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Research Article

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Increased Sensitivity to Stimulation of Acid Secretion by Pentagastrin in Duodenal Ulcer

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ABSTRACT The effect of graded doses of pentagastrin (2.7–6,000 ng/kg·h) on gastric acid secretion was measured in 20 duodenal ulcer (DU) and 20 non-DU subjects. Confirming many previous studies, the mean observed highest response and the mean calculated maximal response were significantly greater in DU than in non-DU subjects. The mean dose (±SE) in ng/kg·h for half maximal response, calculated from responses corrected for basal secretion and normalized for maximal secretion, was 92.1±1.7 in DU and 246.8±24.6 in non-DU subjects, a significant difference. By parallel line bioassay non-DU subjects required 2.8 times more pentagastrin (95% confidence limits 2.1–3.7) than DU subjects for equal response expressed as percent of highest response. Thus, this study shows that, compared with non-DU subjects, DU patients not only secrete more acid in response to stimulation by pentagastrin but also are more sensitive to stimulation by pentagastrin, that is, need smaller doses to achieve the same fraction of maximal response.

INTRODUCTION

On the average patients with duodenal ulcer (DU)[1] secrete more acid than non-DU subjects at rest (1) and in response to stimulants such as histamine (2), betazole (3), pentagastrin (4), insulin (5), and a meal (6). The increased secretion in DU could be due to increased capacity to secrete, increased stimulation of secretion, increased sensitivity to stimulation, or some combination of these. Patients with DU have on the average more parietal cells than controls (7) and this is accompanied by an increased maximal capacity to secrete acid (2–4). Whether, in addition to increased capacity to secrete, DU patients also have increased stimulation, increased sensitivity to stimulation, or both is uncertain.

The purpose of the present study was to compare DU and non-DU subjects in regard to responsiveness of acid secretion to stimulation by pentagastrin. Pentagastrin dose-response studies were performed. DU subjects were found to be more sensitive than non-DU subjects to stimulation of acid secretion by pentagastrin.

METHODS

Pentagastrin dose response studies were performed in 20 male patients with DU disease (mean age 45, range 24–63 yr) and 20 male control subjects (mean age 45, range 22–61 yr). The criteria for the diagnosis of DU were: (*a*) epigastric pain relieved by antacids, and (*b*) ulcer crater, deformed duodenal bulb, or both by radiography. In addition the DU patients also fulfilled these criteria: (*a*) no radiographic evidence of gastric ulcer, (*b*) no clinical or radiographic evidence of gastric retention, (*c*) no recent complications of ulcer disease, (*d*) no upper gastrointestinal surgery, and (*e*) no other significant diseases. At the time of testing 14 of the DU patients had recent ulcer pain and six were asymptomatic. The criteria for control subjects were: (*a*) absence of symptoms suggestive or peptic ulcer disease, (*b*) no upper gastrointestinal surgery, and (*c*) no significant diseases. Informed consent was obtained from each subject. No subject had taken any drug within 24 h of secretory testing.

After a 12-h fast, a radiopaque nasogastric tube (18 French) was fluoroscopically positioned with the tip in the gastric antrum. Gastric juice was aspirated by a vacuum pump with pressures 7–12 mm Hg below atmospheric. The nasogastric tube was manually flushed with 10–20 ml of air and aspirated by hand at 5-min intervals to maintain patency. Each sample comprised the gastric juice collected during 10 min. Acid concentration was determined by

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[1] *Abbreviations used in this paper:* CMR, calculated maximal response; D_{50}, dose for half maximal response; DU, duodenal ulcer; SI, sensitivity index.

titration of 0.2 ml of juice with 0.2 N NaOH to pH 7.0 on an automatic titrator (Radiometer, Copenhagen, Denmark).

Residual juice was collected for 15 min and discarded and then basal secretion was collected for three 10-min periods. In 25 other subjects, basal secretion during the first 30 min did not differ significantly ($P > 0.2$) from basal secretion during the second 30 min: mean (±SE) 1.83±0.24 and 2.06±0.29 meq/30 min, respectively. Pentagastrin (*tert*-butoxycarbonyl-β-alanyl-tryptophanyl-methionyl-aspartyl-phenylalaninamide, Ayerst Laboratories, New York) was then infused in graded doses of 2.7, 8.2, 25, 75, 222, 666, 2,000, and 6,000 ng/kg·h. Each dose was diluted to 17 ml with 0.15 M NaCl and infused for 30 min into a forearm vein by a syringe infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.). The doses were given in the order listed. The total 30-min acid output in milliequivalents was used in the analysis of the data. In separate analyses not reported here it was shown that use of the peak 10- or 20-min outputs did not alter any of the conclusions drawn from analysis of the total 30-min outputs. In previous studies in man (8) it was shown that acid secretory responses to four doses of pentagastrin each infused for 45 min did not differ significantly whether all doses were given on a single day or each dose was given on a separate day. Since any error in estimation of dose for half maximal response (D_{50}) that would result from giving all doses in one day would apply equally to DU and non-DU subjects, and since we felt that it would be impractical to do eight separate tests on each subject, we elected to conduct single-day multiple-dose testing.

