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Research Article

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Mean acid output in response to each dose of peptone was significantly higher in duodenal ulcer patients than in the controls. Gastrin levels in ulcer patients and controls were not significantly different. Within individual patients and controls, both G-total and G17 were significantly correlated with meal-stimulated acid output regardless of whether the absolute, basal-corrected, or distention-corrected values for acid output were examined (median *r* ranged from 0.82 to 0.94, *P* < 0.001). From the individual regression lines, the gastrin concentrations corresponding to half of the highest observed meal-stimulated acid response (D_{50m}) were calculated. Mean D_{50m} for G-total and G17 were significantly lower in duodenal ulcer patients than in controls both in [...]

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ABSTRACT We studied 25 duodenal ulcer patients and 14 age- and sex-matched normal controls to determine whether gastric acid secretion in duodenal ulcer patients is abnormally sensitive to stimulation by gastrin endogenously released in response to meals. Acid response to saline and to 0.5, 1.0, 2.0, 4.0, and 8.0% peptone infused into the stomach was measured by 30 min intragastric titration. Total serum gastrin (G-total) and serum heptadecapeptide gastrin (G17), fasting and 30 min after each test meal, were measured by specific radioimmunoassays. In 19 ulcer patients and 11 normal subjects (controls), acid response to graded doses (11, 33, 100, and 300 pmol $\text{kg}^{-1} \text{h}^{-1}$) of G17-I were also measured.

Mean acid output in response to each dose of peptone was significantly higher in duodenal ulcer patients than in the controls. Gastrin levels in ulcer patients and controls were not significantly different. Within individual patients and controls, both G-total and G17 were significantly correlated with meal-stimulated acid output regardless of whether the absolute, basal-corrected, or distention-corrected values for acid output were examined (median r ranged from 0.82 to 0.94, $P < 0.001$). From the individual regression lines, the gastrin concentrations corresponding to half of the highest observed meal-stimulated acid response (D_{50M}) were calculated. Mean D_{50M} for G-total and G17 were significantly lower in duodenal

ulcer patients than in controls both in the overall group and in pairs of ulcer patients and controls matched on the basis of highest observed meal-stimulated acid responses, or on the basis of maximal acid output in response to synthetic human G17. The dose of exogenously administered G17 required for half maximal G17 acid response mean D_{50G} , was significantly less in patients than in control subjects. In both ulcer and control subjects, D_{50G} correlated significantly with D_{50M} . This and the significant correlation between meal-stimulated G17 and acid response strongly suggest that the endogenously released gastrin was responsible for most, if not all, of the postpeptone acid output.

We conclude that after peptone test meals, gastric acid secretion in duodenal ulcer patients was abnormally sensitive to stimulation by endogenously released gastrin.

INTRODUCTION

Studies with graded doses of pentagastrin (1) and heptadecapeptide gastrin (G17)¹ (2) given by intravenous infusion to duodenal ulcer patients and normal subjects showed that the dose of gastrin required to produce half maximal gastric acid secretory response (D_{50}) was significantly lower in duodenal ulcer patients than in normal subjects. This indicates that duodenal ulcer patients as a group are more sensitive than normal to stimulation by exogenous gastrins. The purpose of this study was to determine whether gastric acid secretion in duodenal ulcer patients is abnormally

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¹Abbreviations used in this paper: D_{50G} , dose of gastrin required to produce half maximal gastric acid secretory response; D_{50M} , gastrin concentration corresponding to half maximal meal-stimulated acid response; G17, heptadecapeptide gastrin; G-total, total serum gastrin.

sensitive to stimulation by gastrin endogenously released in response to protein meals.

Once the measurement of postprandial acid secretion in human subjects became possible by the method of intragastric titration (3), attempts were made to correlate acid secretion with postprandial serum gastrin concentrations, but no correlations were found (3, 4). This, however, is not unexpected, as these studies were based on the acid and gastrin responses to a single level of stimulation by a standard meal in different individuals. Because it is likely that given serum concentrations of endogenous gastrin will not produce similar rates of acid output in all subjects, a correlation between acid secretion and gastrin release might not be found between individuals even if such a correlation were present within individuals. In accordance with this, a significant correlation ($r = 0.97$) between gastric acid secretion and serum gastrin was observed when responses to various intragastric stimuli of different potencies were measured in a group of normal subjects (4). This suggests that if one gives graded doses of a single intragastric stimulus, a correlation between acid and gastrin responses can be expected within individuals.

Feldman et al. (5) measured acid secretion and serum G17 concentrations (using a specific radioimmunoassay) in response to an intragastric amino acid meal and to graded doses of G17 given by intravenous infusion. They found that the rise in plasma G17 concentration in response to the intragastric amino acids could have produced all of the observed acid secretion, suggesting that G17 is the major physiologic stimulant in response to a meal. We therefore compared the sensitivity of duodenal ulcer patients and normal subjects to endogenous gastrin by studying the responses of gastric acid secretion and serum gastrin, including G17, with increasing doses of intragastric peptone.

