Antral Gastrin Cell Hyperplasia in Patients with Peptic Ulcer

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The total number of gastrin (G) cells in the stomach was determined by using a histologic counting method and planimetry in ulcerous and nonulcerous patients. The preoperative basal and postprandial serum gastrin values and the gastrin cell mass in the gastrectomy specimen could be compared in 16 surgical patients. There was a significant correlation between the integrated gastrin response to feeding and the total gastrin cell number in the stomach. No correlation was found between the basal serum gastrin level and the total gastrin cell count. A total gastrin cell number higher than 50 million was found in the stomach of three duodenal ulcer patients with preoperative postprandial hypergastrinemia as well as in one patient with normal serum gastrin values. Gastrin cell counts between 6 and 42 million were found in control stomachs and in patients with gastric ulcer. Preoperative feeding tests could be useful to select patients with an elevated antral G cell number.

THE EXISTENCE OF AN ULCEROGENIC syndrome induced by diffuse hyperplasia of the antral gastrin (G) cell population and hypergastrinemia was postulated several years ago by Polak et al.[12] This hypothesis was based on a histologic study of gastrectomy specimens from nine patients with a biological Zollinger-Ellison syndrome: no pancreatic tumor was seen at surgery in five patients but the density of gastrin cells found in their antrum was 20 times higher than normal. Subsequent observations of duodenal ulcer (D.U.) patients with elevated serum gastrin levels and high densities of antral gastrin cells have been reported. Actually, the existence of a true antral gastrin cell hyperplasia could not be demonstrated in any of these patients because no adequate method for counting the total number of gastrin cells in the antrum was available. Indeed, the size of the antrum is variable from one patient to another[9] and gastrin cell densities in antral biopsy specimens do not provide estimations of the gastrin cell mass.

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In the past three years, adequate methods for counting the total number of gastrin cells in the stomach of animals have been presented.[4-6,16] We have proposed a quantitative histologic method to obtain reliable estimations of the gastrin cell mass in the human stomach in a study of gastrectomy specimens from patients with peptic ulcer.[9] This study indicated that the local density of gastrin cells varies from one site of the antrum to another and that the occurence of multiple patchy areas of antral gastritis in which no gastrin cells are found is a major factor in causing this variability. A well distributed and extensive sampling of the antral mucosa is thus required to obtain the mean value of the gastrin cell density per mucosal surface unit. Multiplication of the mean density of cells with the antral surface measured by planimetry gives the absolute value of the total cell population. The principle of this method has been described earlier by Card and Marks for parietal cell populations in man.[3] To our knowledge at this time there is only one other study,[13] which employed an acceptable quantitative technique to assess G cell numbers in the human antrum.

In the present work the preoperative basal and postprandial serum gastrin levels have been studied in patients with peptic ulcer. These parameters have been compared with the total number of gastrin cells in the gastrectomy specimens from the patients submitted to subtotal gastric resection.

Materials and Methods

Patients

Forty-eight patients entered this study. All were referred to the department for peptic ulcer disease resistant to conventional medical therapy and were

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tested for basal and postprandial serum gastrin levels before surgery. Twenty-eight duodenal ulcer patients were treated by highly selective vagotomy (H.S.V.). The remaining nine D.U. patients were submitted to a Billroth II gastrectomy. The indication for gastrectomy was a very high acid secreting capacity (one patient), elevated postprandial serum gastrin levels with high acid secreting capacity (three patients), partial duodenal stenosis (two patients) and unfitness for H.S.V. (three patients). Four gastric ulcer patients and two patients with recurrent ulcer after vagotomy were also submitted to gastrectomy. In one patient with a small duodenal angioma without ulcer the duodenal bulb as well as the antrum were resected. His stomach was included as a "normal" control. Four additional control stomachs were resected immediately after bilateral nephrectomy in decerebrated donors for kidney grafts. No ulcers or mucosal abnormalities were found in these specimens.

In addition, basal and postprandial gastrin levels were measured in 17 healthy volunteers none of which had a clinical history of gastrointestinal or hormonal disease and in 63 patients with chronic duodenal ulcer responsive to medical therapy.