Calculated maximal response (CMR) and D_{50} were estimated by linear regression analysis according to the equation:

$$\text{response} = \text{CMR} - D_{50}\ (\text{response/dose}) \qquad (1)$$

The least squares regression line of response/dose, x, versus response, y, gave estimates of CMR (y-intercept) and D_{50} (negative slope) and their standard errors. This particular linearization of the Michaelis-Menten equation was chosen because it gives the best estimates of these parameters (9).

In dose-response studies, high basal rates can give falsely low estimates of D_{50} if the observed rates are used directly in the analysis. This source of error can be minimized by doing the analysis on response minus basal then calculating the basal-corrected CMR, CMR_c, and the basal-corrected D_{50}, D_{50c}, according to these equations (10):

$$CMR_c = CMR_b + B \qquad (2)$$

$$D_{50c} = D_{50b}\,[1 - (B/CMR_c)] \qquad (3)$$

where CMR_b and D_{50b} are CMR and D_{50} calculated according to Eq. 1 from values obtained by subtracting individual basal secretion rates from individual responses to each dose of pentagastrin, and B is basal rate of secretion.

In estimating CMRs and D_{50}s the responses to the two lowest doses of pentagastrin were excluded because they were only slightly greater than basal secretion and their inclusion markedly decreased the linear correlation coefficients. Subscripts to CMR and D_{50} are used to indicate whether the values are derived from individual (i) data or from means (m); from data uncorrected (u) for basal or corrected (c) for basal; and from absolute (a) values or from values normalized (n) as a percent of highest observed response.

The statistics used in parallel line bioassays can be applied to the present problem of relative sensitivity of two groups of subjects to a single drug. In conventional bioassay a standard and an unknown drug are compared in a single population of test objects and the ratio of amount of unknown drug to amount of standard drug needed for equal responses is expressed as a potency ratio with statistically defined confidence limits. In the present case we are comparing the response of two different populations to the same drug so any difference in apparent "potency" can be interpreted as a difference in sensitivity of the two populations to the drug. "Potency" and "sensitivity" can be looked on as complementary properties, potency applying to drugs and sensitivity to test objects. In the present study, the "potency ratio" of pentagastrin was calculated by a 3+3 dose parallel line assay (11). For this analysis the pentagastrin doses that were in the straight line portion of the log dose versus percent response curve (Fig. 4) were used: 25, 75, and 222 ng/kg·h in the DU group and 75, 222, and 666 ng/kg·h in the non-DU group.

The sensitivity of individual subjects was reflected in their individual D_{50}s. As an additional measure of individual sensitivity we used a sensitivity index calculated as the basal-corrected response to 75 ng/kg·h of pentagastrin expressed as percent of the highest observed response to pentagastrin. The correlations between these two indices of sensitivity and basal acid output and highest observed response to pentagastrin were examined.

Student's t test, Spearman's rank-order correlation coefficient, correlation coefficient, and analysis of variance were used in the statistical analysis of the data (12). Differences were designated as significant if $P < 0.05$.

RESULTS

Basal secretion. The mean basal acid secretion, expressed either as absolute rate (Table I) or as percent of highest observed acid secretion (Fig. 3), was greater in DU than in non-DU subjects but the differences were not statistically significant.

Response to pentagastrin. Each dose of pentagastrin from 75 to 6,000 ng/kg·h produced significantly greater mean rates of acid secretion in the DU group than in the non-DU group (Table II and Fig. 1) and these differences persisted after basal acid secretion was subtracted (Fig. 2). Individual responses are included in Table III. The greater response of DU as compared with non-DU subjects was also apparent when the responses were normalized as percent of highest observed response regardless of whether basal secretion was not (Fig. 3) or was (Fig. 4) subtracted.

Highest observed response. The highest observed response to pentagastrin was greater in DU than in non-DU subjects both when calculated as the highest mean response to any of the doses of pentagastrin used (Table II) or as the mean of the individual highest responses independent of dose of pentagastrin (Table I).