METHODS

Subjects. The study group consisted of 25 male patients with duodenal ulcer (mean age 51 yr, range: 23–69 yr) and 14 male control subjects (mean age 46 yr, range: 29–60 yr). All patients had documentation of their ulcers by upper gastrointestinal series and/or upper gastrointestinal endoscopy. They all fulfilled the following criteria: (a) no radiological or endoscopic evidence of concomitant gastric ulcer; (b) no clinical, radiological, or endoscopic evidence of pyloric stenosis; (c) no gastrointestinal bleeding within 4 wk before the study; (d) no previous gastric surgery; and (e) no other significant medical diseases. Control subjects had no symptoms suggestive of peptic ulcer disease, no previous gastric surgery, and no significant medical diseases. No subject had taken any drug within 72 h of secretory testing.

Measurement of acid secretion in response to peptone. After a 12-h fast, a radiopaque nasogastric tube that had a polyethylene tube attached to it (AN 10, H. W. Anderson Products, Inc., New York) was fluoroscopically positioned

with the tip in the midgastric antrum. Basal gastric secretion was aspirated by continuous suction at 7–12 mm Hg negative pressure with a vacuum pump. Residual juice was collected for 15 min and discarded, and then basal secretion was collected for two 15-min periods. To maintain patency the tube was manually flushed with 10–20 ml of air and aspirated by hand at 5-min intervals. The basal acid concentration was determined by titration of 0.2 ml of juice with 0.2 M NaOH to pH 7.0 on an automatic titrator (Radiometer Co., Copenhagen, Denmark). A previous validation study in this laboratory on 25 other subjects indicated that basal secretion during the first 30 min did not differ significantly from basal secretion during the second 30 min (1). Liquid test meals, 500 ml each, containing peptone (Bacto-Peptone, Difco Laboratories, Detroit, Mich.) at the following concentrations, 0 (0.15 M NaCl), 0.5, 1.0, 2.0, 4.0, and 8.0% (wt/vol), were adjusted to the same osmolality (320 mosmol kg^{-1}) and pH 7.0 by the addition of NaCl and 4 N HCl, respectively. Each meal was instilled in the stomach through the nasogastric tube by gravity over 2 min. After each meal, gastric acid secretion was measured for 30 min by intragastric titration (3). Briefly, this involved continually mixing the gastric contents past a combined pH and reference electrode (Radiometer Co.) by removing and reinserting 30-ml portions of gastric contents seven times per minute with an automatic syringe (BBL Microbiology Systems, Becton, Dickinson & Co., Cockeysville, Md.). Intragastric pH was maintained at 7.0 with the automatic titrator, which instilled 0.5 M NaOH from an automatic burette through the polyethylene tube. The number of millimoles of HCl secreted was assumed to be equal to the millimoles of NaOH necessary to maintain intragastric pH at 7.0. After 30 min, the gastric contents were completely aspirated, the stomach was washed with 100 ml of 0.15 M NaCl, and the next meal was instilled in increasing order of concentration as listed above.

Preliminary studies

Maximal peptone dose. To determine the dose of peptone that would produce a maximal acid response, dose-response studies from 0 to 16% were done in two ulcer patients. The secretory response was less with the 16% peptone test meal than with the 8% meal; 11.3 ± 1.6 and 14.5 ± 1.7 mmol 30 min^{-1} , respectively. This was thought to be the result of the higher osmolality (632 mosmol kg^{-1}) of the 16% dose. Dose-response tests with the additional 16% dose were also performed on four additional subjects, two ulcer patients and two controls, with the osmolality of all the other peptone meals adjusted to 320 mosmol kg^{-1} . The results indicated that the acid response reached a plateau in all four subjects with 8% peptone; mean acid output being 9.0 ± 2.7 and 8.2 ± 2.0 mmol 30 min^{-1} for 8 and 16% peptone, respectively. Because of these and the following findings with 10% peptone (see below), it was decided that the highest dose of peptone to be used would be 8% and that all meals would be adjusted to the osmolality of 8% peptone, 320 mosmol kg^{-1} .

30 vs. 45 min intragastric titration and additional 10% dose. In four subjects, two duodenal ulcer and two control, the test was repeated on 2 separate d in random order. On one day, the test proceeded as usual but an additional, higher dose of peptone (10%) was given. The osmolality of all meals was adjusted to that of 10% peptone, 395 mosmol kg^{-1} . On another day, in addition to the higher dose, intragastric titration was extended to 45 min instead of 30 min. It was observed that the 15–30- and 30–45-min acid outputs in response to each dose of peptone did not differ significantly

from each other, and that the cumulative acid output to all doses of peptone using these two intervals was also similar (20.8 ± 4.2 and 18.8 ± 4.0 mmol 105 min^{-1} , respectively). Furthermore, increasing the peptone dose to 10% did not cause a significant increase in acid output over the 8% dose (13.1 ± 2.0 and 13.3 ± 2.2 mmol 30 min^{-1} , respectively).