Secretion Tests

The basal and postprandial serum gastrin levels were determined before surgery. The same parameters were determined at least six weeks after gastrectomy in six patients who accepted to undergo a second test. Blood specimens were taken through an intravenous catheter 15 minutes and five minutes before eating and respectively 20, 30, 40, 60, 80 and 100 minutes after starting a test meal. The standard meal consisted of 150 g grilled steak, toast with butter and a cup of coffee. The serum gastrin values were estimated by radioimmunoassay as described previously.[8,17] The basal concentration of gastrin was taken as the mean values of both basal samples and the peak gastrin level as the mean of the two successive highest values. The integrated gastrin responses were calculated following the method described by Stern and Walsh.[15] The gastric acid secretion was studied after an overnight fast. The stomach was emptied through a nasogastric tube and the basal acid output (B.A.O.) was measured by continuous collection of the gastric secretion for one hour. The basal secretion was subdivided into four 15 minute samples. Pentagastrin was then infused intravenously at a dose of 2 μg/kg/h for 90 minutes. Six further 15 minute samples were collected, volumes were measured and acid concentrations determined using phenol red as indicator. Maximum acid output (M.A.O.) was calculated by totaling the four last samples. In addition, two patients with a borderline increase in basal gastrinemia were submitted to a secretin test, and the two patients with recurrent duodenal ulcer after vagotomy underwent an insulin test.

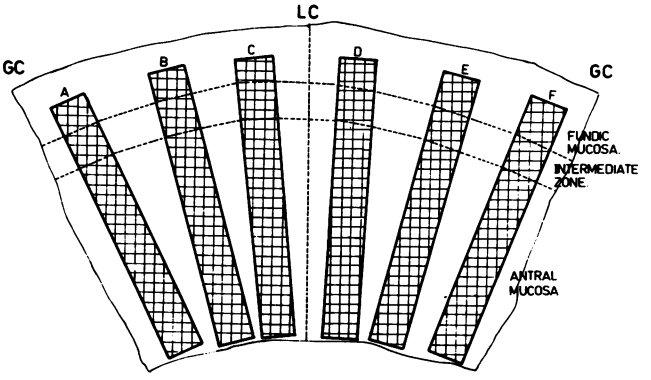

FIG. 1. Diagram of the six strips cut from each gastric specimen. GC, greater curvature; LC, lesser curvature.

Histoimmunologic Study

Immediately after resection, the stomach was opened along the greater curvature and rinsed in cold saline. The gastric mucosa was dissected from the seromuscular layer, pinned flat on a cork plate and fixed in Bouin's solution. Six longitudinal mucosal strips were cut from the entire length of the gastric specimen (Fig. 1). The strips were subdivided at right angles into smaller pieces, which were numbered and embedded in paraffin. The perimeter of the gastric specimen and of each strip was traced on drawing paper. Paraffin sections, 7 μm thick were cut from the left edge of each gastric piece. The gastrin cells were stained with the indirect immunoperoxidase method[2] using the antigastrin antibody of which the specificity has been described earlier.[8,9,17] The sections were counterstained with hematoxylin in order to differentiate nucleated gastrin cells from nonnucleated cytoplasmic fragments.

Surface of the Antrum and of the Transition Zone

A transitional zone 0.5–4 cm in width, where oxyntic and antral glands were intermingled, was observed in all specimens. The limit between oxyntic mucosa and the transitional zone was determined in the histologic sections of each strip by noting the position of the most proximal antral gland. The limit between the intermediate zone and the pure antral mucosa was determined by noting the most distal oxyntic gland containing peptic cells. The position of these limits was marked on the drawing after correction for tissue retraction. The surface of antrum and transition zone was then determined by planimetry.

Mean Concentration of Gastrin Cells and Total Number

The total number of nucleated gastrin cells was counted in one complete paraffin section from each mucosal piece. All G cell nuclei were clearly visible with the hematoxylin stain. In this way counting non-nucleated cytoplasmic fragments resulting in over-estimation of gastrin cell numbers was avoided. The true section thickness[11] and the mean nuclear diameter[1] of the gastrin cells was determined in cross sections from each gastric specimen. The mean concentration of gastrin cells per mm^2 of mucosal surface was calculated in the antrum and in the transition zone after correction for tissue retraction, section thickness and nuclear diameter as described elsewhere[9].

The surface of the antrum and of the transition zone was expressed in square millimeters. Multiplication of the surface and the mean concentration of gastrin cells per square millimeter gave the total numer of gastrin cells in both areas. The sum of both values represents the total number of gastrin cells in the stomach.

