Aging and the alimentary tract

Helicobacter pylori independent chronological change in gastric acid secretion in the Japanese

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Abstract

***Background*—Gastric acid secretion in Japanese subjects decreases with aging. One of the possible causative mechanisms of this attenuated acid secretion is speculated to be a *Helicobacter pylori* induced chronic gastritis. The infection rate of this microorganism has decreased recently in Japan.**

***Aims*—To investigate whether gastric acid secretion has altered over the past 20 years, and if so, what the influence of *H pylori* infection might be in the Japanese population.**

***Subjects and methods*—Gastric acid secretion, serum gastrin and pepsinogen I and II concentrations, and *H pylori* infection were determined in 110 Japanese subjects in both the 1970s and 1990s.**

***Results*—Basal acid output as well as maximal acid output have greatly increased over the past 20 years, not only in individuals with *H pylori* infection but also in those without infection. Furthermore, subjects with *H pylori* infection tended to show decreased gastric acid secretion in comparison with those without infection, particularly in geriatric subjects. There was a positive correlation between gastric acid secretion and serum pepsinogen I concentrations.**

***Conclusions*—In Japan, both basal and stimulated gastric acid secretion have increased over the past 20 years; some unknown factors other than the decrease in *H pylori* infection may play an important role in this phenomenon.**

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Keywords: gastric acid; *Helicobacter pylori*; aging; gastrin

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Gastric acid secretion is under the control of various factors including race, sex, and age. In Western countries, the level of gastric acid secretion is reported to be maintained with aging.[1–4] On the other hand, acid secretion decreases in the elderly in Japan due to encroaching atrophic gastritis.[5 6] In Japan, the rate of *Helicobacter pylori* infection is very high with a resulting higher incidence of gastritis and gastric mucosal atrophy.[5 7–10] The decrease in acid secretion with chronological aging in Japan may therefore result from *H pylori* infection. It is not clear at present however whether *H pylori* is the sole factor responsible for the decrease in acid secretion with aging. Furthermore, the infection rate of *H pylori* has recently been reported to be decreasing in Japan as well as in other countries.[11 12]

With these conflicting factors in mind, we have investigated whether gastric acid secretion has altered over the past 20 years with and without the influence of *H pylori* infection in the Japanese, both non-elderly and elderly.

Materials and Methods

MATERIALS

One hundred and ten healthy volunteers in the Amagasaki area were used for the analysis. One group comprised normal individuals whose gastric acid secretion had been investigated in the early 1970s. The other group was investigated in the early 1990s. Male:female ratios, social class, and dietary habits of the volunteers were similar between the groups. Each group was further subdivided into four groups by age and the presence or absence of *H pylori* infection. Accordingly, eight groups were analysed and compared (table 1). Individuals with a history of peptic ulcer, gastric surgery, malignancy, renal failure, or other gastrointestinal diseases were excluded. Subjects being treated with drugs known to affect gastric secretion were also excluded.

Written consent was obtained from all individuals. The study was approved by the institutional ethical committee.

MEASUREMENT OF GASTRIC ACID SECRETION

Gastric acid secretion was measured at 0800 hours after a 12 hour fast. Gastric tubing with multiple openings was inserted into the stomach and gastric juice was aspirated. After insertion of the tubing, basal acid output (BAO) was measured by titrating the acidity of the gastric juice collected during the basal condition for one hour. Maximal acid output (MAO) was then measured by administrating 6 μg pentagastrin (Zeneca Pharmaceutical Co. Ltd, Osaka, Japan) intramuscularly and collecting the gastric juice for an additional hour as a sum of six 10 minute outputs after pentagastrin injection.[13]