Single-day vs. multiple-day tests. In two subjects, one duodenal ulcer patient and one control, the acid secretory responses did not differ significantly whether the test meals were given sequentially on a single day or individually in random order on 6 separate d. The correlation coefficient of the pairs of results in the two subjects was 0.96 and the mean variation of individual results was 10.3%.

G17 maximal acid output. On a separate day, maximal acid output in response to intravenous infusion over 30 min by a syringe infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.) of 300 pmol $\text{kg}^{-1} \text{ h}^{-1}$ G17 (synthetic human G17-I, Imperial Chemical Industries, Inc., Los Angeles, Calif.) was measured in 23 of the 25 duodenal ulcer patients and 13 of the 14 controls, using conventional methods (gastric aspiration and in vitro titration) (6). Earlier dose-response studies from this laboratory (2) showed that this dose of G17 produced maximal acid output both in normal subjects and in duodenal ulcer patients. Furthermore, dose-response studies in three normal subjects and three duodenal ulcer patients indicated that the maximal acid output achieved by 300 pmol $\text{kg}^{-1} \text{ h}^{-1}$ G17 and by 7.8 nmol ($6 \mu\text{g}$) $\text{kg}^{-1} \text{ h}^{-1}$ pentagastrin did not differ significantly.

G17 dose-response study. On another day, after collection of 30 min basal secretion as described above, acid output in response to intravenous infusion of 11, 33, 100, and 300 pmol $\text{kg}^{-1} \text{ h}^{-1}$ G17 (see above) was measured for 30 min after each dose in 19 of the 25 duodenal ulcer patients and 11 of the 14 controls. The doses of G17 were given sequentially in the order listed, and each dose was given for 30 min by a syringe infusion pump. The method and validation of the test have been previously described in detail (1, 2). It was established that the acid secretory responses did not differ significantly whether the doses of G17 were given sequentially on a single day or individually in random order on 4 separate d.

Gastrin estimation. During the peptone-meal study, blood for gastrin determination was drawn with an indwelling venous catheter before the first meal and 30 min after the instillation of each test meal, and was kept at 4°C . At the end of the test, the sera were immediately separated by centrifugation and stored at -20°C for subsequent radioimmunoassay.

Serum total carboxy-terminal immunoreactive gastrin (G-total). This was measured by radioimmunoassay. All samples were tested in duplicate. Antibody 1296, a rabbit antigastrin prepared by immunization with G17 conjugated to bovine serum albumin, was used at a final dilution of 1:300,000 (7). With this antiserum, human G17 and human big gastrin were measured on a nearly equimolar basis. Cross-reactivity with porcine cholecystokinin was $<5\%$ (8).

Serum immunoreactive G17. Serum G17 concentration was measured using L6, an antibody that has almost absolute specificity for G17 I and II. The characteristics of this antibody have been recently described in detail (9). Samples were run in duplicate at 1:10 dilution and read against a standard curve of G17 diluted in 10% gastrin-free serum prepared by charcoal extraction.

Statistical methods. Linear regression by least-squares and *t* tests, paired and unpaired as appropriate, were used (10). In calculation of D_{50} for serum gastrin vs. acid, we expressed our results using the more simple linear model, as we did not find a better fit with logarithmic transformation of the gastrin variable. For the D_{50} of G17 dose-response studies, linear regression analysis was performed according to the

following equation, which gave D_{50} as the negative slope: response = calculated maximal response - D_{50} (response/dose). In calculation of D_{50} where correction for basal effects were required, the following formula (11) was used: $D_c = D_b [1 - (B/M)]$, where D_c = corrected D_{50} , D_b = basal-subtracted D_{50} , B = basal rate of acid secretion, and M = maximal rate of acid secretion observed. Values are expressed as mean \pm SEM. *P* values of <0.05 are considered significant.

RESULTS

Gastric acid secretion

Basal and in response to peptone. The mean basal acid output and stimulated acid output after the peptone test meals was significantly greater in the duodenal ulcer patients than in the controls with all doses of peptone but not with saline alone. The mean acid output following saline alone was significantly higher ($P < 0.005$) than the mean basal acid output for both normal (3.5 ± 0.5 and 2.2 ± 0.5 mmol 30 min^{-1} , respectively) and ulcer (4.8 ± 0.7 and 3.5 ± 0.5 mmol 30 min^{-1} , respectively) subjects. The mean cumulative acid output of duodenal ulcer patients (61.2 ± 4.9 mmol 180 min^{-1}) was significantly greater ($P < 0.001$) than that of the controls (41.4 ± 5.7 mmol 180 min^{-1}).

