Effect of selective gastric vagotomy on histamine concentration in gastric mucosa of patients with duodenal ulcer

H. TROIDL, H. ROHDE, W. LORENZ, G. HÄFNER AND H. HAMELMANN*

SUMMARY
In a prospective controlled trial, histamine concentrations in human gastric mucosa were determined fluorometrically in 23 patients 6–11 months after selective gastric vagotomy with drainage and in patients who had undergone other types of operation for duodenal ulcer. The study was in two parts: part 1, a synchronous investigation of mucosal histamine concentrations in patients who had undergone vagotomy, in duodenal ulcer patients before operation and in control subjects; part 2, a consecutive study of the same patients before and after vagotomy.

In part 1, patients with Hollander-negative vagotomy were found to have significantly higher mucosal histamine concentrations than ‘healthy’ control subjects or duodenal ulcer patients before operation. Patients with recurrent ulcer, however, had as low mucosal histamine concentrations as duodenal ulcer patients who had not been operated on. In part 2, all duodenal ulcer patients showed an increase in gastric mucosal histamine concentration after vagotomy (P<0.01). The smallest increase was in a patient with an incomplete vagotomy. Control patients who were not operated on but who underwent endoscopy and biopsy twice in the period of investigation, did not show any increase in mucosal histamine concentration between the times of the first and the second biopsy. The overall results of selective vagotomy and drainage in this study, with respect both to clinical Visick gradings and to radiological and acid secretory findings, were comparable to those reported by other authors. No significant change in numbers of patients operated on was found after vagotomy. Thus, selective gastric vagotomy with a drainage procedure leads to increased concentrations of histamine in the mucosa of the body of the stomach in man. The mechanism is not clear, but might be through inhibition of histamine release from mast cell stores.

A remarkable feature of several review articles on the pathological functions of histamine published in the past 15 years has been that a relationship of this substance to peptic ulceration has either not been mentioned at all, or else has been considered to be of only minor significance (Dunér and Pernow, 1960; Code et al., 1964; Lindell and Westling, 1966). There were several reasons for this; for example, although gastric ulcers were produced in rats by subcutaneous injections of histamine (Buchner et al., 1928) and duodenal ulcers were produced in dogs by intramuscular histamine in beeswax (Varco et al., 1941), it became increasingly evident that the clinical counterparts in man of these observations in animals were more in the form of acute haemorrhagic lesions (stress ulcers) than of chronic duodenal ulcers (Lorenz and Feifel, 1970; Seidel et al., 1973a; Lorenz et al., 1974). Secondly, attempts to correlate changes in the histamine content of whole blood, gastric juice and tissue with the occurrence or prevalence of peptic ulcer yielded conflicting results. Thus, the finding of elevated blood histamine concentrations in patients with florid duodenal ulcer (Riboli, 1940; Parrot et al., 1943) was thought to be due to increased mobilization of stored histamine (Guggenheim, 1951). However, these observations either could not be confirmed (Shimkin et al., 1943) or else seemed to be true for only a minority of patients (Lips et al., 1947; Surkes, 1948). We know that the histamine content of whole blood is a poor index of histamine release in man (Lorenz et al., 1972). In a small number of patients, Smith (1959) found no difference in the histamine content of gastric body mucosa when he compared duodenal ulcer patients with patients who had gastric carcinoma. Similarly, Borbola et al. (1951) were unable to detect significant differences between the histamine concentrations in the gastric juice of control subjects and that of patients with duodenal ulcer. A special case—but none the less remarkable—was the finding of increased urinary excretion of histamine in patients with the Zollinger–Ellison syndrome (Dotevall et al., 1963; Dotevall and Walan, 1970). This finding did not apply to duodenal ulcer patients in general (Björöd, 1963). Finally, studies on mucosal histamine formation did not show any significant difference between patients with duodenal ulcer and those with gastric carcinoma (Lindell and Westling, 1966). Thus, until recently, the hypothesis that histamine was involved in human peptic ulcer disease lacked corroborative evidence.