Results

The serum gastrin assay (Fig. 2) indicated that only two D.U. patients had a slightly elevated basal serum gastrin concentration. Secretin infusion did not increase the gastrin level in these patients. The integrated gastrin response to feeding was far beyond the normal level in four of the 37 surgical D.U. patients. One had a low maximal acid output (M.A.O.) (20.5 mEq/hour) and underwent proximal vagotomy while the three remaining patients (F,J,K) had slightly increased M.A.O. (above 40 mEq/hour) and were submitted to gastrectomy (Table 1). One patient with recurrent duodenal ulcer after truncal vagotomy (S) had elevated basal and postprandial gastrin levels. His peak acid output (P.A.O.) after insulin was 4.0 mEq/hour. The second patient (T) with duodenal ulcer recurring after vagotomy had virtually normal basal and postprandial gastrin levels and a P.A.O. after insulin of 0.6 mEq/hour. After gastrectomy the postprandial serum gastrin values of patients F, J and K were below normal (Table 1).

The mean total number of gastrin cells (Fig. 3) was lower in the gastric ulcer patients than in duodenal ulcer patients and controls. All three patients F, J and K with chronic duodenal ulcer, elevated postprandial serum gastrin values and high acid secretion had more than 50 million gastrin cells in their stomach. This elevated gastrin cell mass was due to an antral surface of more than 15 cm^2 in patients F and J and to a high concentration of gastrin cells per square millimeter in patients J and K. Patient S with a higher postprandial gastrin response and a recurrent ulcer after vagotomy had 42 million gastrin cells in his stomach. One patient (I) with a double pyloric and duodenal ulcer,

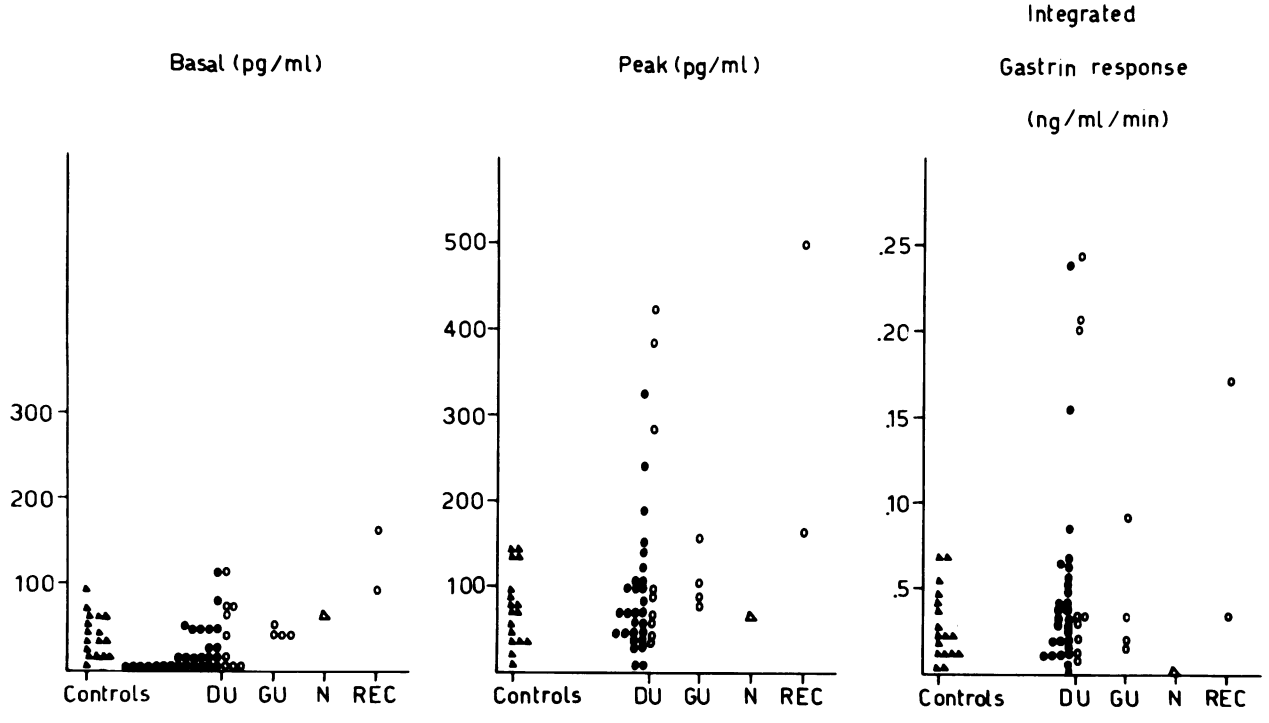

FIG. 2. Basal and postprandial serum gastrin values in 17 controls ▲, 37 duodenal ulcer (DU) patients (● not submitted to gastrectomy, ○ submitted to gastrectomy), 4 gastric ulcer (GU) patients, one patient with duodenal angioma (N) and two patients with recurrent ulcer (REC) after truncal vagotomy.