When the individual stimulated acid outputs were corrected by subtracting basal acid output, mean gastric acid responses remained significantly greater in the ulcer patients than in the controls in response to 0.5, 2.0, and 4.0% peptone meals. The mean basal-corrected cumulative acid output in response to all doses of peptone was significantly higher ($P < 0.005$) in the ulcer patients (37.2 ± 2.7 mmol 180 min^{-1}) than in the controls (25.6 ± 2.5 mmol 180 min^{-1}). When the acid output after the saline-control meal was subtracted, to correct for the effect of gastric distention, mean stimulated acid output was significantly higher in the ulcer patients than in the controls with the 0.5, 2.0, 4.0, and 8.0% peptone test meals. Again, the mean cumulative acid output after correction for distention was significantly higher ($P < 0.03$) in the ulcer patients (29.0 ± 3.0 mmol 120 min^{-1}) than in the controls (18.2 ± 3.9 mmol 120 min^{-1}). Acid output was also expressed as a percentage of the highest observed meal-stimulated acid output in each subject. The mean acid output was significantly higher in the ulcer patients than in the controls with 0.5, 1.0, 2.0, and 4.0% peptone test meals (Fig. 1).

Postprandial acid secretion before and after healing of ulcer. In five patients, peptone dose-response tests were performed within 72 h of endoscopic demonstration of an active duodenal ulcer and again 4–8 wk later when the ulcer had healed at re-endoscopy. No significant differences in acid secretion were observed between the tests done when the ulcer was active and when the ulcer had healed. The cumulative acid outputs were 78.4 ± 8.5 and 72.0 ± 15.4 mmol 180 min^{-1} , respectively.

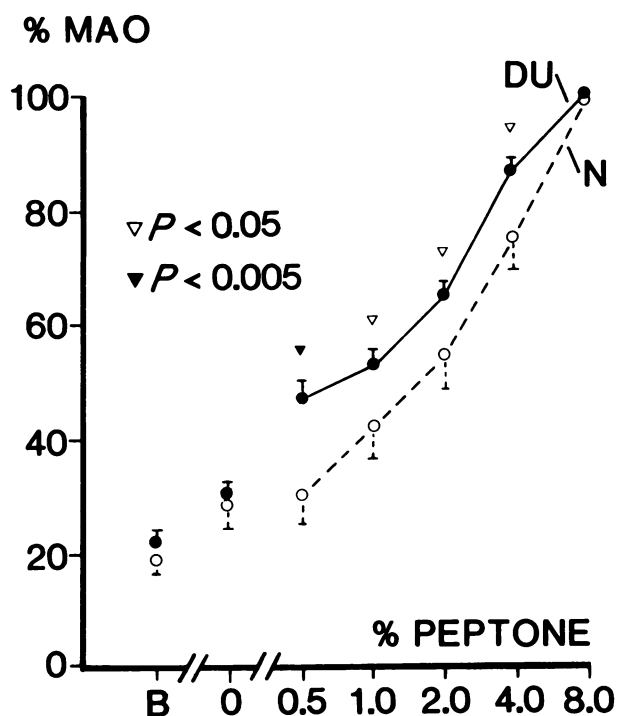


FIGURE 1 Mean (\pm SE) gastric acid secretion expressed as percentage of the maximal peptone-stimulated acid output (MAO), basally (B) and in response to increasing doses of intragastric peptone in 25 duodenal ulcer (DU) and 14 control (N) subjects.

G17 maximal acid output. The mean acid output after G17 infusion was significantly higher ($P < 0.03$) in the 23 duodenal ulcer patients (25.2 ± 1.6 mmol 30 min^{-1}) than in the 13 controls (18.9 ± 2.3 mmol 30 min^{-1}). There was a significant correlation between G17 maximal acid output and meal-stimulated maximal acid output in both the ulcer ($r = 0.70$, $P < 0.001$) and control subjects ($r = 0.66$, $P < 0.05$). In ulcer and control subjects, meal-stimulated maximal acid output represented 65.2 ± 6.8 and $64.6 \pm 3.4\%$, respectively of the G17 maximal acid output.

Serum gastrin. The mean fasting serum gastrin concentrations (femtomoles per milliliters) were similar in the duodenal ulcer patients and the controls for both G-total (27.4 ± 1.9 and 32.7 ± 4.4 , respectively) and G17 (12.6 ± 0.7 and 14.4 ± 1.2 , respectively). The mean levels in response to peptone test meals were also similar (Fig. 2). The mean integrated serum gastrin levels (nanomoles per minute per liter) were similar in the ulcer patients and the controls for both G-total (6.5 ± 0.5 and 6.8 ± 0.8 , respectively) and G17 (2.8 ± 0.3 and 2.8 ± 0.3 , respectively). Likewise, the mean basal-corrected integrated serum gastrin levels were similar in the ulcer patients and controls for both G-total (2.8 ± 0.4 and 2.6 ± 0.5 , respectively) and G17 (1.1 ± 0.3 and 1.0 ± 0.2 , respectively). In both the patients and the