Two observations which have been made quite recently, however, have put histamine back into the reckoning. First, histamine H₂-receptor antagonists were shown to heal peptic ulcers in man (International Multicentre Trial, 1975); secondly, storage and inactivation of histamine in the acid-producing gastric mucosa of duodenal ulcer patients were shown to be different from storage and inactivation in control subjects (Troidl et al., 1976a; Barth et al., 1977).

Since vagotomy is known to reduce gastric acid secretion, we decided to investigate the effect of vagotomy on the histamine stores in the mucosa of the body of the stomach in man. Preliminary reports of this work have already been published (Troidl et al., 1975a, 1976b).

Patients and methods
Design and protocols of the study
Tissue histamine content, especially the histamine content of gastric mucosa, is influenced by numerous genetic, humoral and environmental factors (Lorenz and Pfleger, 1968; Lorenz and Feifel, 1970; Seidel et al., 1973a; Lorenz et al., 1974). Secondly, attempts to correlate changes in the histamine content of whole blood, gastric juice and tissue with the occurrence or prevalence of peptic ulcer yielded conflicting results. Thus, the finding of elevated blood histamine concentrations in patients with florid duodenal ulcer (Riboli, 1940; Parrot et al., 1943) was thought to be due to increased mobilization of stored histamine (Guggenheim, 1951). However, these observations either could not be confirmed (Shimkin et al., 1943) or else seemed to be true for only a minority of patients (Lips et al., 1947; Surkes, 1948). We know that the histamine content of whole blood is a poor index of histamine release in man (Lorenz et al., 1972). In a small number of patients, Smith (1959) found no difference in the histamine content of gastric body mucosa when he compared duodenal ulcer patients with patients who had gastric carcinoma. Similarly, Borbola et al. (1951) were unable to detect significant differences between the histamine concentrations in the gastric juice of control subjects and that of patients with duodenal ulcer. A special case—but none the less remarkable—was the finding of increased urinary excretion of histamine in patients with the Zollinger–Ellison syndrome (Dotevall et al., 1963; Dotevall and Walan, 1970). This finding did not apply to duodenal ulcer patients in general (Björöd, 1963). Finally, studies on mucosal histamine formation did not show any significant difference between patients with duodenal ulcer and those with gastric carcinoma (Lindell and Westling, 1966). Thus, until recently, the hypothesis that histamine was involved in human peptic ulcer disease lacked corroborative evidence.

Two observations which have been made quite recently, however, have put histamine back into the reckoning. First, histamine H₂-receptor antagonists were shown to heal peptic ulcers in man (International Multicentre Trial, 1975); secondly, storage and inactivation of histamine in the acid-producing gastric mucosa of duodenal ulcer patients were shown to be different from storage and inactivation in control subjects (Troidl et al., 1976a; Barth et al., 1977).

Since vagotomy is known to reduce gastric acid secretion, we decided to investigate the effect of vagotomy on the histamine stores in the mucosa of the body of the stomach in man. Preliminary reports of this work have already been published (Troidl et al., 1975a, 1976b).