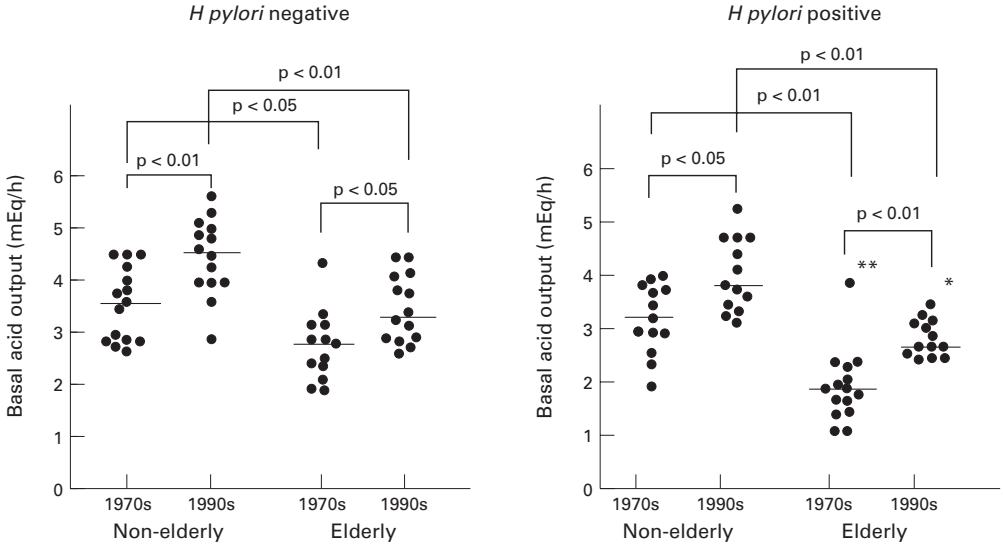

*Figure 1: BAO in the eight groups. Each dot represents a single case. Horizontal lines indicate medians of individual groups. **Significant difference (p<0.01) between H pylori positive and negative groups (group 7 v group 3); *significant difference (p<0.05) between H pylori positive and negative groups (group 8 v group 4).*

ASSAY OF SERUM GASTRIN, *H PYLORI* ANTIBODY, AND PEPSINOGEN I AND II

Blood samples were obtained early in the morning. Serum was separated and stored at –80°C until the assay. Serum gastrin concentrations were measured by radioimmunoassay (Gastrin Riakit II, Dainabot Co. Ltd, Tokyo, Japan).[14] Anti-*H pylori* IgG antibody was measured by the HM-CAP immunoassay (Determiner Helicobacter, Enterle Products Inc., Westbury, New York, USA).[15–17] This assay system is reported to have 98.7% sensitivity and 100% specificity in a Western country[18] and 100% sensitivity and 96% specificity in Japan in comparison with the urea breath test.[7] A cut off optical density of 0.30 was chosen according to Asaka *et al*.[7] Serum pepsinogen I and II concentrations were also measured by radioimmunoassay (Dainabot Co. Ltd, Tokyo, Japan) as possible indicators of the histological status of the gastric mucosa.[14 19 20]

STATISTICAL ANALYSIS

Comparisons were made by Stat View 4.0 software (Abacus Concepts, Inc., Berkeley, California, USA) using a non-parametric Mann-Whitney U test. Linear regression analysis was performed by the same software.

TABLE 1 *Patient details*

Group	*H pylori status**	*Young/old†*	*Years investigated‡*	*Age§*	*M/F*
1	Negative	Non-elderly	1970s	50 (3)	8/7
2	Negative	Non-elderly	1990s	48 (3)	7/7
3	Negative	Elderly	1970s	76 (1)	6/6
4	Negative	Elderly	1990s	76 (2)	7/7
5	Positive	Non-elderly	1970s	46 (3)	7/6
6	Positive	Non-elderly	1990s	48 (3)	7/6
7	Positive	Elderly	1970s	75 (2)	7/9
8	Positive	Elderly	1990s	76 (2)	6/7

*Antibody against *H pylori* present (positive) or absent (negative).
†Non-elderly (<65 years); elderly (>65 years).
‡1970s (1971–5); 1990s (1991–5).
§Results are expressed as mean (SEM).