TABLE 1.

Patients	Diagnosis	Preoperative B.A.O.	Preoperative M.A.O.	Preoperative B.G.	Preoperative P.G.	Preoperative I.G.R.	Postoperative B.G.	Postoperative P.G.	Postoperative I.G.R.	Tot. G cell (.10⁶)	Conc. (cells/mm²)	Surf. (cm²)
A	N	—	—	59	68	0.0	—	—	—	11.49	1702	5.97
B	D.D.	—	—	—	—	—	—	—	—	14.75	3250	4.18
C	D.D.	—	—	—	—	—	—	—	—	24.80	2984	7.94
D	D.D.	—	—	—	—	—	—	—	—	32.20	4936	5.42
E	D.D.	—	—	—	—	—	—	—	—	42.00	4981	7.51
F	D.U.	12.9	56.4	63	385	20.3	50	41	−1.8	59.80	3067	18.14
G	D.U.	1.3	29.8	72	94	1.3	66	75	−0.1	6.80	956	7.03
H	D.U.	3.7	85.8	40	65	2.1	62	65	−0.6	26.25	2574	9.13
I	D.U.	8.8	119.4	72	97	0.8	50	45	−1.2	74.00	3835	17.67
J	D.U.	1.6	48.5	118	425	24.4	5	6	−0.9	104.24	4580	20.54
K	D.U.	2.6	44.3	15	284	20.6	4	3	0	75.00	6546	10.22
L	D.U.	17.1	58.3	9	67	3.3	0	0	0	38.18	3152	9.17
M	D.U.	—	—	10	47	3.2	—	—	—	14.47	2607	5.50
N	D.U.	0.8	29.7	3	42	3.3	—	—	—	41.92	3104	9.58
O	G.U.	4.0	31.4	48	158	9.2	42	40	−2.4	20.80	3132	9.38
P	G.U.	0.8	25.2	45	83	1.8	16	20	−0.15	6.80	931	6.71
Q	G.U.	—	—	55	90	2.0	12	35	1.3	12.90	1003	10.46
R	G.U.	—	—	48	103	3.5	17	15	−0.96	8.41	880	8.86
S	REC	1.5	8.2	170	500	17.2	—	—	—	42.20	3696	10.94
T	REC	9.2	21.8	95	165	3.5	—	—	—	26.50	3326	7.38

Preoperative basal acid output (B.A.O.) and maximal acid output with pentagastrin (M.A.O.) expressed in mEq/h; preoperative and postoperative basal serum gastrin (B.G.) peak gastrin value after a test meal (P.G.) expressed in pg/ml and integrated gastrin response (ng per ml per 100 min) after a test meal. Total gastrin cell population in the stomach (Total G cell), concentration of gastrin cells per mm² of antral mucosal surface (Conc.), surface of the antrum in cm² (Surf.).

N: Normal stomach with duodenal angioma; D.D.: decerebrated donors for kidney grafts; D.U.: duodenal ulcer patients; G.U.: gastric ulcer patients; REC: patients with recurrent ulcer after complete vagotomy.

a B.A.O. of 8.8 mEq/hour, a M.A.O. of 120 mEq/hour and normal postprandial serum gastrin levels (Table 1) had 74 million gastrin cells. The other duodenal ulcer patients had a gastrin cell mass which was similar to that of the patients without ulcer.

Neither the absolute gastrin cell numbers nor the gastrin cell concentrations correlated with the basal serum gastrin values in our patients (Fig. 4). A significant ($p < 0.01$) correlation ($r = 0.67$) of the gastrin cell number was observed with the postprandial gastrin peak value (Fig. 5). A good correlation ($r = 0.79$) was found with the integrated gastrin output values (Fig. 6).

