Gastric ulcers with and without associated duodenal ulcer have different pathophysiology

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Summary
1. Maximal acid output after pentagastrin stimulation, and fasting and postprandial serum gastrin concentrations were determined in 25 normal subjects, 30 patients with corpus gastric ulcers, 10 patients with prepyloric ulcers and 30 patients with both duodenal and gastric ulcers.

2. Corpus ulcers and prepyloric ulcers formed one distinct group. Maximal acid output was abnormally low in the corpus ulcer patients and no different from normal in prepyloric ulcer patients, whereas fasting serum gastrin and postprandial integrated gastrin response was abnormally high in the former and no different from the normal in the latter. Furthermore, as in the normal subjects, a significant negative correlation between maximal acid output expressed in mmol h⁻¹ kg⁻¹ body weight and postprandial integrated gastrin response was observed in the corpus and prepyloric ulcer patients taken as a group.

3. In complete contrast patients with both duodenal and gastric ulcers, in whom postprandial integrated gastrin response was statistically highest amongst the three types of gastric ulcers, had a significantly positive correlation between maximal acid output and the integrated gastrin response.

4. These findings suggest the operation of different pathophysiological mechanisms in gastric ulcers with and without associated duodenal ulcers.

Key words: gastric ulcer, integrated gastrin responses, maximal acid output, pentagastrin.

Abbreviation: EG, integrated gastrin response.

Introduction
Fasting serum gastrin (Trudeau & McGuigan, 1971; Korman, Soveny & Hansky, 1972; Wesdorp & Fischer, 1974; Petersen, Schrumpf & Myren, 1975) and meal-stimulated serum gastrin (Korman et al., 1972) have been shown to be higher in patients with gastric ulcers than in normal subjects. Gastrin secretion in gastric ulceration is generally believed to be secondary to the degree of gastric acidity, the relationship being an inverse one (Walsh & Grossman, 1975). However, studies so far (Trudeau & McGuigan, 1971; Wesdorp & Fischer, 1974; Petersen et al., 1975) have attempted only to relate the fasting serum gastrin to gastric acidity as measured in the basal state, or after submaximal stimulation with pentagastrin or histamine.

In normal subjects and patients with liver cirrhosis (Byrnes, Lam & Sircus, 1976; Lam, 1976), a significant inverse relationship was observed between the integrated gastrin response to a standard protein meal and maximal acid output. In duodenal ulcer subjects, however, a significant inverse correlation between postprandial integrated gastrin response and maximal acid output was not obtained, but the subjects with normal acid secretion had a significantly higher gastrin response than the acid hypersecretors (Byrnes et al., 1976; Fritsch, Housemen & Rick, 1976; Lam & Sircus, 1976). Johnson (1965) described three groups of gastric ulcers: type I were ulcers of the body of the stomach (here referred to as corpus ulcers) associated with hyposecretion of acid; type II were gastric ulcers associated with duodenal ulcers or duodenal ulcer scar; type III were prepyloric...
Ulcers. Both types II and III have normal or hyper-secretion of acid.

The relationship between the postprandial gastrin response and maximum acid output in these three types of gastric ulcers may be important in the understanding of their pathophysiology. This forms the basis of the present study.

Methods

Subjects (Table 1)

Gastric ulcer patients. A series of 70 patients with gastric ulcers was studied. All had their gastric ulcers (and associated duodenal ulcers, if any) demonstrated by radiology and endoscopy, and the gastric ulcers were shown to be benign by endoscopy and multiple biopsies. Ten patients had ulcers situated immediately proximal to the pyloric opening (prepyloric ulcers). Thirty ulcers were found elsewhere in the stomach and were designated corpus ulcers. Of these 18 were located at the angulus incisura, seven were situated higher up on the lesser curve, and five were found on the posterior wall. An associated duodenal ulcer was present in 30 patients. The duodenal ulcers were all active at endoscopy. Of these 30 patients, nine had prepyloric ulcers, 15 ulcers occurring at the incisura and six had lesser-curve ulcers proximal to the incisura.