Results

Age distribution among groups 1, 2, 5, and 6, and among groups 3, 4, 7, and 8 was not significantly different (table 1). Sex distribution was not different among all the groups. Gastric acid secretion in elderly subjects was lower than that in non-elderly individuals both in the 1970s and 1990s, irrespective of the presence of *H pylori* infection (figs 1 and 2). When the effect of *H pylori* infection on gastric acid secretion was investigated for each period, the infection decreased BAO and MAO both in the 1970s and 1990s and mainly in elderly persons (figs 1 and 2).

When the data obtained in the 1970s were compared with data from the 1990s, it was confirmed that acid secretion in the 1990s was higher in both the non-elderly and elderly, regardless of *H pylori* infection (figs 1 and 2). While both BAO and MAO were elevated in the 1990s, the increase in MAO was more prominent than that of BAO. Therefore, MAO:BAO ratios in elderly individuals, for example, have increased from 3.28 to 4.25 (p<0.01) in *H pylori* negative individuals and from 3.69 to 4.04 (p<0.05) in *H pylori* positive subjects over the past 20 years (table 2). Although the differences did not reach statistically significant levels, a similar increase in the MAO:BAO ratio was also observed in non-elderly individuals. These observations indicated that not only basal gastric acid secretion but also the responsiveness of acid secretion to pentagastrin has increased over the past 20 years in Japan.

Serum gastrin concentrations in *H pylori* positive elderly subjects were however higher than in non-elderly subjects, both in the 1970s and 1990s. In *H pylori* negative subjects, gastrin concentrations in the elderly were greater than those in non-elderly subjects only in the 1970s (fig 3). Although *H pylori* infection tended to increase serum gastrin concentrations in both the 1970s and 1990s, irrespective of age, the

TABLE 2 *MAO:BAO ratio in the eight groups*

Group	*MAO:BAO ratio*	*Gastrin (pg/ml)*
1	3.77 (0.14)	81.8 (5.7)
2	4.12 (0.17)	92.7 (4.4)
3	3.28 (0.14)	104.8 (5.6)
4	4.25 (0.20)	102.0 (5.7)
5	3.82 (0.26)	88.4 (6.0)
6	3.90 (0.07)	93.9 (4.8)
7	3.69 (0.31)	114.1 (3.5)
8	4.04 (0.06)	114.0 (4.8)

Differences in the MAO:BAO ratio were significant between groups 3 and 4 ($p<0.01$) and groups 7 and 8 ($p<0.05$).
Differences in gastrin concentrations were significant between groups 1 and 3 ($p<0.01$), groups 5 and 7 ($p<0.01$), and groups 6 and 8 ($p<0.05$).

difference did not reach statistically significant levels (fig 3).

There was a negative correlation between BAO and serum gastrin in the 1970s ($r=-0.61$, $p<0.05$) and also in the 1990s ($r=-0.56$, $p<0.05$). When the correlations between these two parameters were compared, it was clear that basal acid secretion in the 1990s was higher than that in the 1970s in spite of almost the same concentrations of gastrin (fig 4).

Serum pepsinogen I concentrations were higher in the 1990s than in the 1970s, irrespective of age and *H pylori* infection (fig 5). In *H pylori* positive subjects, the elderly showed lower pepsinogen I concentrations than non-elderly subjects. Pepsinogen II concentrations, however, were higher in *H pylori* positive subjects than in *H pylori* negative individuals not only in the 1970s but also in the 1990s, irrespective of the age of the subjects (fig 6). This result confirmed the reports by Hunter *et al*[21] and Wagner *et al*.[22] There was a strong positive correlation between serum pepsinogen I and gastric acid secretion (BAO: $r=0.71$, $p<0.01$; MAO: $r=0.79$, $p<0.01$) as shown in fig 7.

