Effects of Helicobacter pylori gastritis on gastric secretion in healthy human beings

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Feldman, Mark, Byron Cryer, and Edward Lee. Effects of Helicobacter pylori gastritis on gastric secretion in healthy human beings. Am. J. Physiol. 274 (Gastrointest. Liver Physiol. 37): G1011–G1017, 1998.—Helicobacter pylori gastritis is common, but effects on gastric secretion are not well understood. We measured basal and pentagastrin-stimulated gastric acidity, pepsin activity, and fluid output, as well as serum gastrin concentrations and H. pylori antibody levels, before and after treatment of H. pylori gastritis in 28 men and women. Subjects were studied before and 1 and 3 mo after a course of bismuth, metronidazole, and tetracycline. Elimination of H. pylori gastritis, accomplished in 14 subjects, increased basal and pentagastrin-stimulated gastric acidity (by 15 meq/l) and basal acid output significantly (by 2.1 meq/h 1 mo after therapy). Elimination of H. pylori had an opposite effect on pepsin secretion, significantly decreasing pepsin output by 30%. Elimination of H. pylori significantly reduced nonparietal fluid output by 35%, without affecting fluid output from parietal cells. Serum gastrin and H. pylori antibody levels declined significantly after elimination of H. pylori. None of these changes was observed in 14 subjects whose H. pylori gastritis was resistant to antimicrobial therapy. In summary, eradication of H. pylori infection increases gastric acidity by reducing nonparietal gastric secretion from peptic and other cells.

gastric acidity; pepsin activity; serum gastrin; nonparietal secretion; pentagastrin

Helicobacter pylori are rod-shaped bacteria that commonly infect the human stomach, even in healthy, asymptomatic individuals. H. pylori attract neutrophils and lymphocytes into the fundic mucosa, where acid-secreting parietal cells and pepsin-secreting chief cells reside, and into the antral mucosa, where gastrin-secreting cells reside (34). To what extent, if at all, the chronic, active gastric inflammation accompanying H. pylori infection affects gastric secretion is uncertain. Several previous studies have examined effects of H. pylori infection on gastric acid secretion, usually in duodenal ulcerodenal ulcer patients, but they have come to different conclusions (1, 3, 6–8, 11, 11a, 12, 16–20, 25, 27, 28, 30, 32, 33, 37–41). To address this question, we first measured basal and maximal pentagastrin-stimulated gastric secretion in men and women with H. pylori gastritis, then tried to eliminate the chronic active H. pylori-related gastritis with antimicrobial drugs that have no direct effect on gastric secretion, and finally remeasured basal and maximal gastric secretion, both in individuals in whom the therapy had been successful in eliminating H. pylori gastritis and, for comparison, in those in whom therapy had been unsuccessful as assessed by tissue stains for the organism. Specifically, we measured basal and pentagastrin-stimulated gastric acidity, pepsin activity, and fluid outputs before and 1 and 3 mo after completion of a 2-wk course of bismuth, metronidazole, and tetracycline. From these data we calculated basal acid output (BAO) and maximal acid output (MAO), basal pepsin output (BPO) and maximal pepsin output (MPO), and parietal and nonparietal fluid secretion rates, both in subjects whose infection was successfully eradicated and, for comparison, in subjects whose infection persisted. We also analyzed fasting serum gastrin concentrations and H. pylori serum antibody levels before and after antimicrobial therapy in these two groups of subjects (eradicated and not eradicated).

METHODS

Subjects. We studied 14 men and 14 women between the ages of 25 and 89 yr (mean ± SE, 47 ± 3 yr) with no history of peptic ulcer disease, gastrointestinal malignancy, or upper gastrointestinal surgery and with no chronic gastrointestinal symptoms (heartburn, epigastric pain, indigestion, bloating, abdominal fullness, nausea, or vomiting). All but one were identified on screening of healthy volunteers for H. pylori seropositivity. The one seronegative individual had participated in recent studies in our laboratory and was known to have H. pylori gastritis. No subject was receiving gastric antisecretory medication. None had taken any antimicrobial agent, including bismuth, within the previous 2 wk. Each participant gave us informed, written consent and was paid for participating.