Control subjects. These consisted of 15 healthy doctors and nurses as well as 10 patients from the general medical wards who had recovered from an unrelated illness, e.g. pneumothorax, who had no past history of ulcer dyspepsia and in whom all medications had been withdrawn for at least 2 days.

All subjects studied were Chinese, and all gave informed consent for the study. The study was approved by the Committee on Higher Degrees and Research Grants, University of Hong Kong.

Gastrin study

Fasting commenced at 20.00 hours, and on the following morning, at 09.00 hours, a slow intravenous infusion of sodium chloride solution (150 mmol/l) was started. After the subject had rested for 15 min the first blood sample was taken (zero - 15 min) and 15 min later (zero time) a further sample was taken, subsequent to which the patient ate a standardized meal consisting of 50 g of protein, 40 g of carbohydrate and 40 g of fat in the form of a milk drink (60 g of Sustagen in 60 ml of milk) and Chinese style rice congee (130 g of minced beef in 240 ml of plain congee with 5 ml of cooking oil). Further blood samples were taken at 15, 30, 45, 60, 90 and 120 min after the commencement of the meal. Each sample was stored immediately at 4°C. The serum from all samples was extracted by centrifugation immediately at the end of the test and stored at -20°C for subsequent radioimmunoassay of gastrin.

Maximal acid output

On a separate day, after an overnight fast, all subjects had their maximal acid output measured, i.e. the total acid output in the hour after an intramuscular injection of 6 μg of pentagastrin/kg total body weight (Baron, 1973). The output was expressed as mmol/kg total body weight as in this way the differences of this value between the sexes (Lam & Sircus, 1975) and between the different ethnic groups (Lam, 1975) could be substantially decreased.

Serum gastrin

Gastrin estimations by radioimmunoassay were performed in duplicate with a modification of the method of Yalow & Berson (1970). The details of the assay have been previously reported (Byrnes et al., 1976; Lam & Lai, 1976). Sensitivity was below 2.5 pmol/l of serum. Within assay and between assay coefficients of variation were 6-2 and 13% respectively. The antiserum reacted equally with G-13, G17, G-34 and 'big big' gastrin.

The integrated gastrin response after the standard meal (ΣG) of each subject was derived by computing the total area under the response curve from zero to 120 min.

Statistical analysis

For comparison of the two samples, Wilcoxon's non-parametric test (Documenta Geigy, 1970) was used. Correlation of two samples was performed by Spearman's non-parametric rank correlation (Documenta Geigy, 1970). Values are given as mean ± SD.

Results

The mean age and sex distribution of the gastric ulcer patients were closely similar to the normal control subjects (Table 1). Patients with corpus ulcers had a significantly lower mean maximum
Acid and gastrin in gastric ulcer

**TABLE 1. Age (mean ± SD) and sex distributions of patients and control subjects**

Age differences not significant: (1) vs (5); (2) vs (5); (3) vs (5); (4) vs (5).

<table>
<thead>
<tr>
<th></th>
<th>Corpus (1)</th>
<th>Duodenal ulcer associated (2)</th>
<th>Prepyloric (3)</th>
<th>Total (4)</th>
<th>Normal subjects (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>30</td>
<td>30</td>
<td>10</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.8 ± 16-0</td>
<td>50.4 ± 16-0</td>
<td>50.8 ± 12.7</td>
<td>49.7 ± 15.3</td>
<td>47.5 ± 15.1</td>
</tr>
<tr>
<td>Males</td>
<td>23</td>
<td>22</td>
<td>8</td>
<td>53</td>
<td>19</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

**TABLE 2. Maximal acid output after pentagastrin stimulation**

Mean values ± SD are shown. Significance of differences (P): <0.05, a(1) vs a(5), a(1) vs a(2), a(1) vs a(3), b(1) vs b(5), b(1) vs b(3); <0.01, b(2) vs b(5). Not significant: a(2) vs a(5), a(3) vs a(5), a(4) vs a(5), a(2) vs a(3), b(3) vs b(5), b(4) vs b(5), b(1) vs b(2), b(2) vs b(3).

