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Acid secretory capacity and plasma gastrin concentration after administration of omeprazole to normal subjects

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SUMMARY

In a randomized double-blind study, two groups of eight healthy volunteers received either placebo or omeprazole 40 mg o.m. for 14 days. Fasting plasma gastrin concentration and peak acid output in response to a maximal intravenous dose of pentagastrin were measured before, during and after the 14 days of treatment. Omeprazole caused a 68% (mean) decrease in the peak acid output when measured 24 hours after the last dose, with a simultaneous increase in the fasting plasma gastrin concentration. When measured 1, 2, 3 and 8 weeks after cessation of treatment, there was no significant difference in the peak acid output between the two groups. The study demonstrates that there is no increase in the acid production capacity after 2 weeks of treatment with omeprazole. Thus it would appear that the rise in the plasma gastrin concentration during short-term treatment with omeprazole does not induce parietal cell hypertrophy or hyperplasia.

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INTRODUCTION

Omeprazole, a substituted benzimidazole, is a potent inhibitor of gastric acid secretion.[1] Omeprazole has a prolonged antisecretory effect, acid secretion returning to pretreatment values approximately one week after cessation of treatment.[1,2] In a series of studies in duodenal ulcer patients, we observed a dose-dependent decrease of 24-hour intragastric acidity, with a 97% decrease after one week of treatment with omeprazole 30 mg o.m.[3] This marked decrease of intragastric acidity was associated with a significant increase in fasting plasma gastrin concentration. Other studies performed in healthy volunteers, with once-daily treatment with omeprazole 30 mg o.m. for 2–4 weeks, confirmed that there is an increase in plasma or serum gastrin concentration during omeprazole treatment.[2,4] These studies also showed that the increased gastrin concentration returned to the pretreatment level approximately 1 week after cessation of treatment.

The object of the present study was to determine whether the increase in plasma gastrin concentration occurring during omeprazole treatment could have a trophic effect on the parietal cell mass in man, as studies in rats have shown that pentagastrin administration causes increased acid production capacity and parietal cell hyperplasia.[5] The present study was undertaken to observe the effect of omeprazole on the parietal cell mass, as assessed by peak acid output to maximal stimulation with pentagastrin.

SUBJECTS AND METHODS

Subjects, ethical approval and safety studies

Sixteen healthy male subjects with a median age of 25 years (range 22–30) and a median weight of 75 kg (range 66–83) participated in the study.

The subjects gave informed written consent before entry to the study. The study was approved by the Ethical Committees of the University of Gothenburg and the Royal Free Hospital, London. Full haematological and biochemical safety tests were performed before and after the treatment period.

Study design

The study was performed in two centres, using identical techniques and equipment. At each centre four subjects received omeprazole 40 mg, and four received placebo once in the morning for 14 days. The treatments were randomly allocated and the study was conducted as a double-blind trial. The study design is outlined in Figure 1.

EXPERIMENTAL PROCEDURE

Gastric acid secretion

Each subject participated in a total of seven gastric secretion tests starting at about 9.00 a.m. (see Figure 1). The test during treatment was performed 24 hours after the last dose—when the next dose of drug would have been given had the

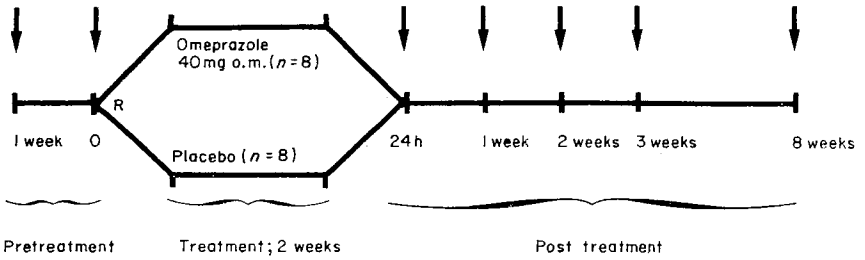

Figure 1. Study design. Arrows indicate gastric secretion test and duplicate sampling of fasting gastrin.

treatment been continued. After an overnight fast, a double-lumen nasogastric tube (Salem Sump Tube 14CH, A Brunswik, Belgium) was passed and positioned in the most distal part of the stomach. The position of the tube was checked by the recovery of 50 ml water, which was infused through the tube and immediately aspirated. The position of the tube was accepted if the recovery was at least 45 ml. A thin polyethylene catheter (Intramedic PE 160) was attached to the tube, and the tip of this catheter was positioned in the fundus. To estimate any loss of gastric contents through the pylorus, the stomach was continuously perfused via the polyethylene catheter with a solution of phenol red (3 mg litre^{-1}) in normal saline at a rate of 220 ml 15 min^{-1}. The gastric contents were aspirated continuously, using a suction pump which provided intermittent negative pressure, and were collected in 15-minute samples.