H. pylori antimicrobial therapy. We treated subjects with 524 mg bismuth subsalicylate, 250 mg metronidazole, and 500 mg tetracycline four times daily for 14 days. We prescribed 500 mg amoxicillin four times daily instead of tetracycline for one woman intolerant to tetracycline in the past. Subjects were interviewed at the beginning, middle, and end of the 2-wk course of antimicrobial agents to encourage compliance and to record adverse side effects on a standardized questionnaire. The regimen was generally well tolerated. The only symptom besides darkening of the stool, which was reported significantly more commonly after than before therapy, was diarrhea (P = 0.02).

Experimental procedures. Before and 1 mo (29 ± 1 days) and 3 mo (90 ± 3 days) after completion of antimicrobial therapy, subjects reported to our secretory laboratory in the morning, having fasted since 11 PM or earlier the prior evening. On each study day we obtained a venous blood sample and froze the serum at 0°C until the time for assays. H. pylori serum antibodies were measured using a solid-phase fluorescence immunoassay (Pylori-G antibodies Fiax...
test kit; Bio Whittaker, Walkersville, MD) and were expressed in optical density units per milliliter. Serum gastrin concentrations were measured by RIA as previously described and were expressed in picograms per milliliter (13).

After collecting blood, we intubated the stomach with a gastric tube modified so that we could pass biopsy forceps through its tip to obtain gastric mucosal biopsies after gastric secretion measurements. This modification does not affect the high recovery of gastric juice through the tube (4). We positioned the tip of the gastric tube in the distal stomach under fluoroscopic guidance. We removed residual gastric contents through the gastric tube by aspiration for at least 15 min, after which we collected basal fluid by intermittent suction for exactly 15 min. Next, we injected a maximally effective dose of pentagastrin (6 μg/kg sc) and collected gastric fluid for the next three consecutive 15-min periods. We measured the volume of each 15-min aspirated gastric juice sample, its pepsin activity (11), and its osmolality (9, 10). We measured the acidity (H+ concentration) of each sample with a pH electrode (29), and a measurement that correlates closely with acidity by in vitro titration to pH 7 with 0.1 N NaOH (9). Serum osmolality was also measured at the beginning of the experiment (15 min before pentagastrin) and in the middle of the experiment (15 min after pentagastrin).

We expressed acidity in milliequivalents per liter, pepsin activity in international units per milliliter, and osmolality in milliosmoles per kilogram H2O. In 13 of the 83 basal juice samples (16%), pepsin activity could not be measured accurately from our standard curves; these samples are omitted from mean data and statistical analyses. We calculated BAO by first multiplying the volume of the initial 15-min sample (in liters) by its acidity (in meq/l) and then multiplying the product by 4 (meq/h). We calculated MAO by summing the three 15-min acid outputs after pentagastrin injection and then dividing the sum by 0.75 meq/h. We calculated BPO by first multiplying the volume of the sample by its pepsin activity (IU/ml) and then by multiplying the product by 4 IU/h. We calculated MPO by summing the three 15-min pepsin outputs after pentagastrin injection and then dividing the sum by 0.75 IU/h. From measurements of gastric acidity, osmolality, and fluid output we calculated the parietal component and the nonparietal components of fluid output (ml/15 min), using a two-component model of gastric secretion (9, 10, 11a, 26). The model assumes the osmolality of the nonparietal component is the same as plasma and the acidity and osmolality of the parietal component are 160 meq/l and 10%- plasma (≈320 mosmol/kgH2O), respectively (9, 10).

Immediately after completion of the gastric secretory analysis and with the gastric tube still in place, we obtained fundic mucosal biopsies under fluoroscopic guidance using an endoscopic biopsy forceps (4). We also obtained antral mucosal biopsies at the 3-mo visit (4), as well as an additional biopsy for a rapid urease test (CLO test; Tri-Med Specialists, Lenexa, KS). All 28 subjects returned for their 1-mo visit, and 27 for returned for a rapid urease test (CLO test; Tri-Med Specialists, Lenexa, KS). All 28 subjects returned for their 1-mo visit, and 27 for returned for a rapid urease test (CLO test; Tri-Med Specialists, Lenexa, KS). All 28 subjects returned for their 1-mo visit, and 27 for.