Discussion

Our data confirmed the extreme variability of the absolute G cell number in the human stomach. In our patients with peptic ulcer this number varied between 7 and 104 million. Besides the concentration of the gastrin cells per square millimeter of antral mucosa, the total size of the antrum was a prominent factor in the individual variations in total G cell number. The patient with the highest cell count also had the largest antral surface, but no correlation between G cell concentration and antral size was found in the other patients. These observations corroborate our previous opinion that estimations of G cell density alone on the basis of endoscopic biopsy specimen are unlikely to provide adequate information about the

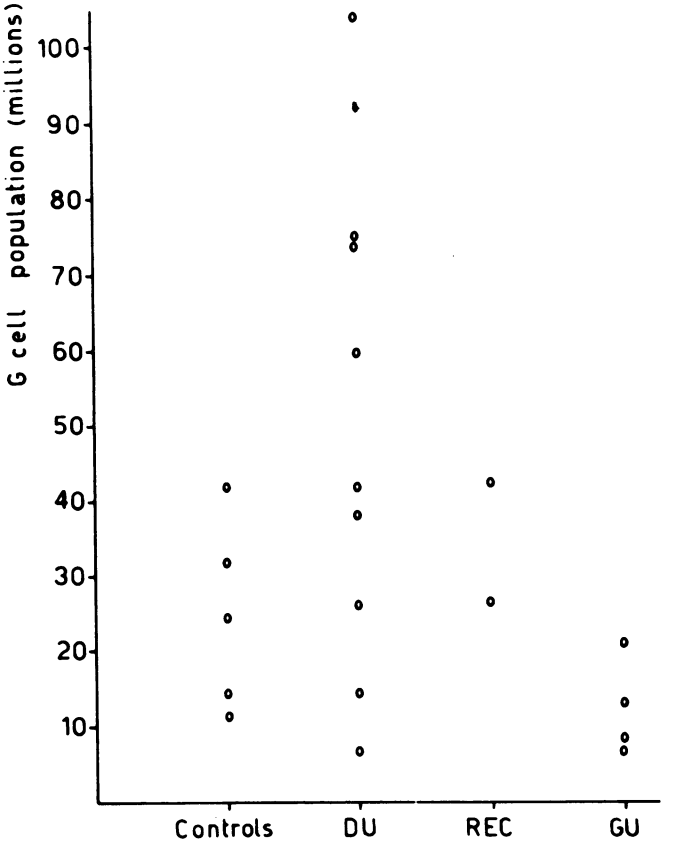

FIG. 3. Total G cell population in the stomach. Controls = values in patients A, B, C, D, E. (Table 1). DU = duodenal ulcer, REC = recurrent ulcer after vagotomy and GU = gastric ulcer.

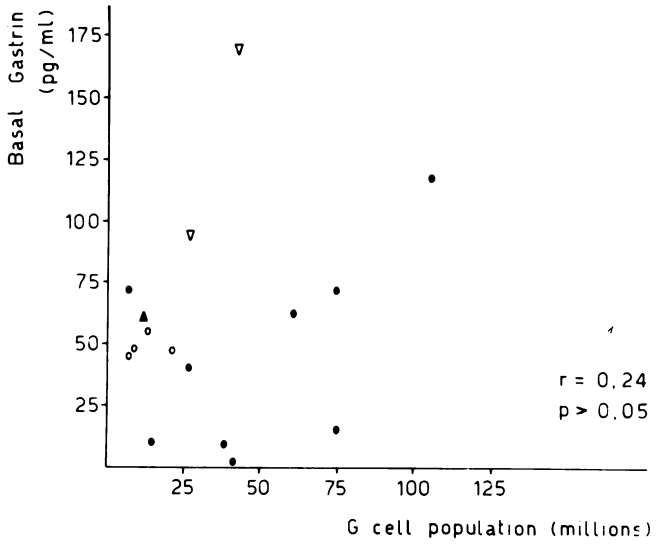

FIG. 4. Correlative study between preoperative basal serum gastrin values and the total G cell population in the stomach. No correlation was found. DU patients (●), patient with duodenal angioma (▲). GU patients (○) and patients with recurrent ulcer after vagotomy (▽).

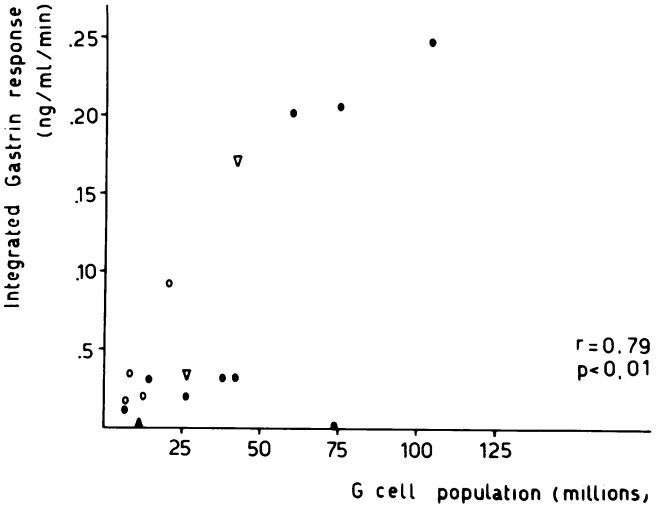

FIG. 6. Correlation between the total G cell number and the integrated gastrin response. DU patients (●), patient with duodenal angioma (▲). GU patients (○) and patients with recurrent ulcer after vagotomy (▽).