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<th>Normal subjects (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal acid output mmol/h</td>
<td>30</td>
<td>30</td>
<td>10</td>
<td>70</td>
<td>25</td>
</tr>
<tr>
<td>(a)</td>
<td>9.7 ± 6.4</td>
<td>15.9 ± 6.2</td>
<td>16.8 ± 8.0</td>
<td>13.4 ± 7.2</td>
<td>14.1 ± 4.9</td>
</tr>
<tr>
<td>mmol h⁻¹ kg⁻¹ total body wt. (b)</td>
<td>0.20 ± 0.13</td>
<td>0.32 ± 0.13</td>
<td>0.34 ± 0.12</td>
<td>0.27 ± 0.14</td>
<td>0.28 ± 0.07</td>
</tr>
</tbody>
</table>

**TABLE 3. Fasting and postprandial peak and postprandial integrated gastrin response (ΣG)**

Mean values ± SD are shown. Significance of differences (P):

- a(1) vs a(3) < 0.05
- b(1) vs b(5) < 0.05
- c(1) vs c(2) < 0.05
- a(1) vs a(5) < 0.01
- b(2) vs b(5) < 0.01
- c(1) vs c(3) < 0.05
- a(2) vs a(3) < 0.01
- b(1) vs b(3) < 0.05
- c(1) vs c(5) < 0.01
- a(4) vs a(5) < 0.01
- b(2) vs b(3) < 0.01
- c(2) vs c(5) < 0.01
- c(4) vs c(5) < 0.01

Not significant: a(3) vs a(5), a(1) vs a(2), b(1) vs b(2), b(3) vs b(5), b(4) vs b(5), c(3) vs c(5).

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<th>Prepyloric (3)</th>
<th>Total (4)</th>
<th>Normal subjects (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting (pmol/l) (a)</td>
<td>30</td>
<td>49.6 ± 7.0</td>
<td>48.3 ± 4.9</td>
<td>45.7 ± 3.8</td>
<td>25.6 ± 2.7</td>
</tr>
<tr>
<td>Peak (pmol/l) (b)</td>
<td>30</td>
<td>93.1 ± 9.6</td>
<td>117.3 ± 9.9</td>
<td>97.8 ± 6.5</td>
<td>59.2 ± 4.5</td>
</tr>
<tr>
<td>Σ G (nmol min⁻¹ ml⁻¹) (c)</td>
<td>10</td>
<td>12.2 ± 1.1</td>
<td>5.0 ± 0.7</td>
<td>9.8 ± 0.7</td>
<td>5.1 ± 0.4</td>
</tr>
</tbody>
</table>

Acid output than the control subjects, whether this was expressed in mmol/h (P = 0.05) or in mmol h⁻¹ kg⁻¹ total body weight (P < 0.05) (Table 2). The mean outputs in patients with both duodenal and gastric ulcers and those with prepyloric ulcers approximated to those of the control subjects, but were significantly higher than those of the corpus ulcer group.

In patients with gastric ulcers the mean fasting serum gastrin and postprandial integrated gastrin response (ΣG) values were both significantly higher (P < 0.01) than values for the control subjects. The mean peak serum gastrin values, however, were not statistically different (Table 3, Fig. 1). When the patients were subdivided, the mean fasting and peak serum gastrin values in patients with corpus
Fasting and postprandial serum gastrin concentrations in 10 patients with prepyloric ulcers (---), 30 with corpus ulcers (-----) and 30 with duodenal ulcers associated with gastric ulcers (---). Mean values ± SEM are shown. PM, Protein meal.

There was no significant correlation between maximal acid output as expressed in mmol/h and ΣG in the control subjects, but a significant correlation was obtained when the output was expressed as mmol h⁻¹ kg⁻¹ total body weight (Fig. 2). No correlation between maximal acid output and ΣG was found in the gastric ulcer patients taken as a whole (r = 0.02) (Fig. 3). However, a significant negative correlation between maximal acid output in mmol h⁻¹ kg⁻¹ and ΣG was observed in the patients with corpus ulcers and prepyloric ulcers, taken as a group. In addition a significant positive correlation was seen in those patients with both duodenal and gastric ulcers.