Histological examination. We fixed biopsy material in 10% Formalin (Starplex Scientific, Etobicoke, Ontario, Canada) and then stained it with hematoxylin and eosin. E. Lee interpreted mucosal biopsies with no clinical information. He also determined the presence or absence of chronic active gastritis (11). He defined chronic active gastritis as an increase in neutrophils and lymphocytes in the lamina propria. Neutrophils were also seen infiltrating epithelial cells. He also scored the intensity of gastritis in each biopsy as 0 (no inflammation), 1 (mild inflammation), 2 (moderate inflammation), or 3 (severe inflammation) (11). He also reported the presence or absence of stable H. pylori. If there was a question as to whether H. pylori organisms were present after hematoxylin and eosin stain, a Giemsa stain was performed as well (35).

Statistical analyses. Data were analyzed using Systat (version 6.0.1, Statistical Package for the Social Sciences). We used paired t-tests to determine significant differences in H. pylori serum antibody levels, serum gastrin concentrations, and gastric secretion parameters before and after therapy. Because H. pylori serum antibody levels and fasting serum gastrin levels were not normally distributed, we log transformed the data before statistical analysis. We used Wilcoxon tests to determine significant differences in gastritis severity scores before and after therapy. We analyzed subjects whose gastritis was eliminated by therapy as well as subjects whose gastritis was not eliminated by therapy. We considered two-tailed P values ≤ 0.05 as significant.

**RESULTS**

Outcomes in subjects whose H. pylori gastritis was eliminated by antimicrobial therapy. In 14 of the 28 subjects (6 men and 8 women), H. pylori infection was no longer visible by 1- and 3-mo posttherapy biopsies, and gastritis was eliminated (Table 1). Rapid urease tests for H. pylori were also negative in each subject at the final visit. Mean H. pylori serum antibody levels and fasting serum gastrin concentrations decreased significantly by month 3 (Table 1).

Elimination of H. pylori gastritis was associated with a significant (15 meq/l) increase in the mean basal acidity of gastric juice (Table 1 and Fig. 1A). Basal acidity, meq/l

<table>
<thead>
<tr>
<th></th>
<th>Before Therapy</th>
<th>1 Mo After Therapy</th>
<th>3 Mo After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 14)</td>
<td>(n = 14)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>Fun dic gastritis score</td>
<td>2.3 ± 0.2</td>
<td>0.1 ± 0.1‡</td>
<td>0‡</td>
</tr>
<tr>
<td>Antral gastritis score</td>
<td>2.5 ± 0.2†</td>
<td>Not done</td>
<td>0‡</td>
</tr>
<tr>
<td>H. pylori serum antibody, ODU/mL</td>
<td>99</td>
<td>138</td>
<td>57‡§</td>
</tr>
<tr>
<td>Fasting serum gastrin, pg/ml</td>
<td>135 (20–471)</td>
<td>135 (20–471)</td>
<td>17.5 (414)</td>
</tr>
<tr>
<td>Basal acidity, meq/l</td>
<td>23.5 ± 6.7</td>
<td>37.4 ± 5.4</td>
<td>38 ± 6.7</td>
</tr>
<tr>
<td>Pentagastrin-stimulated acidity, meq/l</td>
<td>74.6 ± 9.6</td>
<td>92.6 ± 6.1</td>
<td>87.3 ± 7.4</td>
</tr>
<tr>
<td>Basal fluid output, ml/15 min</td>
<td>32.5 ± 5.1</td>
<td>31.2 ± 4.9</td>
<td>29.0 ± 4.5</td>
</tr>
<tr>
<td>Pentagastrin-stimulated fluid output, ml/15 min</td>
<td>62.6 ± 7.5</td>
<td>61.7 ± 8.4</td>
<td>58.1 ± 7.4</td>
</tr>
<tr>
<td>Basal pepsin activity, IU/ml</td>
<td>60.5 ± 8.4</td>
<td>58.1 ± 9.5</td>
<td>46.9 ± 5.9</td>
</tr>
<tr>
<td>Pentagastrin-stimulated pepsin activity, IU/ml</td>
<td>54.9 ± 4.9</td>
<td>45.6 ± 4.9</td>
<td>41.2 ± 4.9‡</td>
</tr>
</tbody>
</table>