One additional interesting observation is the difference in acid secretion between male and female subjects. Both the BAO and MAO of

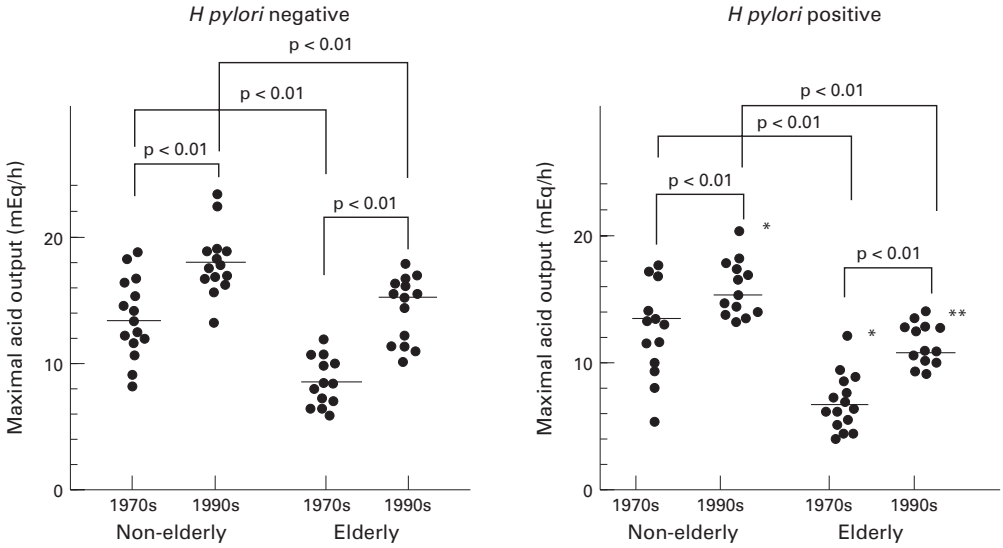

*Figure 2: MAO in the eight groups. Each dot represents a single case. Horizontal lines indicate medians of individual groups. **Significant difference ($p<0.01$) between H pylori positive and negative groups (group 8 v group 4); *significant difference ($p<0.05$) between H pylori positive and negative groups (group 6 v group 2, and group 7 v group 3).*

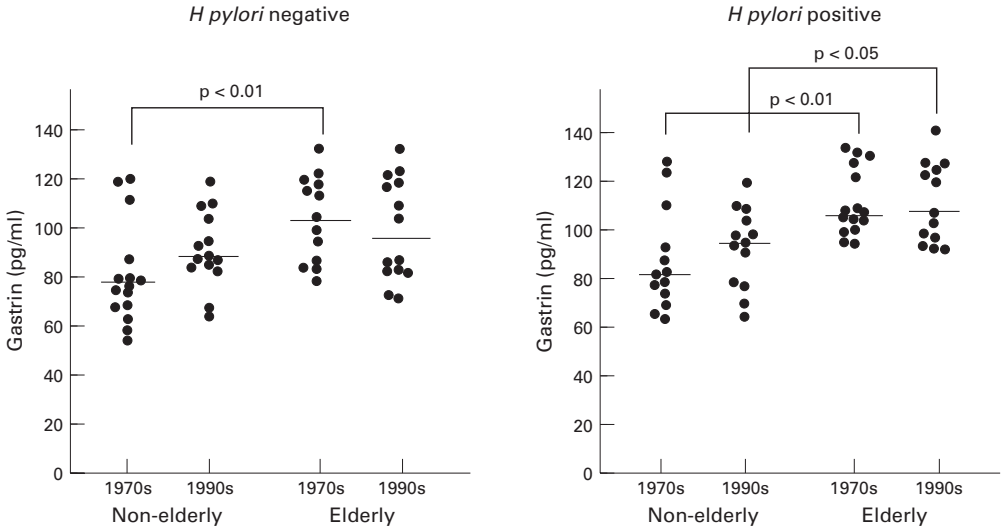

Figure 3: Serum gastrin concentrations in the eight groups. Each dot represents a single case. Horizontal lines indicate medians of individual groups.