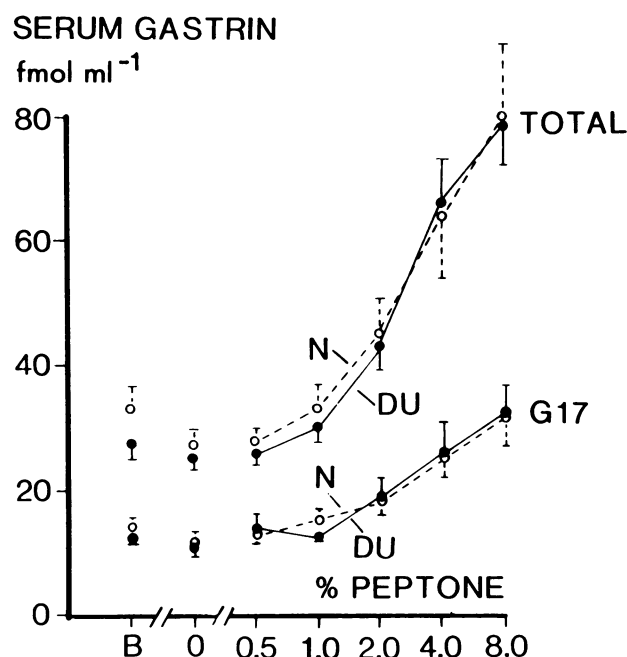


FIGURE 2 Comparison of mean (\pm SE) serum G-total and G17 basally (B) and in response to increasing doses of intragastric peptone in 25 duodenal ulcer (DU) and 14 control (N) subjects. No significant differences were observed between DU and N.

controls, there was no significant change in the mean serum G-total or G17 level after the saline test meal when compared with basal. The lowest dose of peptone that produced a significant rise above basal of mean G-total and G17 was 2% in both patients and controls, whereas the lowest dose of peptone that produced significant increase in acid secretion over saline was 0.5% for the ulcer patients and 1% for controls.

Correlation between serum gastrin concentration and meal-stimulated acid output. In each subject, the correlation coefficient between serum gastrin concentrations and gastric acid outputs in response to the graded doses of peptone was calculated and found to be positive. The median correlation coefficients both for acid output vs. G-total and for acid output vs. G17 were highly significant ($P < 0.001$) in both the duodenal ulcer patients and in the controls (Table I). These correlation coefficients remained highly significant regardless of whether uncorrected values for acid output and serum gastrin concentrations were used, or whether they were corrected by subtracting values observed during the basal period or during the period in which the stomach was distended with 0.15 M NaCl (Table I).

The relationship between mean meal-stimulated serum gastrin concentrations and mean acid output after infusion of the graded doses of peptone in the duodenal ulcer patients and the controls is depicted for G17 in Fig. 3. The curve for the duodenal ulcer patients is distinctly to the left of that of the controls.

TABLE I
Median Correlations between Serum Gastrin
(G-total or G17) and Acid Output

	DU	N
G-total vs. acid output		
Uncorrected	0.90 (0.60–0.98)	0.84 (0.62–0.96)
Basal corrected	0.90 (0.60–0.99)	0.85 (0.55–0.97)
Distention corrected	0.94 (0.67–0.99)	0.92 (0.43–0.97)
G17 vs. acid output		
Uncorrected	0.84 (0.46–0.99)	0.86 (0.49–0.98)
Basal corrected	0.82 (0.40–0.99)	0.84 (0.55–0.98)
Distention corrected	0.89 (0.48–0.99)	0.85 (0.42–0.99)

Correlation within individuals between serum gastrin (G-total or G17) and acid output in response to graded doses of peptone meals in duodenal ulcer (DU) and normal (N) subjects. The correlation coefficient was calculated for each subject individually and the table gives the median correlation coefficient (r) with the ranges in parentheses. $P < 0.001$ for each median r . Both the gastrin values and the acid output values were corrected by subtracting the values observed during the basal period or during the period with distention from 0.15 M NaCl.

Among individuals of both ulcer and control groups, there was no significant correlation between peak serum concentration, whether G-total or G17, and maximal acid output in response to peptone; nor between integrated serum gastrin level, whether G-total or G17; and cumulative acid output in response to peptone.

