protein meal. This additional buffer neutralizes acid and would produce falsely low values for acid secretion rates in vivo. Therefore, a stimulant was chosen, amino acids in a cornstarch carrier, that would not be affected by the action of pepsin. It was found that this amino acid meal produced less stimulation of acid secretion than a steak meal in normal subjects. However, amino acids produced higher relative stimulation when compared with histamine in duodenal ulcer patients than in normal subjects in the present study just as it was found for a steak meal in our previous report (3). The previous study which utilized steak as a stimulant was valid because it was performed with an intragastric pH of 5.5 at which there is no action of pepsin. Use of an amino acid meal permitted tests to be performed at pH levels as low as 2.5 without interference by pepsin action.

Effect of pH in normal subjects. Average meal-stimulated acid secretion at pH 2.5 was half the rate achieved at pH 5.5 in spite of the absence of a measurable increase in average serum gastrin concentration at low pH. There are several possible mechanisms by which a meal could stimulate acid secretion without causing a significant rise in total serum gastrin.

First, very small changes in specific serum gastrin compounds, undetectable by our assay system, may occur at pH 2.5 and be sufficient to stimulate submaximal acid secretion. It is known that gastrin circulates in multiple molecular forms (7–9). It was shown previously that some forms of gastrin are more potent than others in stimulation of acid secretion (10, 11). Small changes in serum concentration of the more potent components may have occurred after the acid meal.

Second, gastric distension may have elicited the secretory response to the acid meal without an increase in serum gastrin (12). However, it is hard to reconcile a transient distension stimulus with stimulation of acid secretion for a 3-h period. Unpublished results in our laboratory show that amino acid meals, such as the one used in the present study, are completely emptied from the stomach in 2 h.

Third, direct chemical stimulation of the acid-secreting cells may be produced by contact of amino acids with gastric mucosa in man. Such an effect recently was described in dogs by Debas and Grossman (13).

Finally, it is possible that some hormonal stimulant distinct from gastrin was released at the lower pH. This substance could be similar to the intestinal phase factor described in dogs (14).

Duodenal ulcer subjects. A major purpose of the present studies was to determine whether lowering intragastric pH from 5.5 to 2.5 inhibited acid secretion and gastrin release similarly in normal and duodenal ulcer subjects. Ulcer patients had significantly higher average rates of basal and histamine-stimulated acid secretion than normal subjects. More valid comparisons of changes in acid secretion between the two groups of subjects were sought by normalizing the acid secretory data.

By this procedure the maximal acid secretion rate for each subjects was taken as 100%, and secretion in response to amino acid stimulation could be expressed as a fraction of maximal secretion rates.

The results showed that ulcer patients maintained abnormally high rates of acid secretion at low intragastric pH. This abnormal pattern of secretion became apparent during the 2nd h after stimulation with a meal. During the third 30-min period, ulcer patients secreted at half-maximal rates when intragastric pH was 2.5, whereas normal subjects secreted at less than one-fifth maximal rates (Fig. 5, top). When the data were expressed as percent inhibition, acid secretion was suppressed approximately 40% in both ulcer and normal subjects during the 1st h. From 60 to 120 min after the meal, normal subjects showed 70% suppression at pH 2.5, although ulcer subjects were suppressed only 30%.

One possible reason why acid secretion failed to decrease normally at low pH in ulcer patients is that gastrin release was not suppressed normally. Indeed, acid suppression of gastrin was significantly less in ulcer patients during the 2nd postprandial h.

Evidence has been presented previously that significant amounts of gastrin can be released by food from the human duodenum in ulcer subjects after antrectomy (15). The present study did not discriminate between antral and duodenal gastrin. In normal subjects significant amounts of gastrin apparently were not released from the duodenum or antrum when antral pH was low (e.g., pH 2.5, Fig. 2). It is possible that gastrin released in the ulcer subjects at pH 2.5 originated in the duodenum rather than the antrum, but this question could not be answered in our experiments.

The tendency for ulcer patients to release more gastrin than normal subjects has been reported previously by several groups (16–18). In none of these previous studies was gastric pH maintained constant. It has been suggested that, because intragastric pH is usually lower in duodenal ulcer patients after a meal, there might be "inappropriate" release of gastrin in ulcer patients (19). Our findings support this hypothesis.

We conclude from these experiments that there is an abnormality in the autoregulation of acid secretion and serum gastrin release in patients with duodenal ulcers. This defect in acid secretion can be explained partially by abnormal resistance to suppression of gastrin release at low pH. This defect in suppression of acid secretion and gastrin release at low pH is a new observation. It could be an important factor in the pathogenesis of duodenal ulcer disease. This finding can be added to a list of factors that may contribute to pathogenesis of duodenal ulcer by increasing delivery of acid to the duodenum. Previously reported abnormalities in duodenal ulcer patients have included increased secretory capacity (20), increased release of gastrin in response to a protein meal (16–18), increased rate of gastric emptying (3), and increased sensitivity to stimulation with pentagastrin (21).

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