Calculated maximal response (CMR). The CMR was greater in the DU than in the non-DU group regardless of whether it was calculated from responses of individual subjects (Table I) or from mean responses

TABLE I

*Data from Individual Subjects**

Subject no.	Basal	HOR	SI	D_{50iua}	CMR_{iua}	r
DU subjects	*meq/30 min*		*%*	*ng/kg·h*	*meq/30 min*	
1	13.4	27.6	4.5	20.6	23.9	−0.73
2	0.2	28.5	11.6	135.6	20.7	−0.24
3	4.3	38.0	42.1	75.9	36.3	−0.97
4	12.5	40.0	26.8	49.6	40.9	−0.92
5	2.5	16.5	67.6	24.8	15.7	−0.98
6	11.3	21.5	56.8	28.7	21.4	−0.88
7	4.6	38.9	57.4	21.7	34.8	−0.85
8	0.2	8.8	64.4	18.4	8.3	−0.88
9	7.2	21.3	23.4	84.2	18.6	−0.78
10	2.0	22.5	54.2	47.6	21.8	−0.97
11	0.6	24.4	25.4	146.8	21.1	−0.65
12	0.7	25.1	51.1	33.1	21.4	−0.90
13	3.1	22.1	72.9	21.4	21.0	−0.91
14	1.5	24.1	36.3	109.6	22.4	−0.56
15	1.7	19.2	52.9	32.4	17.8	−0.94
16	0.7	13.4	45.8	103.8	12.9	−0.74
17	2.4	29.9	37.9	88.2	23.5	−0.77
18	0.0	22.2	28.5	115.7	16.9	−0.82
19	0.6	23.7	16.5	12.4	14.9	−0.26
20	4.5	35.5	68.4	39.5	32.7	−0.80
Mean±SE	3.7±0.9	25.2±1.8	42.2±4.5	60.5±9.6	22.4±1.8	−0.78±0.05
Non-DU subjects						
1	0.0	13.0	28.9	174.1	12.2	−0.96
2	0.7	11.6	6.9	533.2	13.5	−0.85
3	1.0	23.1	26.7	122.0	22.6	−0.96
4	1.7	13.7	31.8	75.6	12.8	−0.96
5	0.2	27.9	4.7	186.1	6.5	0.1
6	0.0	4.6	0.0	444.8	1.3	0.3
7	1.5	14.5	65.0	38.3	13.3	−0.84
8	6.2	19.7	36.9	72.3	19.2	−0.89
9	3.6	11.1	0.0	204.2	12.5	−0.48
10	0.7	11.2	38.5	39.5	9.4	−0.83
11	2.0	13.6	16.3	54.5	9.6	−0.65
12	0.0	2.2	26.5	107.0	1.8	−0.77
13	0.0	24.7	19.6	245.8	21.9	−0.96
14	3.6	26.8	54.3	37.5	22.7	−0.88
15	0.9	21.3	11.6	235.9	17.7	−0.51
16	2.7	15.6	15.3	116.3	12.4	−0.69
17	0.0	14.8	5.0	97.7	7.2	−0.12
18	9.8	32.1	0.0	11.8	18.2	−0.30
19	0.0	12.5	19.6	114.9	8.2	−0.75
20	0.2	2.6	58.8	52.1	2.1	−0.47
Mean±SE	1.9±0.6	15.8±1.8	23.3±4.4	148.2±30.3	12.2±1.5	−0.62±0.08

* Basal secretion rate, highest observed response (HOR) to any dose of pentagastrin, sensitivity index (SI) (basal substracted response to 75 ng/kg·h pentagastrin as percent of HOR), dose for half maximal response (D_{50}), calculated maximal response (CMR), and correlation coefficient (r) for linear regression of response on response/dose. D_{50} and CMR were calculated from absolute responses uncorrected for basal secretion.

of groups (Table IV). The CMR calculated from mean values was greater in DU than in non-DU subjects.

Dose for half maximal response (D_{50}). The D_{50} was significantly less in DU than in non-DU subjects both when calculated from responses of individual subjects (Table I) and from mean responses of groups (Table

TABLE II

Mean (±SE) Acid Output (meq/30 min) at rest and in Response to Each Dose of Pentagastrin in 20 DU and 20 Non-DU Subjects

Pentagastrin dose	Acid output		P
	DU	Non-DU	
ng/kg·h	*meq/30 min*		
0	2.7±0.9	1.9±0.6	NS
2.7	3.1±0.8	1.7±0.6	NS
8.2	4.3±0.9	2.3±0.9	NS
25.0	7.6±1.1	2.8±0.8	<0.005
75.0	12.6±1.4	4.7±0.9	<0.001
222.0	17.9±1.9	7.8±1.2	<0.001
666.0	20.8±1.8	10.7±1.4	<0.001
2,000.0	23.4±1.9	13.6±1.6	<0.001
6,000.0	24.7±1.8	14.2±1.6	<0.001

IV). The D_{50} calculated from mean responses of groups was significantly less in DU than in non-DU subjects regardless of whether correction for basal secretion was or was not applied and also regardless of whether absolute responses or responses normalized as a percent of highest observed response were used (Table IV).