Patients and methods
Design and protocols of the study
Tissue histamine content, especially the histamine content of gastric mucosa, is influenced by numerous genetic, humoral and environmental factors (Lorenz and Pfleger, 1968; Lorenz and Feifel, 1970; Seidel et al., 1973a; Lorenz et al., 1974). Secondly, attempts to correlate changes in the histamine content of whole blood, gastric juice and tissue with the occurrence or prevalence of peptic ulcer yielded conflicting results. Thus, the finding of elevated blood histamine concentrations in patients with florid duodenal ulcer (Riboli, 1940; Parrot et al., 1943) was thought to be due to increased mobilization of stored histamine (Guggenheim, 1951). However, these observations either could not be confirmed (Shimkin et al., 1943) or else seemed to be true for only a minority of patients (Lips et al., 1947; Surkes, 1948). We know that the histamine content of whole blood is a poor index of histamine release in man (Lorenz et al., 1972). In a small number of patients, Smith (1959) found no difference in the histamine content of gastric body mucosa when he compared duodenal ulcer patients with patients who had gastric carcinoma. Similarly, Borbola et al. (1951) were unable to detect significant differences between the histamine concentrations in the gastric juice of control subjects and that of patients with duodenal ulcer. A special case—but none the less remarkable—was the finding of increased urinary excretion of histamine in patients with the Zollinger–Ellison syndrome (Dotevall et al., 1963; Dotevall and Walan, 1970). This finding did not apply to duodenal ulcer patients in general (Björöd, 1963). Finally, studies on mucosal histamine formation did not show any significant difference between patients with duodenal ulcer and those with gastric carcinoma (Lindell and Westling, 1966). Thus, until recently, the hypothesis that histamine was involved in human peptic ulcer disease lacked corroborative evidence.

Two observations which have been made quite recently, however, have put histamine back into the reckoning. First, histamine H₂-receptor antagonists were shown to heal peptic ulcers in man (International Multicentre Trial, 1975); secondly, storage and inactivation of histamine in the acid-producing gastric mucosa of duodenal ulcer patients were shown to be different from storage and inactivation in control subjects (Troidl et al., 1976a; Barth et al., 1977).

Since vagotomy is known to reduce gastric acid secretion, we decided to investigate the effect of vagotomy on the histamine stores in the mucosa of the body of the stomach in man. Preliminary reports of this work have already been published (Troidl et al., 1975a, 1976b).
Table I: DETAILS OF PATIENTS