Values are means ± SE, except for H. pylori antibody and fasting serum gastrin values, which are medians with ranges in parentheses; n = no. of patients. *Average of 3 15-min values after pentagastrin. †Mean is not zero because in 1 subject H. pylori was eliminated and fundic gastritis decreased from severe (grade 3) to mild (grade 1) at 1 mo; gastritis and H. pylori were absent at 3 mo. The gastritis was classified as eliminated. ODU, optical density units. ‡P < 0.05 vs. value before therapy. §P = 0.003 vs. value at 1 mo after therapy.
gastric fluid output decreased slightly but not significantly after elimination of H. pylori gastritis (Table 1 and Fig. 1B). As a consequence, mean and median BAO 1 mo after therapy had increased significantly, by 2.1 and 2.8 meq/h, respectively (Table 2 and Fig. 2A). By month 3, mean and median BAO were 1.2 and 1.4 meq/h higher than the pretherapy BAO, although the increase was not significant (Table 2 and Fig. 2A).

Injection of pentagastrin at the end of the first 15-min period increased gastric acidity and fluid output considerably above basal values (Table 1 and Fig. 1, A and B). After elimination of H. pylori gastritis, mean pentagastrin-stimulated gastric juice acidity was significantly higher than at baseline (Table 1 and Fig. 1A). As with basal secretion, there was a small, nonsignificant decrease in mean pentagastrin-stimulated fluid output after elimination of H. pylori gastritis (Table 1 and Fig. 1B). Mean and median MAO to pentagastrin increased 2.9 and 4.9 meq/h, respectively, 1 mo after successful antimicrobial therapy and 1.8 and 1.1 meq/h, respectively, 3 mo after therapy, but these changes were not statistically significant (Table 2).

Mean basal pepsin activity of gastric juice decreased after elimination of gastritis (Table 1), and the 22% decrease in peptic activity at 3 mo approached significance ($P = 0.06$). Mean BPO, the product of basal gastric pepsin activity and fluid output, also decreased after successful antimicrobial therapy, and the 32% decrease at month 3 was significant (Table 2, $P = 0.02$). Mean pepsin activity after pentagastrin decreased after therapy ($P = 0.06$ at 1 mo and $P = 0.04$ at 3 mo; Table 1). As shown in Table 2, MPO to pentagastrin also decreased significantly after elimination of gastritis, by 17% after 1 mo ($P = 0.02$) and by 28% after 3 mo ($P = 0.02$).

Table 3 presents mean gastric fluid output for the entire 1-h experiment, as well as the calculated parietal and nonparietal components. Total fluid output (parietal plus nonparietal) decreased after elimination of gastritis but not significantly. There was a small, insignificant increase in the parietal component of
gastric secretion after elimination of H. pylori gastritis, whereas there was a larger, statistically significant, decrease in the nonparietal component (P = 0.01 at 3 mo).

Outcomes in subjects whose gastritis was not eliminated by antimicrobial therapy. In the remaining 14 subjects (8 men and 6 women), H. pylori organisms, fundic gastritis, and antral gastritis were present in biopsies taken 3 mo after therapy. Thirteen also had positive rapid urease tests at this time. Mean severity of fundic gastritis in these subjects decreased 1 mo after antimicrobial therapy but not significantly. By month 3, gastritis scores were back to baseline (Table 4). Failure to eradicate gastritis was associated with none of the significant changes in gastric secretion, serum gastrin, or H. pylori serum antibodies observed.