Analysis by the 3 + 3 dose parallel line assay method. This analysis (Table V) showed that pentagastrin was 2.82 times (confidence limits 2.12–3.74) more "potent" in the DU group than in the non-DU group. In the context of the present study we construe differences in apparent "potency" to be attributable to differences in sensitivity. Thus this confirms by another method of analysis that DU subjects are more sensitive to stimulation by pentagastrin than non-DU subjects.

Sensitivity index. The basal corrected mean response to 75 ng/kg·h of pentagastrin expressed as percent of highest observed response was significantly greater in DU than in non-DU subjects (Table I).

Correlations between sensitivity and basal or maximal secretion. In neither DU nor non-DU subjects was there a significant correlation between sensitivity, as measured by the sensitivity index, and basal acid output or highest observed response to pentagastrin (Table VI). In the non-DU group, but not in the DU group, there was a significant positive correlation between basal acid output and D_{50}, and between highest observed response and D_{50}.

DISCUSSION

The results of this study indicate that DU patients not only secrete more acid in response to pentagastrin than non-DU subjects, a reflection of the greater parietal cell mass, but also are more sensitive to pentagastrin, requiring significantly lower doses of achieve a certain fraction of maximal response. This difference in sensitivity was found by three different criteria: (*a*) greater percent of maximal response to submaximal doses of pentagastrin in DU than in non-DU subjects, (*b*) lower D_{50} in DU than in non-DU subjects, and (*c*) greater sensitivity of DU subjects than non-DU subjects in a 3 + 3 dose bioassay using doses that produced equal responses expressed as percent of highest observed response.

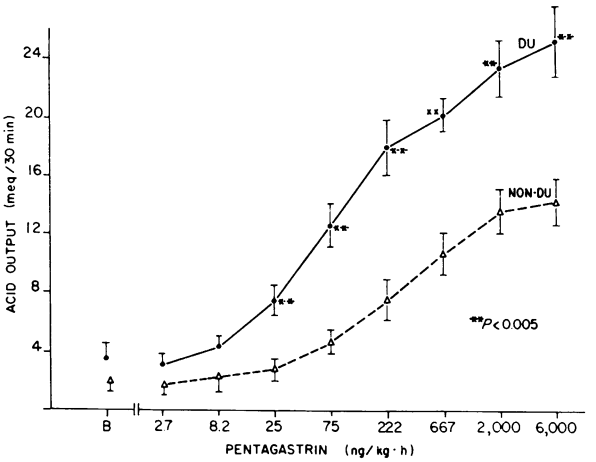

FIGURE 1 Mean acid output in 20 DU and 20 non-DU subjects during infusion of graded doses of pentagastrin. In this and subsequent figures vertical bars indicate 1 SE above and below means.

"Fade," that is decreasing response with time to a constant dose of stimulant, may distort dose-response curves that are based on sequential administration of all doses in one test without intervening rest periods. A detailed study of this effect in cats (13) showed that distortion was minimal; D_{50} and CMR to pentagastrin were not significantly different with separated and

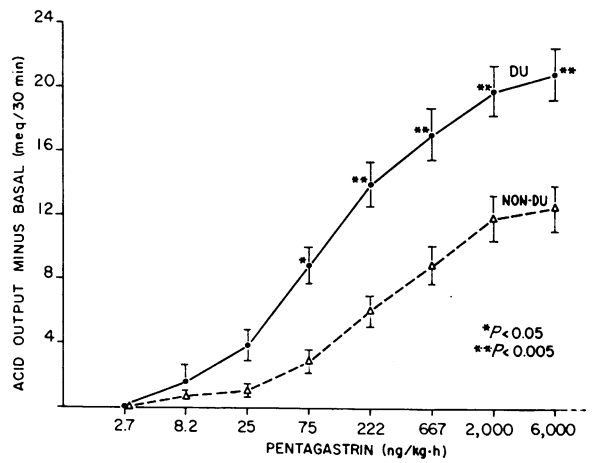

FIGURE 2 Mean acid output minus basal output in 20 DU and 20 non-DU subjects during graded doses of pentagastrin.