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Operation and endoscopy</th>
<th>Interval between Op. and E (mth)</th>
<th>Diagnosis</th>
<th>History</th>
<th>Demonstration of ulcer</th>
<th>Overall results (Visick)</th>
<th>Earlier or concomitant diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>56</td>
<td>170</td>
<td>SV+F</td>
<td>5.1.73</td>
<td>DU</td>
<td>20</td>
<td>(+)</td>
<td>II</td>
<td>Pyloric stenosis*</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>74</td>
<td>170</td>
<td>SV+HM</td>
<td>29.1.73</td>
<td>DU</td>
<td>20</td>
<td>+</td>
<td>I</td>
<td>Glomeronephritis (1932)</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>62</td>
<td>160</td>
<td>SV+HM</td>
<td>8.12.72</td>
<td>DU</td>
<td>5</td>
<td>+</td>
<td>I</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>87</td>
<td>182</td>
<td>SV+HM</td>
<td>16.2.73</td>
<td>DU</td>
<td>6</td>
<td>+</td>
<td>I</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>69</td>
<td>165</td>
<td>SV+GE</td>
<td>16.10.72</td>
<td>DU</td>
<td>13</td>
<td>+</td>
<td>I</td>
<td>Pyloric stenosis*</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>98</td>
<td>185</td>
<td>SV+HM</td>
<td>12.3.73</td>
<td>DU, RDU</td>
<td>5 (+)</td>
<td>(+)</td>
<td>II</td>
<td>Carcinoid, hemicolectomy (1967)</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>75</td>
<td>168</td>
<td>SV+HM</td>
<td>9.2.73</td>
<td>DU, RDU</td>
<td>12</td>
<td>+</td>
<td>IV</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>68</td>
<td>175</td>
<td>SV+HM</td>
<td>15.1.73</td>
<td>DU</td>
<td>2</td>
<td>n.d.</td>
<td>IV</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>63</td>
<td>174</td>
<td>2/3, BI</td>
<td>7.10.63</td>
<td>RUJ</td>
<td>1</td>
<td>+</td>
<td>IV</td>
<td>Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>50</td>
<td>174</td>
<td>SV+Res, Res, BI</td>
<td>28.5.73</td>
<td>DU, RUJ</td>
<td>1</td>
<td>+</td>
<td>IV</td>
<td>Postoperative insufficiency of anastomosis</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>104</td>
<td>176</td>
<td>TG</td>
<td>5.7.71</td>
<td>DU, GU</td>
<td>6</td>
<td>+</td>
<td>I</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>62</td>
<td>168</td>
<td>2/3, BI</td>
<td>25.4.67</td>
<td>GU, RUJ</td>
<td>19</td>
<td>+</td>
<td>II</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>37</td>
<td>87</td>
<td>187</td>
<td>TV+F</td>
<td>8.10.75</td>
<td>DU, RDU</td>
<td>7</td>
<td>0</td>
<td>IV</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>41</td>
<td>50</td>
<td>155</td>
<td>SV+AT (BI)</td>
<td>13.11.72</td>
<td>DU</td>
<td>18</td>
<td>+</td>
<td>I</td>
<td>Hepatitis (1968) Pyloric stenosis (1972)*</td>
</tr>
<tr>
<td>Part 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>31</td>
<td>66</td>
<td>172</td>
<td>SV+HM</td>
<td>15.6.73</td>
<td>DU</td>
<td>15</td>
<td>+</td>
<td>I</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>44</td>
<td>57</td>
<td>161</td>
<td>SV+HM</td>
<td>18.6.73</td>
<td>DU</td>
<td>12</td>
<td>+</td>
<td>II</td>
<td>Diabetes, emphysema (1968)</td>
</tr>
<tr>
<td>17</td>
<td>35</td>
<td>53</td>
<td>159</td>
<td>SV+HM</td>
<td>13.6.73</td>
<td>DU</td>
<td>15</td>
<td>+</td>
<td>II</td>
<td>None</td>
</tr>
<tr>
<td>18</td>
<td>28</td>
<td>71</td>
<td>174</td>
<td>SV+HM</td>
<td>8.8.73</td>
<td>DU</td>
<td>3</td>
<td>(+)</td>
<td>II</td>
<td>None</td>
</tr>
<tr>
<td>19</td>
<td>22</td>
<td>79</td>
<td>169</td>
<td>SV+HM</td>
<td>5.10.73</td>
<td>DU</td>
<td>4</td>
<td>+</td>
<td>I</td>
<td>Perforated gastric ulcer; suture only</td>
</tr>
<tr>
<td>20</td>
<td>39</td>
<td>47</td>
<td>166</td>
<td>SV+HM</td>
<td>15.5.73</td>
<td>DU</td>
<td>3</td>
<td>(+)</td>
<td>II</td>
<td>Oesophagitis with ulceration</td>
</tr>
<tr>
<td>21</td>
<td>33</td>
<td>80</td>
<td>169</td>
<td>SV+GE</td>
<td>14.5.73</td>
<td>DU</td>
<td>8</td>
<td>+</td>
<td>I</td>
<td>None</td>
</tr>
</tbody>
</table>

Op., Operation and histological examination; E, endoscopy with histological examination of biopsies; R, radiology; Pat., patient; SV, selective gastric vagotomy; TV, truncal vagotomy; Res., resection; F, Finney pyloroplasty; HM, Heinecke-Miculicz pyloroplasty; GE, gastroenterostomy; TG, total gastrectomy; AT, antrectomy; BI/II, Billroth anastomosis; DU, duodenal ulcer; RUD, recurrent duodenal ulcer; GU, gastric ulcer; RUJ, recurrent ulcer in jejunum. Demonstration of ulcer: +, yes; 0, no; (+) uncertain but probable (e.g. scar); n.d., not determined.