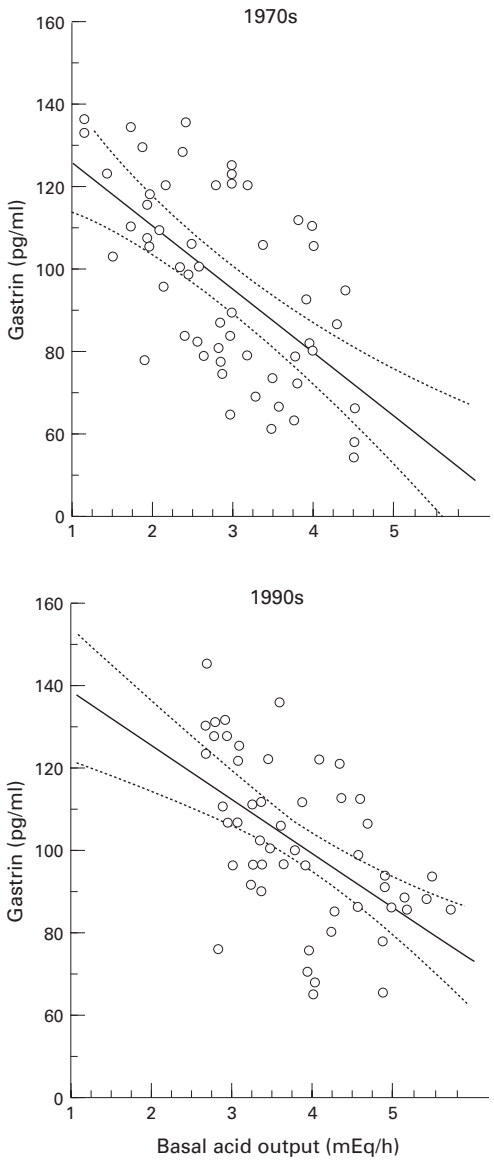

Figure 4: Correlation between serum gastrin concentrations and BAO in the 1970s and 1990s. Each dot represents a single case. Solid lines represent the regression plots; dotted lines represent 95% confidence bands.

female groups were higher than those of male groups, mainly in elderly persons irrespective of *H pylori* infection (table 3).

Discussion

The observations that gastric acid secretion decreases with aging in Japan is in sharp contrast to the observations reported from many Western countries.[1–6] The causative mechanism of the decreased acid secretion in elderly persons has been attributed to a higher prevalence of *H pylori* infection in Japan in comparison with that in Western countries.[7–10] Indeed, in one Western country, a group of elderly subjects with a very high positive rate of *H pylori* infection (81.8% antibody positive rate) was reported to show decreased gastric acid secretion in response to the injection of gastrin.[23] Infection with *H pylori* causes chronic inflammation in the gastric mucosal tissue with resulting atrophy of the gastric gland.[24–26] This atrophy is believed to be a major cause of the decreased acid secretion in the elderly.[27] This study clearly demonstrated decreases in BAO and MAO in elderly subjects in the 1970s as well as in the 1990s, confirming previous reports in Japan.[5 6]

The interesting point to be noted in this study is that even in non-infected elderly subjects, there was lower acid secetion than in younger subjects. These data suggest the presence of factors other than *H pylori* which decrease acid secretion. This concept is also supported by the work of Satoh *et al*[28] and Schlewper *et al*.[29] Satoh *et al* found a positive correlation between age and extent of endoscopy proven atrophic gastritis in both *H pylori* positive and negative patients. Schlewper *et al* clearly suggested the presence of *H pylori* unrelated atrophic gastritis in the Japanese in their comparison of Japanese and Dutch working populations.