An intravenous infusion of pentagastrin was started after a 1-hour collection of basal acid secretion. During the first test only, pentagastrin was infused at two different doses: 1.2 and 2.0 μg kg^{-1} hour^{-1} each for 1 hour. This first test was performed to determine the dose of pentagastrin required to produce maximal acid output in each subject.[1] In the following six acid secretory tests, stimulated acid output was collected for 1 hour using the dose that produced the greatest peak acid response.

The volume and pH of each 15-minute sample was recorded and the hydrogen ion concentration was measured by titration to pH 7 with 0.1 M sodium hydroxide using an autotitrator (Radiometer, Copenhagen). After filtration (Millipore filter 1.2 μm) and alkalinization (0.4 ml 2.5 M sodium hydroxide added to 10 ml aspirate), the phenol red concentration in both the perfusion fluid and the gastric content was measured spectrophotometrically at 560 nm. The hydrogen ion content in the gastric aspirate was then corrected for losses, and acid secretion was expressed in mmol 15 min^{-1}.

Basal acid output (BAO) was defined as twice the sum of the gastric acid output in the third and fourth 15-minute collections. Peak acid output (PAO) was defined as the sum of the highest two consecutive 15-minute periods, multiplied by 2. Both BAO and PAO are expressed in mmol hour^{-1}.

Fasting plasma gastrin concentration

Two blood samples (5 ml each) were taken before each gastric secretion test for the determination of fasting plasma gastrin. The samples were taken 10 min apart, via the cannula which was to be used later for the pentagastrin infusion. The samples were collected in heparinized tubes. After cooling for 10 min, the samples were centrifuged and the plasma transferred to plastic tubes and stored at −20°C. All samples were analysed in one batch and measured by radioimmunoassay using antibody Gas 179 (Professor S. R. Bloom, Hammersmith Hospital).[6]

Postprandial plasma gastrin concentration

At the analysis of the results of the secretory experiments and their associated plasma gastrin concentrations, it was found that the gastrin concentrations varied greatly between individuals in the omeprazole group. To find a possible explanation for these variations we therefore, 18 months later, recalled the eight subjects who had received omeprazole to measure their gastrin release capacity in response to a test meal. After an overnight fast, venous blood samples (5 ml each) were collected before and after identical meals. Three samples were collected before the meal and seven were taken over a 2-hour period after the completion of the meal. The meal was given at breakfast time and was composed of a fish gratin (36 g protein, 25 g fat, 44 g carbohydrate) and milk (300 ml). The blood samples were separated and stored, and their gastrin concentrations analysed in a single batch as described above.

STATISTICAL ANALYSIS

The statistical evaluation of PAO was made by using a two-sided Student's *t* test for between-group comparison on each test occasion. Wilcoxon's signed rank test was used to compare the gastrin value during treatment with the mean of the two pretreatment values.

RESULTS

Gastric acid secretion

Peak acid output. The maximal acid output was obtained by giving 1.2 μg kg^{-1} $hour^{-1}$ of pentagastrin to three subjects in the placebo group and to four in the omeprazole group. The other five placebo and four omeprazole subjects required the higher dose of pentagastrin (2.0 μg kg^{-1} $hour^{-1}$) to produce a maximal acid response.

Repeated determination of PAO was very reproducible, the mean within-subject coefficient of variation in the placebo group being 11%. Omeprazole caused a mean 68% decrease in PAO (95% confidence interval 54–82%), measured 24 hours after the last dose ($P = 0.001$). When PAO was measured 1, 2, 3 and 8 weeks after cessation of treatment, there was no significant difference between the two groups (all *P*-values > 0.50; Figure 2).