* Pyloric stenosis defined according to Kirk (1970).
Table 1: HISTAMINE CONCENTRATIONS IN CORPUS MUCOSA OF PATIENTS WITH DUODENAL AND GASTRIC ULCER AFTER OPERATION

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Response to insulin</th>
<th>Hollander</th>
<th>Bachrach</th>
<th>SV and recurrent ulcer</th>
<th>1 Sample</th>
<th>2 Sample</th>
<th>3 Sample</th>
<th>X of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>38:0</td>
<td>36:0 24:6</td>
<td>32:9</td>
<td>35:0</td>
<td>37:0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>29:4</td>
<td>37:6 38:0</td>
<td>35:0</td>
<td>37:0</td>
<td>50:2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>35:2</td>
<td>38:4 37:4</td>
<td>37:0</td>
<td>37:0</td>
<td>37:0</td>
<td></td>
</tr>
</tbody>
</table>

Other operative procedures

<table>
<thead>
<tr>
<th>Cases</th>
<th>SV</th>
<th>Hollander</th>
<th>Bachrach</th>
<th>SV and recurrent ulcer</th>
</tr>
</thead>
</table>

'Escape' group

<table>
<thead>
<tr>
<th>Cases</th>
<th>SV</th>
<th>Hollander</th>
<th>Bachrach</th>
<th>SV and recurrent ulcer</th>
</tr>
</thead>
</table>

SV, Selective gastric vagotomy. Response to insulin: +, positive; -, negative; n.d., not determined.

The median value for Cases 1–5 is 51:6 μg/g, for Cases 6–8 35:0 μg/g.

et al., 1973). Since in a study on histamine and vagotony all these factors may act as covariables which are difficult to define and very difficult to control, we used two experimental concepts in the same trial.

Part 1: a synchronous investigation of vagotomized subjects, duodenal ulcer patients before operation and various other groups of subjects acting as controls: In a prospective study, lasting from April to September 1973, biopsies of gastric mucosa were taken for histamine estimation in 100 consecutive patients who were admitted for endoscopy in our gastroenterology unit by physicians not involved in the study (for details see Troidl et al., 1976a). Biopsies were also obtained from 3 patients with recurrent ulcer (Cases 6, 8 and 13, Table 1) who were admitted for endoscopy in September 1973 soon after the prospective study ended. Two of the 103 patients who were operated on were excluded from the trial because of cholecystitis, which has an influence on gastric histamine content (Troidl et al., 1976a) (Table 1).

Part 2: consecutive investigation of the same subjects before and after vagotomy: All duodenal ulcer patients who were included in the prospective study (see above) and who subsequently underwent vagotomy were included in the second part of our trial (Table 1). Thus, in this part of the study control subjects and vagotomized patients were not tested synchronously; but since the patients served as their own controls it was possible to exclude many variables which had not been excluded in the first part of the trial.

The design of the study, which has been described in detail elsewhere (Troidl et al., 1976a), included case history, a clinical questionnaire, oesophagogastroduodenoscopy, pathological examination of the biopsy specimens, radiology of the stomach, intestine and biliary tract, gastric secretory tests (pentagastrin and insulin) and recording of operative findings in patients coming to surgery. The diagnoses were established according to Troidl et al. (1976a) and Rohde et al. (1977). Control subjects and patients were classified according to the present diagnosis, concomitant diseases and previous history (Troidl et al., 1976a). By these criteria, 2 of the patients who had been operated on for peptic ulcer were excluded from the trial (Table 1). To avoid the introduction of bias, the results of the histamine estimations were not recorded until the patients had been finally classified.

Patients

The median male and female patients in the trial included 32 control subjects, 11 patients with duodenal ulcer without subsequent operation, 40 patients with various other abdominal diseases (Troidl et al., 1976a) and 23 patients who underwent operation for duodenal or gastric ulcer (Table 1). Since all patients treated surgically in the trial were male, only the 21 male control subjects and 17 male duodenal ulcer patients (51:4 μg/g) without operation, 7 before operation, Table 1) were considered in the comparison of gastric mucosal histamine concentration. The control subjects were patients with non-specific abdominal complaints who had been found to be 'healthy' with respect to their upper gastrointestinal tract. The duodenal ulcer patients were those in whom the presence of the ulcer was established by endoscopy, radiology and histological examination.