GASTRIC ACID mmol 30 min⁻¹

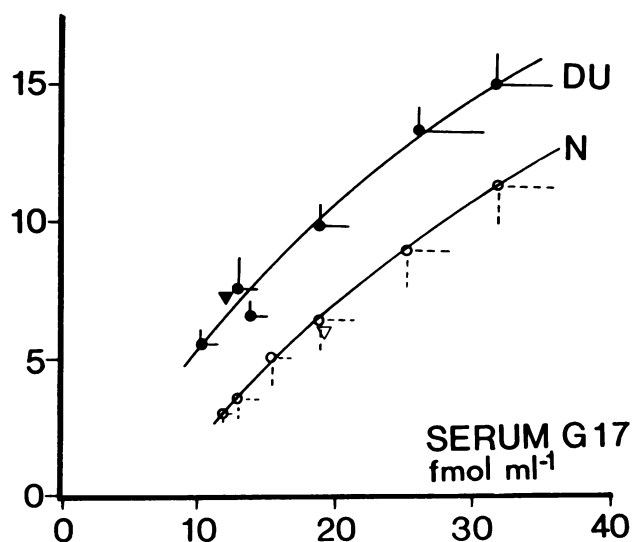


FIGURE 3 Comparison of the relationship between mean (\pm SE) serum G17 and mean (\pm SE) gastric acid output after the 0–8% peptone test meals in 25 duodenal ulcer (DU) and 14 control (N) subjects. Mean D_{50M} for DU (●) and N (▽) are also shown.

Half-maximal acid response and corresponding serum gastrin concentrations. From the regression line of each subject, the serum gastrin concentration corresponding to half of the observed maximal acid output in response to the peptone tests meals was calculated. This serum gastrin concentration was designated D_{50M} . Duodenal ulcer patients had a significantly lower D_{50M} than the controls with respect to both G-total and G17, irrespective of whether the absolute values or the basal-corrected values were used (Table II).

It was possible to match 13 of the control subjects with 13 duodenal ulcer patients with respect to maximal acid output in response to peptone to within 1.5 mmol 30 min⁻¹ for each pair. The D_{50M} of the duodenal ulcer patients remained significantly less than that of their matched controls with respect to both G-total and G17 (Table III). The mean maximal acid output observed in the remaining 12 duodenal ulcer patients was significantly higher than that of the 14 controls. In these 12 ulcer patients, the mean D_{50M} for both G-total and G17 was still significantly lower than that of the controls, but not significantly different from the ulcer patients whose acid secretion matched that of the controls.

It was also possible to match 10 of the control subjects with 10 of the duodenal ulcer patients for their G17 maximal acid output to within 2 mmol 30 min⁻¹ for each pair. The D_{50M} of the duodenal ulcer patients was significantly less than that of their matched controls with respect to both G-total and G17 (Table III). The mean G17 maximal acid output of the remaining 13 ulcer patients who underwent this test was significantly higher than that of the 13 controls who had the test performed. In the latter 13 ulcer patients, the mean D_{50M} for both G-total and G17 was still significantly lower than that of the controls, but not significantly different from the ulcer patients whose G17 maximal acid output matched that of the controls.

In both ulcer patients and controls, there was no significant correlation between D_{50M} , whether G-total or

TABLE II
Serum Gastrin Concentrations Corresponding to D_{50M}

	Ulcer	Control	P
G-total			
Uncorrected	29.4 \pm 1.5	43.6 \pm 6.0	<0.005
Basal corrected	10.7 \pm 1.9	18.9 \pm 3.0	<0.01
G17			
Uncorrected	11.4 \pm 0.7	18.3 \pm 2.1	<0.0005
Basal corrected	2.4 \pm 0.8	6.2 \pm 1.3	<0.01

Mean \pm SE serum gastrin concentrations (femtomoles per milliliter) corresponding to half of the observed maximal acid output in response to graded doses of peptone (D_{50M}) in 25 duodenal ulcer and 14 control subjects. Basal corrected refers to both acid and gastrin secretion.

TABLE III
*D*_{50M} Serum Gastrin Concentrations Matched for Meal-Stimulated and G17-Stimulated MAO

	Matched			Unmatched		
	Control	Ulcer	<i>P</i>	Control	Ulcer	<i>P</i>
Meal-stimulated MAO	12.3±1.2	12.1±1.2		11.5±1.3	19.3±1.2	<0.0005
G-total <i>D</i> _{50M}	40.6±5.6	27.6±2.4*	<0.03	43.6±6.0	31.3±1.8*	<0.05
G17 <i>D</i> _{50M}	18.1±2.3	10.9±0.8*	<0.005	18.3±2.1	12.0±1.2*	<0.01
<i>n</i>	13	13		14	12	
G17 MAO	21.4±2.6	21.5±2.5		18.9±2.3	28.1±1.8	<0.003
G-total <i>D</i> _{50M}	43.3±7.0	28.8±2.4*	<0.05	44.9±6.3	31.0±2.1*	<0.01
G17 <i>D</i> _{50M}	20.5±2.5	10.9±1.4*	<0.03	19.2±2.1	11.6±0.9*	<0.005
<i>n</i>	10	10		13	13	

Mean±SE *D*_{50M} serum gastrin concentrations (femtomoles per milliliter) in duodenal ulcer and control subjects matched for meal-stimulated and G17-stimulated maximal acid output (MAO, millimoles per 30 min). Comparison of remaining unmatched ulcer patients with all controls also shown.