Table 3. Parietal, nonparietal, and total fluid output during 4 15-min periods combined before and 1 and 3 mo after therapy in subjects whose H. pylori gastritis was and was not eliminated

<table>
<thead>
<tr>
<th>Before Therapy</th>
<th>1 Mo After Therapy</th>
<th>3 Mo After Therapy</th>
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<tbody>
<tr>
<td><strong>Eliminated</strong></td>
<td></td>
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<tr>
<td>Parietal fluid</td>
<td>162 ± 22</td>
<td>165 ± 20</td>
</tr>
<tr>
<td>Nonparietal fluid</td>
<td>58 ± 9</td>
<td>51 ± 11</td>
</tr>
<tr>
<td>Total fluid output</td>
<td>220 ± 26</td>
<td>216 ± 29</td>
</tr>
<tr>
<td><strong>Not eliminated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parietal fluid</td>
<td>168 ± 18</td>
<td>164 ± 16</td>
</tr>
<tr>
<td>Nonparietal fluid</td>
<td>54 ± 6</td>
<td>47 ± 5</td>
</tr>
<tr>
<td>Total fluid output</td>
<td>222 ± 20</td>
<td>211 ± 16</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 14 subjects except where otherwise indicated. *P = 0.01 vs. before therapy.

In subjects whose gastritis had been eliminated (Tables 2–4, Fig. 1, C and D, and Fig. 2B).

DISCUSSION

One approach to study the effect of H. pylori gastritis on gastric secretion in healthy human beings would be to measure secretion before and after naturally acquired acute H. pylori infection. However, acute infection usually occurs in childhood and is rarely recognized (34). Isolated cases of intentional ingestion of H. pylori (30) or apparent laboratory outbreaks (18) suggest that acute infection leads to a transient state of hypochlorhydria lasting weeks to months.

A second, more commonly utilized approach to examine effects of H. pylori infection on gastric secretion has been to compare gastric secretion rates in age- and sex-matched subjects with or without chronic H. pylori gastritis (1, 6, 7, 11a, 12, 20, 33, 37–40). In several case-control studies, BAO in H. pylori positive individuals without ulcers has been reported to be significantly lower than (12, 33) not significantly different from (6, 11, 11a, 20, 38), and significantly higher than (7) the BAO in H. pylori negative controls. Meal-stimulated acid secretion has been reported to be similar in H. pylori positive and negative subjects when measured in vivo intragastric titrations at pH 7 (38) or at pH 5 (12, 33) and to be either similar or increased in infected subjects at pH 2.5, depending on the concentration of meal administered (38). Acid secretion stimulated by an intravenous infusion of the neurotransmitter gastrin-releasing peptide has been reported to be increased in H. pylori positive subjects (7). The only
consistent finding among case-control studies is that H. pylori gastritis and human gastrin-17, a reflection of functional parietal cell mass, is similar in H. pylori positive cases and H. pylori negative controls (6, 7, 11a, 12, 20, 33, 38, 39).

A third approach, and the one that we chose, is to measure gastric secretion before and after H. pylori eradication, an approach that avoids certain problems inherent in case-control studies, because each treated individual can serve as his or her own control. Before therapy, mean BAO and MAO were within the normal range (Table 2), indicating that acid outputs in infected individuals, even the elderly, are usually close to normal. Unless atrophic gastritis, which is uncommon in Americans, is present, acid secretion is fairly well preserved in H. pylori-infected elderly subjects (11, 12, 21). Thirteen studies evaluating gastric secretion before and after H. pylori eradication have been reported (3, 6–8, 16–19, 25, 27, 28, 32, 41), but ten were performed in duodenal ulcer patients (3, 6, 7, 16, 19, 25, 27, 28, 31, 32). In our opinion, eradication of H. pylori infection in duodenal ulcer patients does not clarify the influence of H. pylori gastritis on gastric secretion in healthy individuals for two reasons. First, duodenal ulcer patients in case-control studies have higher mean gastric acid secretion rates and serum gastrin concentrations than H. pylori-infected controls without duodenal ulcer (6, 7, 20, 33, 39). Second, after elimination of H. pylori gastritis in duodenal ulcer patients, acid secretion does not decrease to normal levels (3, 6, 7, 16, 19, 25, 27, 31, 32). Thus increased gastric acid secretion rates in duodenal ulcer patients cannot be attributed to H. pylori gastritis alone.