In most subjects, infection with *H pylori* is believed to be established in childhood and at least by the age of 40 years in Japan, and the infection continues until its termination by administration of a large amount of antibiotics.[7] Several methods are available to detect the presence of infection.[30 31] The detection of IgG antibody to *H pylori* in serum, which was used in this study, is one of the most sensitive and specific methods available.[7 18 30–32] Furthermore, detection by this method is not influenced by the patchy distribution of this microorganism in the stomach, often observed in the elderly. This method was the only way to determine possible infection with *H pylori* in subjects whose gastric acid secretion was investigated in the 1970s. In subjects with advanced gastric atrophy and achlorhydria, the titre of serum anti-*H pylori* antibody may fall off and become seronegative in the course of developing more severe atrophic gastritis. There is a possibility therefore that some subjects in the *H pylori* negative group, especially those tested in the 1970s, may in fact be false negatives. It is not likely, however, that many false negative subjects were included in the *H pylori* negative groups in this study. Our subjects had high serum pepsinogen I concentrations. Especially in subjects classified into the *H pylori* negative groups, no subject had a serum pepsinogen I concentration below 30 ng/ml. This clearly showed the absence of cases of severe atrophic gastritis in this study.[19 20] Furthermore, several papers from Japan and Western countries have shown that subjects who had developed progressive atrophic gastritis remained *H pylori* seropositive, although the *H pylori* infection rate as measured by staining of gastric biopsy specimens declined with increasing atrophy.[33–35] Thus, the immunoassay of anti-*H pylori* antibody, which has high sensitivity (over 98%) and specificity (over 96%) not only in Western countries but also in Japan, may be reliable enough to detect gastric *H pylori* infection in this study.

When the effects of *H pylori* infection on BAO and MAO were tested, the infection was demonstrated to decrease gastric acid secretion mainly in the elderly. This is quite reasonable,

since a possibly long lasting infection in elderly persons should cause higher grade atrophy of the gastric glands with a resulting decrease in gastric acid secretion. Furthermore, several recent studies indicated that a decrease in gastric acid secretion accelerates colonisation of the fundic gland mucosa by *H pylori* leading to the induction of corpus gastritis and a further decrease in acid secretion.[36–38]

When acid secretion was compared between the 1990s and 1970s, it was clearly shown to be augmented in the 1990s. It should be emphasised that the augmentation of gastric acid secretion was not influenced by *H pylori* infection. Even in the individuals without *H pylori* infection, the increased acid secretion was observed in the 1990s both in the young and old. It is evident therefore that the increase in acid secretion over these past 20 years has been caused not only by the decreased infection rate of *H pylori* but also by some unknown factors. Although this additional modifying factor has not been identified, the improvement in gastric acid secretion over 20 years may be related to changes in dietary habits in Japan. There has been a remarkable increase in dietary fat intake and a modest increase in protein consumption over the past 20 years.[39] High dietary fat is a well known risk factor for colorectal cancers.[40] With the increased consumption of fat in Japan, we have observed a remarkable increase in the number of patients suffered from colorectal cancers.[41] The changes in dietary habits, especially the increased consumption of fat, may therefore be a possible factor influencing the change in acid secretion.

Although the causative mechanism of increased acid secretion in the past 20 years in Japan is not fully understood, our data confirmed the presence of a strong positive correlation between gastric acid secretion and serum pepsinogen I concentrations. Our data also indicated that pepsinogen I concentrations in the 1990s were higher than those in the 1970s. As serum pepsinogen I is known to be a good predictive indicator of gastric mucosal atrophy, the attenuated gastric mucosal atrophy in the 1990s may be a factor which is related to the increased acid secretion.[19 20]

It should be mentioned that gastric acid secretion in Japanese subjects is still lower than that in Europeans and Americans, even in the 1990s.[4] As *H pylori* is reported to induce chronic gastritis more easily in subjects with decreased acid secretion,[25 42 43] the low gastric acid secretion in the Japanese may be one of the