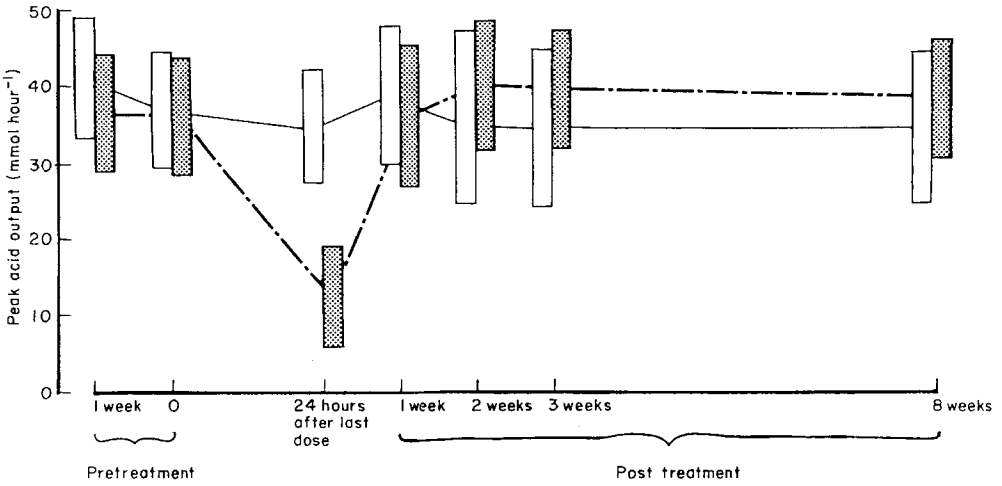

Figure 2. Ninety-five per cent confidence intervals for the expected peak acid output in healthy subjects before, during and after 2 weeks of treatment with either omeprazole 40 mg o.m. (n = 8) or placebo (n = 8). The lines join mean values for each group. (▩) Omeprazole; (□) placebo.

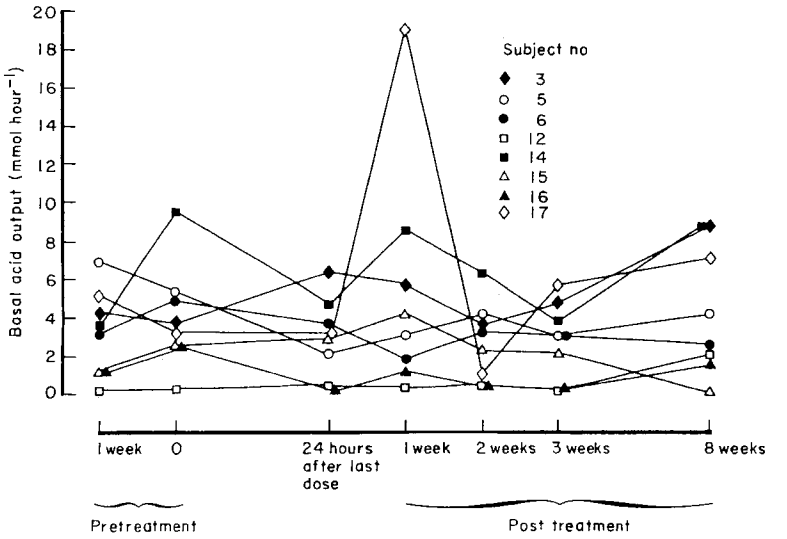

Figure 3. Basal acid output in eight healthy subjects before, during and after 2 weeks of treatment with placebo. Each value represents one experiment.

Basal acid output. The results obtained in the placebo group revealed large intra-individual variations in BAO: the mean within-subject coefficient of variation was 68% (Figure 3). However, it can be seen in Figure 4 that the BAO was completely inhibited in five of the eight subjects when measured 24 hours after the last dose of omeprazole.