Four previous studies reported gastric acid secretion rates before and after elimination of H. pylori gastritis in patients without duodenal ulcers (7, 8, 17, 41). Yasunaga et al. (41) eradicated H. pylori gastritis with bismuth, tetracycline, and metronidazole in 16 Japanese patients with large gastric folds detected on mass gastric cancer screening. Seven to 29 wk later, gastric fold thickness had decreased and both BAO and MAO increased significantly (41). Gutierrez et al. (17) eradicated H. pylori gastritis in 11 Columbian patients with dyspepsia and detected substantial increases in BAO and MAO. Unfortunately, the time after eradication and the regimen(s) used were not specified and they probably were not uniform. El-Omar et al. (7) eradicated H. pylori infection in 14 healthy Scottish volunteers (mostly men) with a 3-wk course of bismuth, metronidazole, and amoxicillin and found no change in BAO 1 mo later. However, in a subsequent study in infected patients and healthy volunteers, El-Omar et al. (8) reported a significant increase in MAO 6 mo after eradication in subjects who were initially hypochlorhydric.

Ours is the largest H. pylori eradication study of gastric secretion performed in healthy, infected individuals, allowing us to examine the effect of H. pylori gastritis on gastric secretory physiology. The study included as many women as men (14 of each), measured gastric pepsin as well as acid secretion, and, perhaps most importantly, included a treated but noneradicated control group. Inclusion of such a control group permitted us to conclude with a higher degree of certainty that the changes in gastric secretion we observed were actually a consequence of elimination of H. pylori gastritis and not due to the passage of 3 mo of time or to nonspecific effects of the antimicrobial regimen employed. No previous eradication study included a treated but not cured control group (4, 6, 17, 18, 20, 25–27, 30, 31, 41).

Our finding that elimination of H. pylori antral gastritis lowered fasting serum gastrin concentrations is consistent with the results of several previous eradication studies performed in duodenal ulcer patients (3, 6, 7, 16, 25, 27, 31, 32) and in normal subjects (7). Eradication of H. pylori gastritis also lowers serum gastrin levels after a meal in ulcer patients (16, 25, 27, 32) or during intravenous infusion of gastrin-releasing peptide in ulcer patients or healthy subjects (6, 7). The mechanism for the reduction in serum gastrin levels after elimination of H. pylori antral gastritis is not certain because there are no changes in the density of antral gastrin (G) or somatostatin (D) cells (14). It is likely that cytokines derived from inflammatory cells within the gastric antrum are responsible for the hypergastrinemia, either by augmenting antral G cell function or suppressing antral D cell function.

In individuals whose H. pylori gastritis was eradicated, we observed a decline in basal and pentagastrin-stimulated gastric pepsin output, due more to a fall in gastric juice pepsin concentrations than in total gastric fluid output, although both of these parameters decreased. This novel finding suggests that the chronic gastric inflammation associated with H. pylori infection somehow facilitates pepsin secretion from chief and/or mucous neck cells. H. pylori gastritis also has been associated with elevated serum pepsinogen concentrations (12, 32), which return to normal after eradication of H. pylori infection (32). The identity of the putative facilitator of enhanced pepsinogen release into gastric juice (and blood) in individuals with H. pylori gastritis is speculative, but it is likely a cytokine. PGE2 released by inflammatory cells is one candidate because PGE2 augments pepsinogen secretion from dispersed chief cells (36).

Another change we observed after elimination of H. pylori gastritis was a significant increase of ~15 meq/l in basal and pentagastrin-stimulated acidity of gastric juice, despite a decline in serum gastrin levels. Thus gastric acidity and pepsin activity moved in opposite directions after cure of H. pylori gastritis. Even greater increases in gastric acidity after eradication of H. pylori gastritis than we observed have been reported in dyspeptic Colombian patients (17). Our subjects had a mean BAO and MAO well within the normal range before therapy, whereas the Colombian patients with dyspepsia were acid hyposecretors before therapy and had normal BAO and MAO values after therapy (17). Mean BAO increased by 2.1 and 1.2 meq/h at month 1 and month 3 in our study (Fig. 2B), by 1.8 meq/h between month 2 and month 7 in the Japanese study of...
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patients with enlarged gastric changes (41), and by 2.0 meq/h in the Columbian study of dyspeptic patients (17). Mean MAO increased by 2 to 3 meq/h in our study, by 9.5 meq/h in Columbian patients with dyspepsia and hypochlorhydria (17), by 13.3 meq/h in Japanese patients with large gastric folds (41), and by 11.5 meq/h in Scottish and Irish patients and volunteers with hypochlorhydria (8). Labenz et al. (24) have also observed in duodenal ulcer patients on omeprazole therapy increases in gastric acidity (decreases in pH) after eradication of H. pylori.