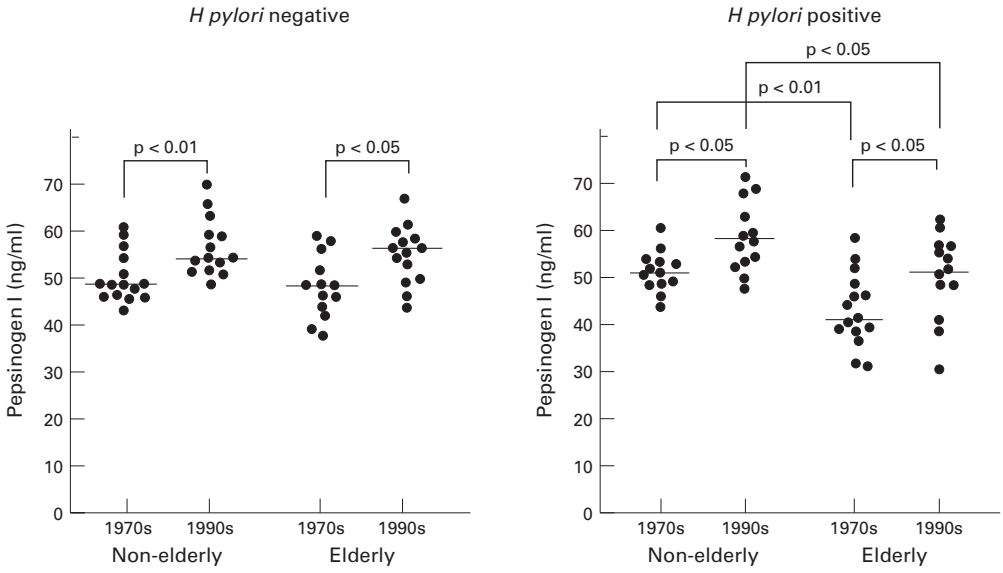

Figure 5: Serum pepsinogen I concentrations in the eight groups. Each dot represents a single case. Horizontal lines indicate medians of individual groups.

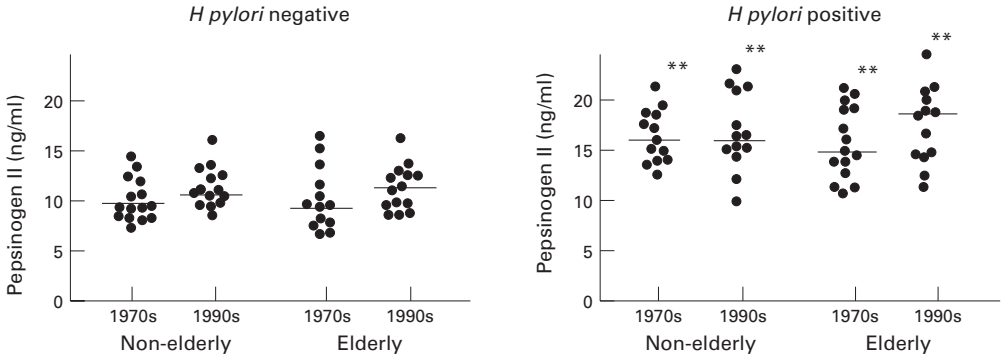

*Figure 6: Serum pepsinogen II concentrations in the eight groups. Each dot represents a single case. Horizontal lines indicate medians of individual groups. **Significant difference ($p<0.01$) between H pylori positive and negative groups (group 5 v group 1, group 6 v group 2, group 7 v group 3, and group 8 v group 4).*