capacity of the stomach to secrete gastrin in peptic ulcer patients.[9] Not only is extensive sampling of the mucosa required to obtain reliable estimations of the mean G cell density, but the antral mucosal surface is needed to calculate the total gastrin cell mass. Unfortunately, harmless methods allowing this determination in the stomach *in situ* are still not available.

The fact that no mucosal lesions were seen in our control stomachs is not an absolute criterion of normality. Using a similar counting method in four nonulcerous stomachs, Royston et al.[13] have estimated antral G cell numbers ranging from 7 to 15 million.

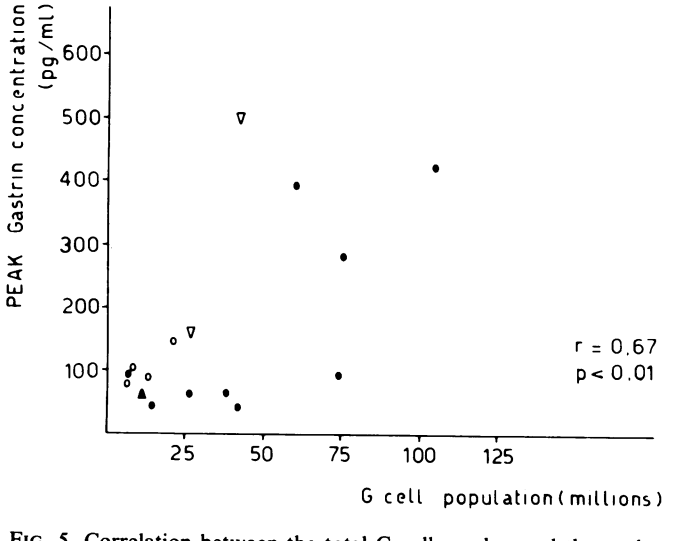

FIG. 5. Correlation between the total G cell number and the peak gastrin concentration. DU patients (●), patient with duodenal angioma (▲). GU patients (○) and patients with recurrent ulcer after vagotomy (▽).

If the gastrin cells of the intermediate zone[9,14] had been counted in the latter study, the control values would probably have been similar to ours.

Several D.U. patients with a slightly elevated basal gastrinemia, a higher gastrin response to feeding and an increased antral G cell density have been described.[7] The possibility that these patients belong to a separate clinical entity, called antral G cell hyperplasia was suggested, although the absolute G cell mass had not been determined in the antrum. Most of these patients had undergone previous truncal vagotomy, which is known to increase basal and postprandial gastrin levels[10] and possibly also G cell mass in the stomach.[6] No gastrin cell hyperplasia was found in our two patients with recurrent ulcer after vagotomy. In four gastric specimens from D.U. patients we found a G cell population of more than 50 million cells. Such a high absolute value could actually represent antral G cell hyperplasia if our control values and those reported by Royston et al.[13] truly represent the normal G cell number. One similar patient with 56 million gastrin cells has been found in the study of Royston et al.[13] This patient had an elevated basal gastrin level (532p moles/L) before gastrectomy, but retained high basal values (77p moles/L) after total gastrectomy. Three of our four patients with a large G cell population had increased gastrin responses to feeding. Suppression of the response by partial gastrectomy confirmed that the excess gastrin was not released by an extragastric tumor. The remaining patient with antral G cell hyperplasia, however, had

a normal gastrin response before gastrectomy. The markedly increased acid secreting capacity of this patient may explain a low gastrin response after a test meal despite a high anatomical capacity to secrete gastrin.

These observations as well as the significant correlation between the G cell mass and the gastrin response to feeding indicate that preoperative feeding tests could be useful to select patients with a high antral G cell number. Four patients with a high postprandial gastrin release were detected from a total of 37 D.U. patients coming to surgery. In none of the 63 D.U. patients responding to medical therapy, an integrated gastrin response to feeding higher than 20 ng/ml was found. It is evident that the proportion of D.U. patients with high G cell numbers in our small group of patients submitted to gastrectomy was by far excessive. Therefore, the hypothesis that G cell hyperplasia is a separate ulcerogenic entity cannot be concluded from our data.

Acknowledgments

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