What is the mechanism for the increased gastric acidity (H + concentration in gastric juice) after cure of H. pylori gastritis? It is possible that excessive ammonia generated from the urease of H. pylori neutralizes some secreted H + and lowers acidity, accounting for the increased acidity observed after eradication of H. pylori. However, Yasunaga et al. (41) have clearly demonstrated that the decline in gastric juice levels NH 3 after H. pylori eradication is much too small to account for the much larger increase in gastric acidity that is observed. The paradox of increased gastric acidity with somewhat reduced gastric juice fluid output after H. pylori eradication (Fig. 1, A and B) suggested to us that gastric acidity may have increased, at least in part, because of lower gastric nonparietal fluid secretion, since higher parietal cell H + secretion would have increased acidity and fluid output. Using a previously validated two-component model of gastric secretion (9, 10) derived from even earlier studies by Fisher and Hunt (11a) and by Makhlof et al. (26), our calculations support the hypothesis that the nonparietal component of gastric secretion falls significantly after eradication of H. pylori gastritis (Table 3). This fall in nonparietal secretion is an attractive mechanism for the increased gastric acidity after cure of H. pylori gastritis because nonparietal gastric fluid dilutes and neutralizes gastric acid (9, 10, 11a, 26).

The source of the increased nonparietal gastric fluid in individuals with H. pylori gastritis (which falls after successful therapy) is speculative. There was no evidence of enterogastric reflux in these studies because bile pigments were not visible in gastric juice samples. One possibility, supported by our pepsin data, is that the excessive nonparietal gastric fluid in individuals with H. pylori gastritis originates from pepsin-secreting chief and/or mucous neck cells. Because circulating gastrin increases both pepsin secretion (11) and nonparietal fluid secretion (9), it is possible that the mild hypergastrinemia associated with H. pylori gastritis is responsible for the elevated nonparietal fluid component. This possibility would explain why serum gastrin levels, nonparietal fluid secretion, and gastric pepsin secretion decreased in parallel after elimination of H. pylori gastritis. Another possible explanation is that an inflammatory cell-derived cytokine, such as PGE 2 (9, 36), may stimulate gastric, nonparietal secretion in individuals with H. pylori gastritis. Finally, the surplus nonparietal fluid output in H. pylori gastritis could represent leakage of interstitial gastric fluid through an epithelial lining damaged by toxic products of H. pylori. This may be a mechanism by which H. pylori, living in the mucus layer on top of the gastric epithelium, extract their essential nutrients from the host.

Regardless of the mechanism, eradication of H. pylori and cure of gastritis eliminate this excessive nonparietal fluid, while preserving parietal cell function, with a resultant rise in gastric acidity.

NOTE ADDED IN PROOF

It has been recently reported that H. pylori gastritis is associated with increased sucrose permeability, supporting our contention that gastric mucosal leakage occurs in these individuals (K. Borch, C. Sjostedt, U. Hannestad, J. D. Soderholm, L. Franzén, and S. Mårdh. Asymptomatic Helicobacter pylori gastritis is associated with increased sucrose permeability. Dig. Dis. Sci. 43: 749–753, 1998).

We thank Mary Walker, Tina Barnett, and Kristy Rushin for expert technical assistance, and Vicky L. Robertson for assistance in manuscript preparation.

This work was supported by the Merit Review Grant from the Department of Veterans Affairs (M. Feldman) and the Southland Financial Corporation Distinguished Chair in Geriatrics, University of Texas Southwestern Medical Center at Dallas (M. Feldman).

Part of the work was presented at the annual meeting of the American Gastroenterological Association in May 1995 and has been published in abstract form (Gastroenterology 108: A747, 1995).

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Received 27 January 1998; accepted in final form 10 March 1998.

REFERENCES