The characteristics of the patients with duodenal and gastric ulcer who were treated by various operations are shown in Table 1. These data on the patients, the operations performed, endoscopic findings and concomitant diseases are given because we know nothing at present about the possible influences of various covariables (Byar et al., 1976) on gastric histamine content in man, but must suspect from the results of experiments in animals that there are many such influences (Lorenz and Pfleger, 1968; Troidl et al., 1976a). Thus, it seemed important to be able to compare the patients whom we studied after operation with patients studied by other authors (Troidl et al., 1975b). Furthermore, the mean reductions in basal and pentagastrin-stimulated acid output in our patients by selective gastric vagotomy with drainage were 52 and 52 per cent respectively, and the incidence of positive Hollander tests was 18 per cent, indicating the outcome to be expected after this type of operation (Troidl et al., 1975b).

Finally, the definition of recurrent ulceration was that used by Weinberg (1964).

Methods

Fluorometric assay of histamine in biopsy specimens: Four samples were taken during endoscopy, 3 for histamine assay and 1 for histological examination. Histamine concentration was determined by a slight modification of our Dowex method (Lorenz et al., 1970) as described by Troidl et al. (1976a). It was expressed as microgrammes of histamine dihydrochloride per gramme wet weight of mucosa. The specificity of the assay was confirmed by fluorescence spectra, formaldehyde and heating test, inactivation of the isolated substance by purified histamine methyltransferase from pig antrum, by purified diamine oxidase from kidney and by reactivity on the isolated guinea-pig ileum (Lorenz et al., 1978). The precision of the entire procedure (sample taking, homogenization and determination of histamine) within the day was 11:6±2:40 (coefficient of variation, VC per cent) in 3 series of 9 experiments when the mean value from 3 biopsies was used for a single estimation. The accuracy of the test was found to be satisfactory by comparing the values obtained by fluorometry with those obtained by bioassay as a 'reference' method (Rohde et al., 1978). A time interval of up to 7 min between the taking of the biopsy and its fixation in 2 ml 1 M HClO₄.
was found to have no influence on tissue histamine concentration.

Accuracy of diagnosis of peptic ulcer: Several problems arose in diagnosing peptic ulcer with the degree of accuracy necessary for the trial (Table I), because the findings at endoscopy, radiology and operation did not always agree. In doubtful cases, the endoscopic and radiological examinations were repeated, and the biopsy specimens taken at preoperative endoscopy and at operation were examined histologically. The final decision on the diagnosis was made in difficult cases on the following grounds (Table I): Case 3 had a positive history with typical symptoms and positive endoscopic and radiological findings, but the findings at operation 3 weeks after the diagnostic procedures were unconvincing. Case 4 was thought not to have recurrent ulceration since, except for radiology, all other findings, including clinical questionnaire, were negative. Case 6 had a good history of ulcer and high acid outputs but an ulcer could not be shown convincingly endoscopically, radiologically or at operation. However, his recurrent ulcer was definite enough! In Case 7 neither the ulcer nor the recurrent ulcer could be identified with certainty at operation, but preoperatively the history and high acid outputs were positive and postoperatively high acid outputs, endoscopy, radiology and history were all positive for ulcer, and yet the patient felt in excellent health (Visick grade 1). The reoperation was performed 2 weeks after the diagnostic procedures. In Case 12 the operation was performed 3 months after the diagnostic procedures. In all patients in this trial, the indications for surgical treatment were the presence of intractable symptoms of ulcer dyspepsia and the demonstration of an ulcer with a sufficient degree of certainty.

Parietal cell counting: This investigation was described by Martini and Schmidt-Wilcke (1975). In addition to the 4 biopsies in our study, 5 specimens were taken, immediately embedded in fresh rat liver and frozen by liquid nitrogen. From each of the biopsies 5 sections were stained by the succinate dehydrogenase reaction (Pearse, 1968) and the parietal cells were counted in 5 areas by the method of Schmidt-Wilcke et al. (1974).