* *P* > 0.2.

G17, and maximal acid output, whether meal stimulated or G17 stimulated.

G17 dose response. The mean acid output, whether uncorrected (Fig. 4) or corrected for basal effect by subtraction, was significantly higher in duodenal ulcer patients than in control subjects after each dose of G17. In each subject a linear regression line was constructed for acid output, *y* vs. acid output/dose, *x*. The median correlation coefficient for ulcer patients was -0.81 (range; -0.50--0.99) and that for normal controls was -0.66 (range; -0.34--0.99). From the regression line of each subject, the G17 dose corresponding to half of the maximal acid output was calculated and designated *D*_{50G}. Mean *D*_{50G} (picomoles per kilogram per hour) was significantly lower (*P* < 0.0005) in duodenal ulcer patients (42.1±3.9) than in control subjects (79.9±5.5). To

correct for the effect of basal acid secretion, basal acid output was subtracted from each response before repeating the linear regression analysis. The resulting median correlation coefficients for ulcer and control subjects were, respectively, -0.73 (range; -0.21--0.98) and -0.63 (range; -0.30--1.0). Mean *D*_{50G} corrected for basal effect was significantly lower (*P* < 0.003) in ulcer patients (41.9±5.4) than in normal subjects (70.4±5.5). Serum gastrin concentrations during infusion of the various doses of G17 were not measured. However, previous G17 dose-response studies in which these were done indicate that increase in serum G17 levels correlated significantly (*r* = 0.999) with an exogenous G17 dose, and that the clearance of G17 in duodenal ulcer patients was identical to that of normal controls (12).

Correlation between G17 *D*_{50M} and *D*_{50G}. *D*_{50M} of serum G17 concentrations in response to peptone test meals was correlated with *D*_{50G} of G17 doses obtained in the G17 dose-response studies. A significant (*P* < 0.01) correlation was observed in duodenal ulcer patients and control subjects regardless of whether the uncorrected (Fig. 5) values (*r* = 0.65 and *r* = 0.72, respectively) or the values corrected for basal effect (*r* = 0.70 and *r* = 0.72, respectively) were used.

DISCUSSION

We have shown that by stimulating gastric acid secretion with increasing concentrations of peptone, a highly significant correlation was observed within individual subjects between the meal-stimulated serum gastrin levels, G-total or G17, and the corresponding acid output. These data provide additional evidence that G17 is a major physiologic mediator of the acid secretory response to intragastrically instilled protein-containing meals. They confirm and extend previous data obtained with intragastric amino acid perfusion

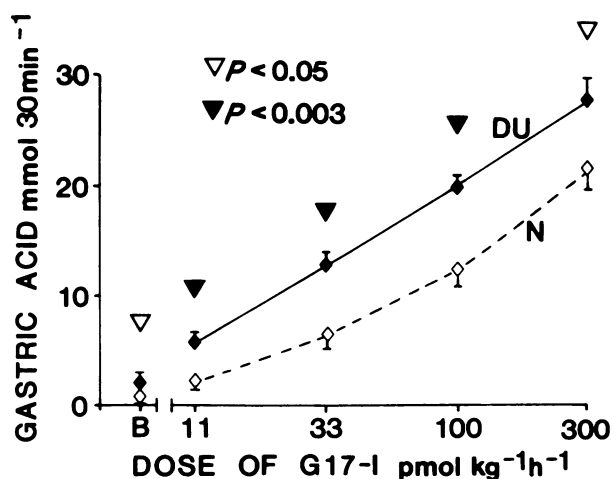


FIGURE 4 Mean (±SE) gastric acid secretion basally (B) and in response to graded doses of G17-I in 19 duodenal ulcer (DU) and 11 control (N) subjects.

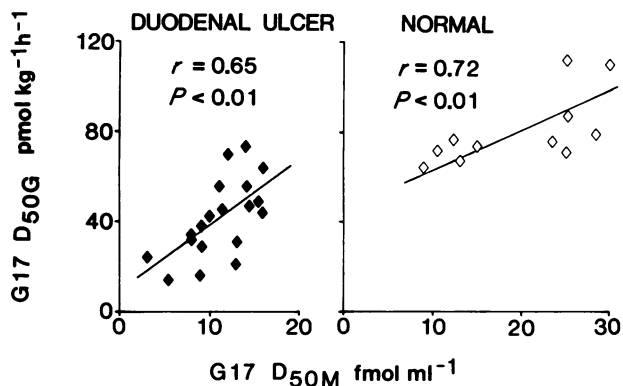


FIGURE 5 Correlation between G17 D_{50M}, i.e., endogenous serum G17 concentration corresponding to half of the observed maximal acid response to peptone test meals, and G17 D_{50G}, i.e., dose of G17-I corresponding to half of the maximal acid output in response to graded doses of exogenous G17-I.