TABLE III

Individual Acid Secretory Responses (meq/30 min) to Graded Doses of Pentagastrin in DU and Non-Du Subjects

Subject no.	Pentagastrin (ng/kg h)								
	0	2.7	8.2	25.0	75.0	222.0	666.0	2,000	6,000
	meq/30 min								
DU subjects									
1	13.4	2.6	2.2	14.4	14.0	17.6	24.6	27.1	27.6
2	0.2	0.1	0.1	0.2	3.4	13.4	26.4	28.5	28.4
3	4.3	5.3	10.0	9.0	18.5	26.3	28.5	38.0	37.3
4	12.5	14.2	7.5	14.2	19.8	37.9	40.0	39.1	40.0
5	2.5	11.3	2.8	7.8	12.0	14.3	15.1	14.6	16.5
6	11.3	7.3	8.5	8.9	17.1	21.5	20.3	19.0	20.6
7	4.6	6.7	15.2	18.9	24.3	32.6	38.2	37.0	38.9
8	0.2	0.3	0.6	4.9	5.8	8.4	8.8	7.6	8.2
9	7.2	1.9	2.9	2.8	10.5	15.8	15.7	15.3	21.3
10	2.0	2.6	3.8	7.7	13.1	15.6	21.6	21.7	22.5
11	0.6	0.6	1.1	1.8	6.7	18.6	12.9	24.4	21.8
12	0.7	1.4	4.7	9.8	13.1	16.5	20.1	21.1	25.1
13	3.1	3.6	5.5	11.3	16.9	16.3	22.1	21.9	20.6
14	1.5	0.8	1.4	1.4	9.7	18.4	23.7	22.3	24.1
15	1.7	5.3	6.9	7.9	11.0	16.7	16.7	16.2	19.2
16	0.7	0.4	0.3	1.3	6.5	10.0	11.5	13.4	12.6
17	2.4	4.0	4.9	4.8	12.8	10.6	15.9	26.8	29.8
18	0.0	0.0	0.0	3.4	6.1	7.2	12.1	17.8	22.2
19	0.6	0.7	3.2	10.9	4.4	5.2	18.6	20.1	23.7
20	4.5	3.3	4.2	10.4	25.7	30.2	24.1	35.5	32.8
Mean	3.7	3.1	4.3	7.6	12.6	17.9	20.8	23.4	24.7
SE	0.9	0.8	0.9	1.1	1.4	1.9	1.8	1.9	1.8
Non-DU subjects									
1	0.0	0.5	2.5	1.4	3.8	7.6	8.0	11.1	13.0
2	0.7	0.1	0.0	0.4	1.5	4.6	9.4	11.6	11.1
3	1.0	1.9	1.4	4.2	6.9	15.0	19.6	21.5	23.1
4	1.7	0.6	1.4	3.4	5.6	10.0	10.4	13.7	12.7
5	0.2	0.4	0.5	0.1	1.5	1.7	2.4	27.9	15.1
6	0.0	0.0	0.0	0.0	0.0	0.6	2.1	4.6	4.4
7	1.5	2.7	1.4	4.6	9.9	12.8	12.2	10.6	14.5
8	6.2	2.3	2.4	4.0	11.2	15.7	17.5	19.7	16.4
9	3.6	2.3	1.2	1.0	2.4	5.5	18.1	11.1	10.2
10	0.7	1.0	3.7	3.9	4.8	8.0	11.2	8.4	9.2
11	2.0	2.2	3.8	3.5	3.9	5.8	5.8	13.6	12.4
12	0.0	0.0	0.6	0.4	0.6	1.3	1.9	1.0	2.2
13	0.0	1.4	1.3	2.2	4.8	10.4	13.9	18.6	24.7
14	3.6	5.2	4.4	8.7	16.2	18.9	20.6	26.8	18.8
15	0.9	0.2	0.1	0.4	3.3	10.9	15.8	21.3	19.2
16	2.7	0.4	1.3	2.3	4.6	2.9	13.9	12.4	15.6
17	0.0	0.0	0.0	0.0	0.7	4.3	9.0	9.7	14.8
18	9.8	11.5	19.4	13.8	7.9	13.8	14.9	17.5	32.1
19	0.1	0.0	1.0	1.7	2.5	4.3	5.4	7.4	12.5
20	0.2	0.9	0.1	0.2	1.6	1.6	1.7	2.6	2.6
Mean	1.9	1.7	2.3	2.8	4.7	7.8	10.7	13.6	14.2
SE	0.6	0.6	0.9	0.8	0.9	1.2	1.4	1.6	1.6

sequential doses. However in dog, a species known to demonstrate marked fade (14), CMR and D_{50} were significantly lower when calculated on results of multiple dose per day compared with single dose per day tests (15). Aubrey and Forrest (8) found no significant difference in responses to separated and sequential doses

of pentagastrin in man. We cannot disprove the possibility that the dose-response curves in this study were distorted by this factor, but even if they were this would not alter the conclusions unless the degree of distortion were different in DU and non-DU subjects. Studies comparing the degree of fade in DU and non-DU subjects are needed to assess this possibility.

High levels of basal secretion cause a decrease in D_{50} but this effect can be corrected for by subtracting basal secretion from each response (10) as was done in this study. Also, differences in peak secretory rate can affect D_{50} (9). In this study the effect on D_{50} of differences in peak responses was minimized by normalizing the response as a percent of highest observed response to pentagastrin. The D_{50} for DU subjects was still significantly less than that of non-DU subjects even after these corrections for basal secretion and peak secretion had been applied.