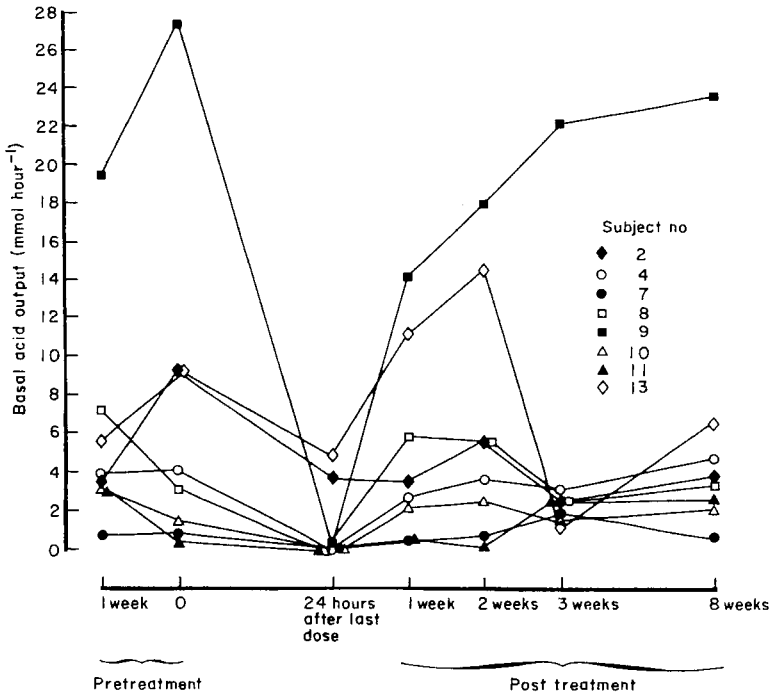

Figure 4. Basal acid output in eight healthy subjects before, during and after 2 weeks of treatment with omeprazole 40 mg o.m. Each value represents one experiment.

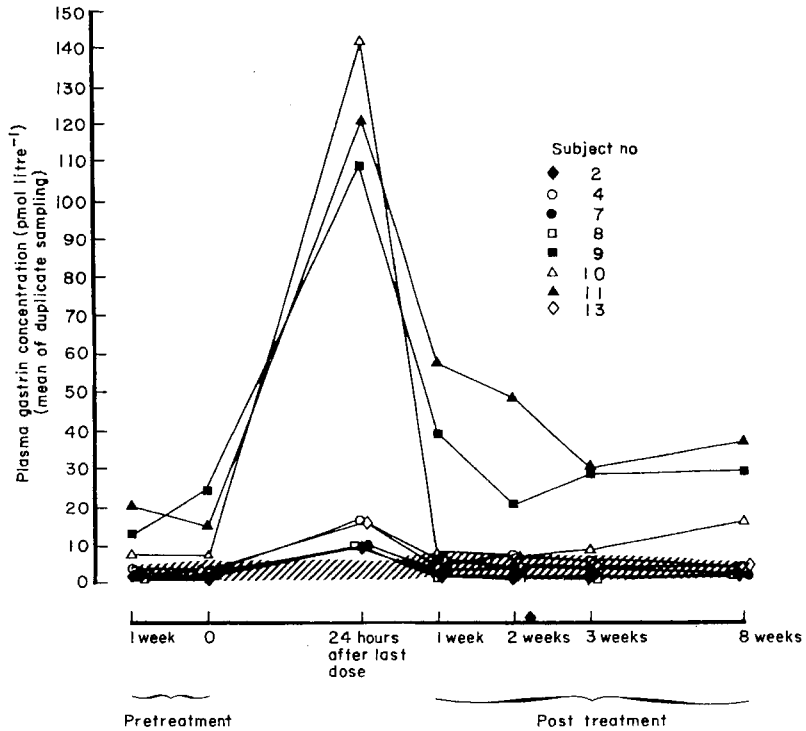

Figure 5. Individual fasting plasma gastrin concentrations in healthy subjects before, during and after 2 weeks of treatment with either omeprazole 40 mg o.m. ($n = 8$) or placebo ($n = 8$). All placebo values are within the shaded area.

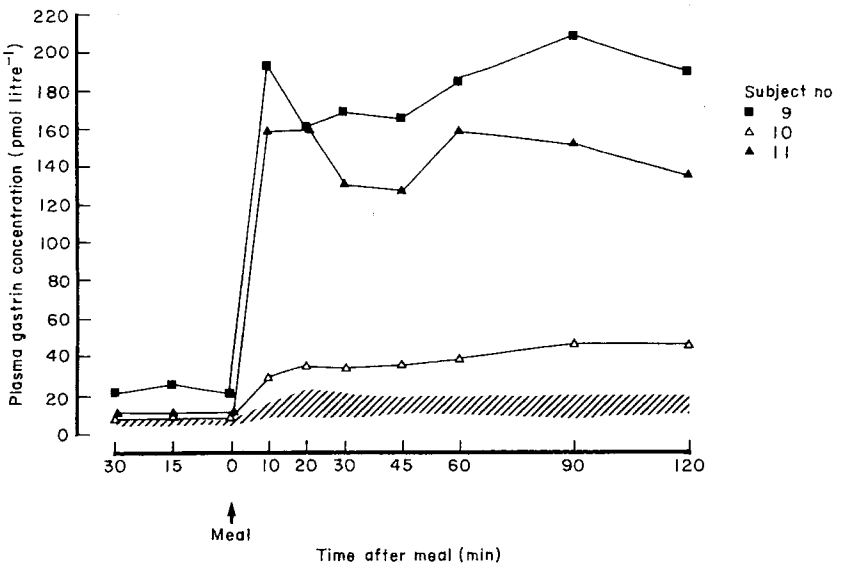

Figure 6. Plasma gastrin concentrations in response to a test meal in eight healthy subjects. Individual values are shown for three subjects who were Asians, values which are within the shaded area are those for five subjects who were Europeans. (■) Subject no. 9; (△) subject no. 10; (▲) subject no. 11. All values for subjects nos 2, 4, 7, 8 and 13 are within the shaded area.