(5). Furthermore, the significant correlation within individuals, but not among individuals, explains the failure in previous attempts (3, 4, 13) to correlate meal-stimulated gastrin and acid responses.

In the present series of duodenal ulcer patients the mean meal-stimulated serum gastrin was similar to that of the normal controls, a finding in keeping with some previous studies (14, 15), including those employing intragastric titration (3, 13), but at variance with others (16). The differences among various studies are not understood but may in part represent the heterogeneity of duodenal ulcer disease (17, 18) and differences in methods.

In agreement with previous findings (3) that the acid response to a steak meal as measured by intragastric titration was higher than normal in duodenal ulcer patients, we observed that the mean acid response to each concentration of peptone test meal was significantly higher in the duodenal ulcer patients than in the controls. The meal-stimulated acid output remained higher in duodenal ulcer patients than in the control subjects even when the basal- and distention (saline)-stimulated secretions were subtracted. Furthermore, postprandial acid responses in patients with endoscopically active duodenal ulcer remained unchanged after the ulcer healed.

The 8% 500-ml peptone dose is likely to be the maximal or near maximal dose because increasing the dose to 10 or 16% did not increase the acid output further. In both ulcer and control subjects, the maximal postprandial acid output correlated significantly with the G17 maximal acid output. These findings therefore suggest that postprandial maximal acid output is dependent on the parietal cell mass, assuming that the latter is a major determinant of maximal acid output. In both ulcer and control subjects, the postprandial maximal acid output averaged about two-thirds of the G17 maxi-

mal acid output. These findings agree with previous studies (4, 19, 20) in which the average meal-stimulated acid output ranged from 40 to 80% of the histalog or pentagastrin acid output, but not with other studies (3, 21) in which the two values were similar. The reason for the differences is not clear, but may be attributable to differences in constituents of the meals, population groups, and methods of measuring gastric acid secretion.

After the submaximal doses of peptone, the ulcer patients attained a significantly greater proportion of their maximal meal-stimulated response than the controls. This increased responsiveness of postprandial acid secretion is related to an increased sensitivity to the circulating gastrin released by the meals. This conclusion is based firstly on the observation that the mean D_{50M}, i.e., the circulating gastrin concentration corresponding to half of the observed maximal postprandial acid response, was significantly less in the duodenal ulcer patients than in the controls. The difference was most striking ($P < 0.0005$) when the circulating G17 was considered. Secondly, the mean D_{50G}, i.e., the dose of exogenous G17 required for half of the G17 maximal acid output, was significantly less in ulcer than in control subjects, as observed both in previous (2) and present studies. Furthermore, in both ulcer and control subjects, there was a significant correlation between the exogenous D_{50G} and the endogenous D_{50M}. These findings strongly suggest: that exogenous circulating G17 was the mediator of the peptone-stimulated acid response, further supporting previous work (5); and that ulcer patients require less circulating gastrin for a given acid response.

The increased sensitivity to endogenous gastrin in the ulcer patients was further demonstrated by matching the controls with ulcer patients having similar postprandial maximal acid output. Even though their postprandial maximal acid output was similar to that of the controls, these ulcer patients still had a significantly lower D_{50M} than the controls. The remaining ulcer patients, whose mean postprandial maximal acid output was significantly higher than that of the controls, also had significantly lower D_{50M}. Thus, these findings demonstrate that duodenal ulcer patients, whether their postprandial maximal acid secretion was within or above the normal limit, had increased acid-secretory sensitivity to postprandial gastrin.

Furthermore, in ulcer patients and control subjects matched for similar G17 maximal acid output, the mean G-total and G17 D_{50M} for the meal-stimulated acid response were significantly lower in the ulcer patients. This was also seen in the remaining ulcer patients whose mean G17 maximal acid output was significantly higher than that of the controls. These findings indicate that a lower D_{50M} was present in the ulcer patients independent of their capacity to secrete acid.

The cause of the increased sensitivity of duodenal

ulcer patients to endogenous gastrin is unknown. It may be the result of vagal hyperactivity as first suggested by Dragstedt (22). An increased cholinergic drive is supported by the pentagastrin dose-response studies of Roland (23), which showed that carbacholine reduced the D_{50} of pentagastrin in the normals but not in the duodenal ulcer patients. The D_{50} with carbacholine in the normals was similar to that of the ulcer patients, suggesting preexisting heightened vagal cholinergic tone in duodenal ulcer subjects.

Our findings thus indicate that a pathophysiologic defect occurs in the gastric phase of acid secretion in duodenal ulcer patients. This defect is present both in patients with normal and increased maximal acid response to G17. The lower D_{50M} in the duodenal ulcer patients also implies that small meals would lead to relatively greater acid secretion in ulcer patients than in normal subjects. Treatment with frequent small meals for duodenal ulcer patients may therefore be inappropriate.

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