The correction for basal secretion (10) used in this study is based on the assumption that the drive for basal secretion has the same kinetics as the exogenous stimulant, pentagastrin in this instance. Even if the assumption is not valid, the correction could still give a valid empirical index of sensitivity. Nevertheless, an independent assessment of the influence of basal secretion on sensitivity is desirable. The finding (Table V) that no significant correlation existed between basal secretion and sensitivity as measured by sensitivity index provides independent confirmation that differences in sensitivity between DU and non-DU groups cannot be ascribed solely to differences in basal secretion. Similarly, the lack of significant correlation between sensitivity index and highest observed response suggests that increased sensitivity is not merely another manifestation of increased capacity to secrete.

Makhlouf (16) calculated the D_{50} of pentagastrin by intravenous inffusion in man from six sets of data on DU and non-DU subjects in published literature and found values ranging from 60 to 300 ng/kg·h. From

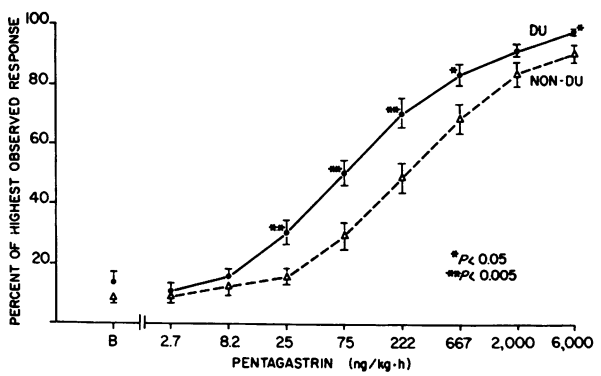

FIGURE 3 Mean acid output expressed as a percentage of highest observed pentagastrin-stimulated response.

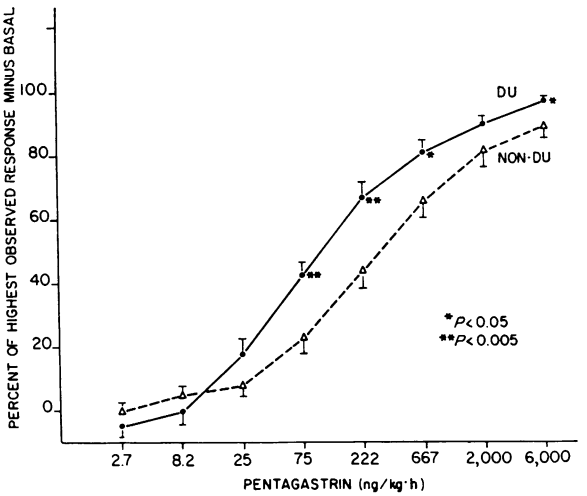

FIGURE 4 Mean acid output minus basal output expressed as a percentage of highest observed pentagastrin-stimulated response.

published studies (17, 18) in which graded doses of pentagastrin were tested in DU patients we estimated the D_{50} to be about 55 ng/kg·h, similar to the D_{50} uncorrected for basal secretion of 61 ng/kg·h for DU patients in the present study (Table I).

We are aware of two previous studies comparing DU and non-DU subjects in regard to sensitivity to stimulation of acid secretion. Wormsley and Mahoney (19) reported that the response to 60 ng/kg·h was 65% of the

TABLE IV

Means (±SE) of Calculated Maximal Responses (CMR) and Doses for Half Maximal Response (D_{50})

	DU	Non-DU	P
	meq/30 min		
Calculated from individual absolute responses, uncorrected for basal			
CMR_{iua}	22.4±1.8	12.2±1.5	<0.001
D_{50iua}	60.5±9.6	148.2±30.3	<0.05
r	−0.78±0.05	−0.62±0.08	
Calculated from mean absolute responses, uncorrected for basal			
CMR_{mua}	23.5±0.8	13.0±1.1	<0.001
D_{50mua}	54.9±5.2	103.3±18.8	<0.05
r	−0.98	−0.93	
Calculated from mean absolute responses, corrected for basal			
CMR_{mca}	24.4±4.7	15.0±0.6	<0.001
D_{50mca}	88.4±0.4	261.4±26.2	<0.001
r	−0.99	−0.99	
Calculated from mean normalized responses, corrected for basal			
CMR_{men}	94.3±0.7	91.5±4.9	NS
D_{50men}	92.1±1.7	246.8±24.6	<0.001
r	−0.99	−0.98	

Subscripts indicate whether values are derived from individual (i) data or from means (m); from data uncorrected (u) or corrected (c) for basal; and from absolute (a) values or values normalized (n) as percent of highest observed response. r is the correlation coefficient for linear regression of response on response/dose.