Fasting plasma gastrin concentration

Fasting plasma gastrin concentrations in the placebo group were at a constantly low level, ranging between 1 and 8 pmol litre^{-1} throughout the study (shaded area in Figure 5). As can be seen in Figure 5, all subjects in the omeprazole group had a rise in fasting plasma gastrin concentration when measured 24 hours after the last dose of omeprazole ($P < 0.01$). It can also be seen that the three subjects who had the highest fasting plasma gastrin concentrations before treatment (nos 9, 10, 11) showed a marked rise in gastrin concentration 24 hours after the last dose of omeprazole. These subjects were of Asian origin, while the remaining subjects were Europeans. One week after the last dose, two of the subjects (nos 9 and 11) still had a plasma gastrin concentration above the pretreatment level. After an additional week, only one of these two subjects (no. 11) had a higher gastrin concentration than before treatment; this value remained slightly above the pretreatment value on the subsequent two tests.

Postprandial plasma gastrin concentration

All eight subjects showed an increase in plasma gastrin concentration in response to the test meal, but the magnitude of the response varied greatly. Two of the three subjects (nos 9 and 11), who showed a marked rise in fasting gastrin concentration during omeprazole treatment, had an exaggerated postprandial gastrin response (Figure 6). The third subject (no. 10) had a more pronounced response to the meal than the remaining five subjects. His gastrin concentration in response to the meal was, unlike the other seven subjects, lower than that observed under fasting conditions during omeprazole treatment.

Tolerance

No adverse experience was reported by any of the subjects and none was observed by the investigators. No clinically significant change in routine haematological and biochemical variables was observed.

DISCUSSION

Gastrin has been shown to have a trophic effect on the gastrointestinal mucosa in animals and man. Studies in rats have shown that repeated administration of gastrin as well as pentagastrin produces parietal cell hyperplasia.[5,7] Mucosal hyperplasia has been observed, with an increased parietal cell count and increased acid secretion capacity in hypergastrinaemic patients with the Zollinger–Ellison syndrome.[8] These patients usually have a fasting serum gastrin concentration that is at least three times that found in normal individuals.[9] A close correlation between the number of parietal cells and the maximal acid output has been demonstrated.[10] On this basis we have assessed the maximal acid response to pentagastrin using the peak acid output as a measure of the parietal cell mass.

In the present study we searched for evidence of gastric acid hypersecretion between 1 and 8 weeks after cessation of treatment, as it was already known that in healthy volunteers there is no evidence of hypersecretion in the first 11 days—a time when normal gastric secretion is gradually recovering from omeprazole inhibition.[2]

The present study shows that once-daily treatment with omeprazole causes a profound inhibition of peak acid output with a simultaneous increase in the fasting plasma gastrin concentration. This agrees with the general concept that a lower acidity in the gastric antrum results in a less restrained gastrin release from the antrum.[11] A previous study gives further support to the idea that the increase in gastrin concentration during omeprazole treatment is due to decreased antral acidity with no direct action on the G-cells: when intragastric acidity was kept constant (pH 5.5) by intragastric titration there was no change in peptone-induced gastrin release despite a pronounced inhibition of acid output.[12]

In the present study it was found that 1 week after cessation of treatment with omeprazole both peak acid output and gastrin fell promptly. This is in agreement with a previous study in which the peak acid output and fasting serum gastrin concentration were studied for only 11 days after 4 weeks of treatment with omeprazole.[2] As we found no increase of gastric acid output at any time after cessation of treatment with omeprazole, it appears that the increased plasma gastrin concentration during two weeks of treatment does not induce parietal cell hyperplasia.