Surgical techniques: Selective gastric vagotomy, Heinecke-Miculicz pyloroplasty and the resections were performed by techniques described by Seidel et al. (1973b). Posterior gastroenterostomy was carried out at the most dependent part of the stomach near the greater curvature, with a short afferent loop.

Statistical methods: Since the gastric mucosal histamine concentrations in duodenal ulcer patients were not normally distributed (Troidl et al., 1976a), the median percentile system was used for parameters of location and variance. Statistical significance was tested by means of the Mann-Whitney test and the Wilcoxon test for paired data (Sachs, 1974). For the histamine assay, a quality control was maintained over the whole period of investigation, using control samples prepared in our laboratory. In this way, precision and relative accuracy could be guaranteed for all histamine determinations over a period of at least 18 months (Rohde et al., 1978).

Results

Part 1

In 5 patients with complete, Hollander-negative vagotomy (Table II) the median (first to third quartiles) for gastric histamine concentration was 51.6 (49.7-63.5) μg/g. This value was higher by 69 per cent than that of duodenal ulcer patients before or without operation—30.5 (24.0-42.5) μg/g; n = 17, P < 0.002—and higher also than that of control subjects—42.6 (31.4-49.6) μg/g; n = 21, P < 0.01. In 3 patients with recurrent ulcer, however (two of whom had Hollander-negative insulin tests), the mucosal histamine content was as low as that of duodenal ulcer patients without operation (range 32.9-37.0 μg/g) (Table II).

After various other types of operation for duodenal and gastric ulcer, histamine concentrations in corpus mucosa showed good agreement with these results (Table II). Thus, in 2 duodenal ulcer patients (Cases 13 and 14) who were treated by combined resection and vagotomy, mucosal histamine concentrations of over 50 μg/g were found. Case 13, who had a positive insulin test, had lower histamine values than Case 14, who had a negative insulin test. Thus, it seemed to be the vagotomy and not the resection which was responsible for the increased histamine concentrations in the gastric mucosa of these patients.

Part 2

In all duodenal ulcer patients from part 1 who were treated by selective vagotomy, an increase of gastric histamine over 50 pg/g were found. The median increase was 56 per cent. Again, it was striking that the smallest increase occurred in a patient who had an incomplete vagotomy (Case 15).
sophisticated techniques were employed to ensure that the results obtained were valid. Thus, for example, the reliability of the histamine assay was confirmed by means of tests of sensitivity, specificity, within-day and day-to-day precision and accuracy using bioassay on guinea-pig ileum as a reference method (Lorenz et al., 1975; Lorenz et al., 1978; Rohde et al., 1978). Quality control in terms of clinical chemistry was ensured throughout the 18 months of the study, two control samples from a pool prepared in this laboratory being used in each daily series of histamine determinations (Rohde et al., 1978). Six to eleven months were allowed to elapse after the vagotomy operation before its effect was measured, to try to ensure that the results obtained would be representative and valid. Every attempt was made to define as exactly as possible both the precise condition of the subjects who were studied and the conditions of the investigation. Such precision seemed to us to be necessary because of previous conflicting results in studies of mucosal gastrin concentration (Creutzfeldt et al., 1976).

Our findings of lower mucosal histamine concentrations in patients with duodenal ulcer than in 'normal' controls, and of increased mucosal histamine concentrations after vagotomy, suggest that abnormalities of histamine storage might be a feature of duodenal ulcer disease. A similar observation to our findings in patients after vagotomy was made by Lundell et al. (1974), who studied the effect of truncal vagotomy on gastric mucosal histamine in rats. The increase in mucosal histamine concentration after vagotomy on gastric mucosa of duodenal ulcer patients after vagotomy, resulting in a decreased concentration of stomach. This hypothesis is supported by previous findings of increased release of histamine from the mucosa of duodinal ulcer patients before operation, resulting in a decreased concentration of histamine in the mucosa (Troidl et al., 1976a). Smith (1959) had previously suggested that incubation with compound 48/80 of gastric tissue obtained from ulcer patients led to more histamine release than similar incubation with gastric tissue obtained from patients with gastric carcinoma. In addition, Lundell et al. (1974) found that after truncal vagotomy in rats, newly formed histamine was more slowly mobilized than in control animals under certain conditions.