**Discussion**

As noted previously the maximal acid output of the Chinese normal control subjects in our study (mean value = 14.1 ± 4.9 mmol/h) is smaller than that found in occidentals (Fung, 1970; Cheng, Lam & Ong, 1977). However, when the maximum acid output is expressed in relation to total body weight, the present value of 0.28 ± 0.07 mmol h⁻¹ kg⁻¹ for Chinese patients is closely similar to that in Scottish patients (0.30 ± 0.01 mmol h⁻¹ kg⁻¹; Lam & Sircus, 1975). Maximal acid output is also related to body height (Hobsley, Whitfield, Faber & Parkin, 1975) and lean body mass (Baron, 1969). We have chosen to examine only the body-weight factor as this is convenient mathematically and as Chinese patients with peptic ulcer do not tend to be obese (Cheng et al., 1977).

This study shows that patients with corpus ulcers, in whom acid hyposecretion is present, have higher fasting and postprandial gastrin values than those with prepyloric ulcers, in whom acid secretion is normal. This inverse relationship is further substantiated by a significant negative correlation...
between the maximum acid output and the integrated gastrin response in these two groups of patients with gastric ulcers. In complete contrast, a positive correlation between these two variables is present in patients with both duodenal and gastric ulcers (Fig. 3). Furthermore these last-named patients have a significantly higher postprandial integrated gastrin response than patients with corpus or prepyloric ulcers. All these suggest that the duodenal-gastric ulcers are pathophysiologically distinct from corpus and prepyloric ulcers.

It has been observed that the maximal acid output is an accurate index of the gastric parietal cell mass (Card & Marks, 1960; Cheng et al., 1977). The serum gastrin response to a large ‘protein’ meal in normal subjects and in duodenal ulcer subjects has been claimed to be an index of the functioning gastrin cell mass (Hansky & Korman, 1973; Feurle, Katlerer, Becker & Cretzfeldt, 1972; Byrnes et al., 1976) and this is strongly supported by the close correlation between the gastrin cell counts obtained by using immunofluorescence on gastric biopsies obtained endoscopically, and the postprandial gastrin values (Asnaes, Bjerregaard, Malmstrom, Hansen, Hardt & Johansen, 1976). An inverse relationship between maximal acid output and integrated gastrin response to a standard ‘protein’ meal has been demonstrated in normal subjects (Byrnes et al., 1976; Lam, 1976), which is further substantiated in our study (Fig. 2). It is highly suggestive, therefore, that an inverse relationship normally exists between the functioning parietal cell mass and the gastrin cell mass. Furthermore, our study shows that this relationship holds true in gastric ulceration unassociated with duodenal ulcer. Anatomical support for this dependence of the gastrin cell mass on the parietal cell mass in gastric ulcer disease is provided by the inverse relationship between the area of the stomach covered by cells secreting acid and pepsin and that bearing mucosa of antral structure (Capper, Butler, Buckler & Hallett, 1966; Du Plessis, 1965).

One hypothesis concerning the pathogenesis of gastric ulceration emphasizes the importance of bile reflux and subsequent atrophic gastritis (Du Plessis, 1965; Rhodes, Barnardo, Phillips, Rovelstad & Hofmann, 1969). This could apply to the group with corpus and prepyloric ulcers, in which an inverse relationship between acid and gastrin secretion is present. This inverse relationship between gastrin release and gastric acidity has been described in atrophic gastritis (Ganguli, Cullen & Irvine, 1971; Strickland, Bhatkal, Korman & Hansky, 1971). However, this is a complex problem, as it has been observed that bile salts stimulate the release of gastrin from the canine antrum (Bedi, Wasunna & Gillespie, 1969), yet on the other hand the involvement of the antrum by gastritis may reduce antral gastrin secretion (Lam, Sircus & Byrnes, 1976). In patients with both duodenal and gastric ulcers a higher gastrin secretion is associated with a higher acid secretion. The gastric ulceration could be related to a defect in the pyloric emptying mechanism with subsequent high gastrin release and high acid secretion (Burge, 1966; Dragstedt & Woodward, 1970).

Acknowledgment

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References