Three of the subjects had much higher fasting plasma gastrin concentrations and a slightly higher inhibition of peak acid output during omeprazole treatment than the other subjects. Their fasting gastrin concentrations were also higher before treatment, but their pretreatment peak acid output values were in the same range as the other subjects'. In order to find a possible explanation for these

variations, we studied the postprandial plasma gastrin response without any omeprazole treatment. Food has a direct stimulant effect on the G-cells in addition to its buffering of the gastric contents; it decreases the intragastric acidity and thereby promotes a less restrained gastrin release. Consequently, one should expect a higher gastrin concentration in response to a meal than under conditions when the only factor affecting the gastrin release is a decreased antral acidity. This observation was also made in all but one (no. 10) of the subjects when the postprandial gastrin concentrations were compared to the fasting gastrin concentrations measured during omeprazole treatment. The three subjects who showed the highest fasting gastrin concentrations during omeprazole treatment also showed the highest postprandial gastrin concentrations. It is uncertain why subject no. 10 had higher fasting gastrin concentrations during omeprazole treatment compared with the postprandial concentrations after the meal stimulation. One possible explanation might be that this test meal was not an optimal combination of acid neutralizing capacity and amino acid stimulation for all subjects, causing an underestimation of the capacity to release gastrin.

The three subjects who had much higher gastrin concentrations both in response to the test meal and during omeprazole treatment were all Asians, whereas the other subjects were Europeans. One report has shown that there are differences between some races: The Southwestern American Indians have much higher fasting and postprandial plasma gastrin concentrations than Caucasians.[13] Another report found no difference in fasting or postprandial gastrin concentrations between Scots and Chinese, but these subjects did not receive identical meals.[14]

The present study indicates that after 2 weeks of treatment with omeprazole there is no increase in the healthy human stomach's capacity to secrete acid. Thus it would appear that the rise in the plasma gastrin concentration during short-term treatment with omeprazole does not induce parietal cell hypertrophy or hyperplasia.

REFERENCES

1 Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. Gut 1983; 24: 270–6.

2 Müller von P, Seitz H K, Simon B, Dammann H G, Feurle G, Huefner M, Lichtwald K, Schmidt-Gayk H. Vierwöchige Omeprazol-Gabe: Einfluss auf Säureverhalten und basale Hormonspiegel. Z Gastroenterologie 1984; 22: 236–40.

3 Sharma B K, Walt R P, Pounder R E, Gomes M De F A, Wood E C, Logan L H. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. Gut 1984; 25: 957–64.

4 Festen H P M, Thijs J C, Lamers C B H W, Jansen J M B J, Pals G, Frants R R, Défize J, Meuwissen S G M. Effect of oral omeprazole on serum gastrin and serum pepsinogen I levels. Gastroenterology 1984; 87: 1030–4.

5 Crean G P, Marshall M W, Rumsey R D E. Parietal cell hyperplasia induced by the administration of pentagastrin (ICI 50, 123) to rats. Gastroenterology 1969; 57: 147–55.

6 Bryant M G, Adrian T E. Gastrin. In: Bloom S R and Long R G, eds. Radioimmunoassay of gut regulatory peptides. Philadelphia: W B Saunders, 1982: 51–9.

7 Johnson L R, Aures D, Håkansson R. Effect

of gastrin on the in vivo incorporation of ^{14}C-leucine into protein of the digestive tract. Proc Soc Exp Biol Med 1969; 132: 996–8.

8 Gregory R A, Grossman M I, Tracy H J, Bentley P H. Nature of the gastric secretagogue in Zollinger–Ellison tumours. Lancet 1967; ii: 543–4.

9 McGuigan J E. The Zollinger–Ellison syndrome. In: Sleisenger M C, Fordtran J S, eds. Gastrointestinal disease. Philadelphia: W B Saunders, 1978: 860–75.

10 Card W I, Marks I N. The relationship between the acid output of the stomach following "maximal" histamine stimulation and the parietal cell mass. Clin Sci 1960; 19: 147–63.

11 Peters M N, Feldman M, Walsh J H, Richardsson C T. Effect of gastric alkalinization on serum gastrin concentrations in humans. Gastroenterology 1983; 85: 35–9.

12 Londong W, Londong V, Cederberg C, Steffen H. Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. Gastroenterology 1983; 85: 1373–8.

13 Sasaki H, Nagulesparan M, Samloff M, Straus E, Sievers M L, Dubois A. Low acid output in Pima Indians. A possible cause for the rarity of duodenal ulcer in this population. Dig Dis Sci 1984; 29: 785–9.

14 Lam S K, Hasan M, Sircus W, Wong J, Ong G B, Prescott R J. Comparison of maximal acid output and gastrin response to meals in Chinese and Scottish normal and duodenal ulcer subjects. Gut 1980; 21: 324–8.