TABLE V

Analysis of Variance of 3 + 3 Dose Parallel Line Assay Comparing Normalized Responses to 75, 222, and 666 ng/kg·h of Pentagastrin in Non-DU and 25, 75, and 222 ng/kg·h of Pentagastrin in DU Subjects

	Degrees of freedom	Sum of squares	Mean square	F	P
1. Linear regression	1	39,545.39	39,545.39	160.1	<0.005
2. Deviation from parallelism	1	84.13	84.13	0.34	>0.25
3. Between control and DU	1	48.57	48.57	0.20	>0.25
4. Deviation from linearity	1	25.73	25.73	0.10	>0.25
5. Difference of curvature	1	0.87	0.87	0.004	>0.25
6. Between treatments	5	39,704.69	7,940.94	32.15	<0.005
7. Between subjects	39	36,851.42	944.91	3.83	<0.005
8. Error	75	18,525.86	247.01		
9. Total	119	95,081.96			

The assay was valid as shown by: highly significant slope of the combined regression line (line 1) and its lack of significant deviation from linearity (line 4); the individual log dose response lines did not differ significantly in slope (line 2) or in curvature (line 5); and the normalized responses selected for analysis did not differ significantly (line 3).

highest observed response in non-DU and 71% in DU, an insignificant difference. By contrast, we found that the response to 75 ng/kg·h was 23% of the highest observed response in non-DU and 42% in DU, a significant difference. We do not know why our results differ from those of Wormsley and Mahoney but differences in details of performing the tests may be responsible. Hunt and Kay (20) studied the effect of graded doses of histamine in five DU and five non-DU subjects. Secretory responses to each dose of histamine, expressed as percent of highest observed response, were similar in DU and non-DU subjects.

All organs that respond to gastrin do not show an increased sensitivity to pentagastrin in DU. Pentagastrin is a stimulant of lower esophageal sphincter contraction when administered by rapid intravenous injection (21). Kun, Sturdevant, Pises, and Isenberg (22) recently examined lower esophageal sphincter responsiveness to bolus injection of pentagastrin in DU and non-DU subjects. The D_{∞} and CMR values obtained in DU and non-DU were quite similar. These data suggest that there are differences between different organs in relative sensitivity. However the kinetics of intravenous shots and continuous infusions may not be comparable. Recently it has been shown that continuous infusions of doses of pentagastrin sufficient to produce maximal rates of acid secretion had no effect on gastroesophageal sphincter pressure (23).

TABLE VI

Spearman's Rank Correlation Coefficient between Various Items in DU and Non-DU Subjects

	DU	Non-DU
BAO and SI	+0.120	+0.086
HOR and SI	−0.269	−0.073
BAO and D_{50iau}	−0.293	+0.609*
HOR and D_{50iau}	+0.167	+0.657*

BAO, basal acid output; SI, sensitivity index, response to 75 ng/kg·h pentagastrin as percent of HOR; HOR, highest observed response to pentagastrin; D_{50iau}, D_{50} calculated from individual absolute uncorrected responses.

* $P < 0.05$.

At least three hypotheses may be offered to explain increased sensitivity to pentagastrin in DU patients. First, it is known that decreasing "vagal tone" to the stomach by vagotomy (24) or by administration of atropine (25) decreases sensitivity for stimulation of gastric secretion by pentagastrin. The converse, increased "vagal tone," might then account for increased sensitivity. Unfortunately there are at present no satisfactory methods by which vagal tone can be measured. A second possibility is that circulating concentrations of inhibitors of gastrin-stimulated acid secretion, such as secretin, cholecystokinin, and other enterogastrones, are diminished in DU patients. Perfection of radioimmunoassay methods for measurement of these substances should help clarify this point. A third possibility is that the rate of disposal of pentagastrin is decreased in DU subjects. If the half-life of pentagastrin were longer in DU, circulating concentrations of pentagastrin would be higher in DU than in non-DU subjects given equal infusion rates. These higher concentrations would produce increased rates of acid secretion without a true increase in sensitivity of the parietal cell itself.

In the present study no information has been gained to support or deny any of the above three hypotheses. The data show clear evidence of a difference between DU and non-DU subjects in sensitivity to stimulation of acid secretion by pentagastrin. This increased sensitivity may play a role in the pathogenesis of duodenal ulcer disease.