To test whether the increased mucosal histamine concentration after vagotomy might be due to daily or seasonal influences within this part of the study, mucosal histamine concentration was determined twice within a day (morning and afternoon) and within a time interval of several weeks or months (Table III). The reproducibility of the assessment of histamine concentration was found to be quite satisfactory both within a day and from day to day. Thus, no alteration with time was found which could explain the increase in histamine concentration in corpus mucosa after vagotomy.

Overall clinical assessment and parietal cell counting
The overall clinical assessment according to Visick and as modified by Goligher (1975), and the endoscopy, radiology and acid secretion tests in the patients in this study yielded results which were comparable to those reported by several other authors (Troidl et al., 1975b). During the entire period within which this investigation was carried out, no significant change was found in the parietal cell mass of the duodenal ulcer patients after vagotomy.

Discussion
We found a significant increase in gastric mucosal histamine concentration after vagotomy, which averaged about 50 per cent. Since the methods used were complicated and the observed increases were only in the nanogram range, it must be emphasized that sophisticated techniques were employed to ensure that the results obtained were valid. Thus, for example,
A second possibility is increased histamine formation after vagotomy. Indeed, in rats, higher activities of specific histidine decarboxylase were observed after truncal vagotomy than before vagotomy (Håkanson and Lindberg, 1970; 1971; Lundell et al., 1973), but in other species, including man, it seems unlikely that such changes take place (Troidl et al., 1976a).

Decreased inactivation of histamine is a third possibility that is worth considering. In duodenal ulcer patients after vagotomy, however, histamine methyltransferase activity was found to be higher than in control subjects and higher also than in duodenal ulcer patients before operation (Barth et al., 1977). Since this enzyme is, as far as we know, the only significant enzyme responsible for histamine inactivation in human gastric mucosa, this explanation also seems unlikely.

Fourthly, the trophic effects of gastrointestinal hormones, and gastrin in particular, on corpus mucosa after vagotomy might explain the elevated tissue histamine levels. However, throughout the whole period of this study, no increase in parietal cell density was found. We would have expected to find such an increase if significant trophic influences had been at work. Histological examination of biopsy specimens also showed that no significant atrophic gastritis was present in any of the vagotomized patients in this study. (An increased number of mast cells in gastric mucosa has been observed by Sturara and Sundberg (1958) in patients with atrophic gastritis.)

Finally, histamine-forming bacteria (lactobacilli) in the superficial layers of the gastric mucosa could conceivably contribute to the histamine content of the gastric mucosa (Horáková et al., 1971). Bacterial histidine decarboxylase requires an acid medium, however, for optimal activity. This possibility is rendered unlikely by our findings in this study of very low basal acid outputs in patients who nevertheless had high mucosal histamine concentrations, and by our previous findings of normal mucosal histamine concentrations in patients with gastric carcinoma (Troidl et al., 1975a). Furthermore, lactobacilli in particular were found only in rats, sheep and horses, which possess a rumen whose luminal pH does not regularly fall below 5 (Horáková et al., 1971).

Acknowledgements
This study was supported by grants from Deutsche Forschungsgemeinschaft (Lo 199/7 and Ha 461/3). We are very grateful to G. Acker, R. Albrecht, M. Ronzheimer and A. Schmal for their excellent technical assistance. Furthermore, we gratefully thank Professor D. Johnston for his critical comments and for improving the language in this communication.

References
BARTH H., TROIDL H., LORENZ W. et al. (1977) Histamine and peptic ulcer disease: histamine methyltransferase activity in gastric mucosa of control subjects and duodenal ulcer patients before and after surgical treatment. Agents Actions 6, 75–79.

Histamine and selective gastric vagotomy

15


Paper accepted 8.8.1977