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REFERENCES

1. Baron, J. H. 1963. Studies of basal and peak acid output with an augmented histamine test. *Gut.* **4**: 136–144.
2. Baron, J. H. 1963. An assessment of the augmented histamine test in the diagnosis of peptic ulcer. *Gut.* **4**: 243–253.
3. Wormsley, K. G., and M. I. Grossman. 1965. Maximal histalog test in control subjects and patients with peptic ulcer. *Gut.* **6**: 427–435.
4. Johnson, D., and K. Jepson. 1967. Use of pentagastrin in a test of gastric acid secretion. *Lancet.* **2**: 585–588.
5. Winkelstein, A., and M. Hess. 1948. Effect of insulin hypoglycemia on gastric secretion in duodenal ulcers and controls. *Gastroenterology.* **11**: 326–336.
6. Fordtran, J. S., and J. H. Walsh. 1973. Gastric acid secretion rate and buffer content of the stomach after eating. Results in normal subjects and in patients with duodenal ulcer. *J. Clin. Invest.* **52**: 645–657.
7. Cox, A. J., Jr. 1952. Stomach size and its relation to chronic peptic ulcer. *Am. Med. Assoc. Pathol.* **54**: 407–422.
8. Aubrey, D. A., and A. P. M. Forest. 1970. Comparison of gastric secretory responses following the administration of histamine acid phosphate and pentagastrin by separate continuous intravenous infusions or by a step-test method. *Scand. J. Gastroenterol.* **5**: 449–457.
9. Colquhoun, D. 1969. A comparison of estimators for a two-parameter hyperbola. *J. R. Stat. Soc. Ser. C.* **18**: 130–140.
10. Grossman, M. I. 1973. What do you do with basal in dose-response studies? A suggested answer. *Gastroenterology.* **65**: 341–344.
11. Colquhoun, D. 1971. Lectures in Biostatistics. An Introduction to Statistics with Applications in Biology and Medicine. Clarendon Press, Oxford. 425 pp.
12. Snedecor, G. W., and W. G. Cochran. 1967. The Iowa State University Press, Ames. 6th edition. 593 pp.
13. Emas, S., and S. O. Svensson. 1972. Dose-response curves for acid output to histamine and pentagastrin determined by two techniques. *Scand. J. Gastroenterol.* **7**: 751–757.
14. Hirschowitz, B. I., and G. Sachs. 1969. Pentagastrin in the gastric fistula dog. *Gastroenterology.* **56**: 456–467.
15. Hirschowitz, B. I., and G. Hutchinson. 1974. Step-dose compared to separate-dose response gastric secretion with histamine and pentagastrin in dogs—a kinetic analysis. *Scand. J. Gastroenterol.* **9**: 207–218.
16. Makhlouf, G. M. 1973. Dose-response curves to gastric secretory stimulants in man. *In* Pharmacology of Gastrointestinal Motility and Secretion. P. Holton, editor. Pergamon Press, Oxford. Vol. 1, Sect. 39(A). 173–194.
17. Aubrey, D. A., and A. P. M. Forrest. 1970. The effect of vagotomy on human gastric secretion. *Br. J. Surg.* **57**: 332–338.
18. Elder, J. B., G. Gillespie, E. H. G. Campbell, I. E. Gillespie, G. P. Crean, and A. W. Kay. 1972. A study of the acid dose-response curve to small doses of pentagastrin in duodenal ulcer patients. *Clin. Sci. (Oxf.).* **43**: 181–191.
19. Wormsley, K. G., and M. P. Mahoney. 1967. Parietal cell responsiveness in duodental ulcer. *Br. Med. J.* **1**: 278.
20. Hunt, J. N., and A. W. Kay. 1964. The nature of gastric hypersection of acid in patients with duodenal ulcer. *Brit. Med. J.* **2**: 1444–1446.
21. Isenberg, J., A. Csendes, and J. H. Walsh. 1971. Resting and pentagastrin stimulated gastroesophageal sphincter pressure in Zollinger-Ellison syndrome. *Gastroenterology.* **61**: 655–658.
22. Kun, T., R. Sturdevant, P. Pises, and J. Isenberg. 1973. Effect of graded doses of pentagastrin on lower esophageal sphincter pressure in duodenal ulcer patients and nonduodental ulcer subjects. *Clin. Res.* **21**: 259.
23. Frank, S. A., C. O. Walker, and J. S. Fordtran. 1973. The effect of continuous pentagastrin (PG) infusion on lower esophageal sphincter pressure (LES). *Gastroenterology.* **64**: 728. (Abstr.)
24. Elder, J. B., G. Gillespie, E. H. G. Campbell, I. E. Gillespie, G. P. Crean, and A. W. Kay. 1972. The effect of vagotomy on the lower part of the acid dose-response curve to pentragastrin in man. *Clin. Sci. (Oxf.).* **43**: 193–200.
25. Konturek, S. J., and J. Oleksy. 1969. The effect of cholinergic and adrenergic blockade on basal and pentagastrin-induced acid secretion. *Scand. J. Gastroenterol.* **4**: 13–16.