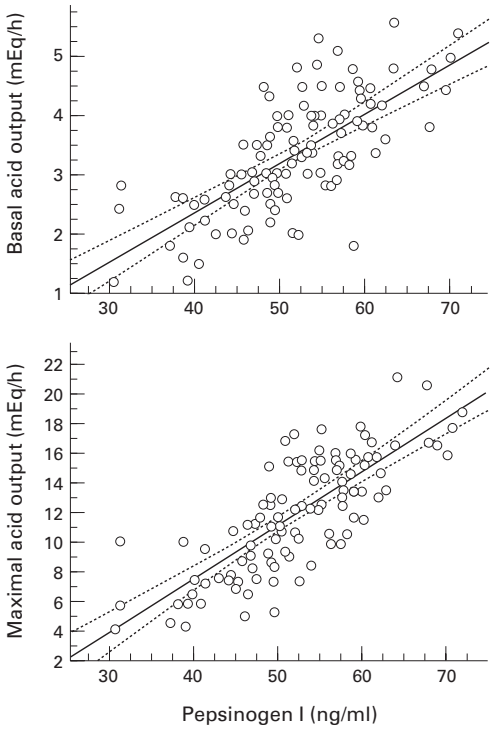

Figure 7: Correlation between serum pepsinogen I concentrations and gastric acid secretion. Each dot indicates a single case. Solid lines represent the regression plots; dotted lines represent 95% confidence bands.

causative factors of the higher incidence of *H pylori* infection and atrophic gastritis in Japan. On the other hand, elevated gastric acid secretion is reported frequently to cause gastric metaplasia in the duodenum.[44 45] This metaplastic epithelium is vulnerable to *H pylori* infection with resulting ulcer formation in the duodenum. The higher duodenal ulcer:gastric ulcer ratio in Western countries than in Japan may therefore be due to *H pylori* infection of the metaplastic gastric epithelium in the duodenum where the acid is stronger than in the Japanese.[46]

When gastric acid secretion in response to endogenous gastrin was investigated, it became clear that larger amounts of acid were secreted in response to the same concentrations of serum gastrin in the 1990s. This result suggested the higher responsiveness of parietal cells to gastrin or the presence of increased parietal cell mass in the 1990s in comparison with that in the 1970s. Although gastrin is a potent endogenous secretagogue for acid secretion, this result suggests that the response of gastric fundic glands to gastrin could be influenced by factors such as *H pylori* infection, chronological age, and the era when the investigation was done.

Reflux oesophagitis and peptic ulcer diseases are more frequently found in elderly women than in elderly men in Japan.[46 47] This is speculated to be due to the higher gastric acid secretion in women. Our data support this idea and confirmed that gastric acid secretion is higher in women than in men, especially in the elderly, irrespective of the presence or absence of *H pylori* infection. This is in sharp contrast to the data reported from many Western countries, where gastric acid secretion is reported to be higher in men than in women.[1 3 4] The lower acid secretion in elderly men observed in this study may therefore be due to factors other than *H pylori* infection, such as drinking or eating foods culturally more prevalent in Japan than in Western countries.

In summary, we have confirmed that gastric acid secretion has increased over the past 20 years from the 1970s in Japan irrespective of *H pylori* infection, suggesting the presence of factors which increase gastric acid secretion other than the decreased infection rate of *H pylori*.

TABLE 3 *Gastric acid secretion in men and women*

Group	*Sex*	*Number*	*Age*	*BAO (mEq/h)*	*MAO (mEq/h)*
1	M	8	52 (4)	3.4 (0.3)	13.3 (1.6)
	F	7	47 (3)	3.7 (0.3)	13.8 (0.7)
2	M	7	48 (4)	4.3 (0.4)	17.5 (1.2)
	F	7	48 (5)	4.6 (0.2)	18.9 (0.8)
3	M	6	76 (2)	2.3 (0.1)	7.4 (0.3)
	F	6	75 (3)	3.3 (0.3)	10.7 (0.6)
4	M	7	75 (3)	3.1 (0.2)	13.6 (1.0)
	F	7	76 (2)	4.0 (0.2)	16.0 (0.8)
5	M	7	48 (4)	3.0 (0.3)	11.0 (1.6)
	F	6	45 (4)	3.5 (0.2)	14.1 (1.2)
6	M	7	52 (4)	3.8 (0.3)	14.9 (1.1)
	F	6	43 (5)	4.5 (0.2)	17.1 (0.4)
7	M	7	75 (2)	1.6 (0.4)	5.7 (0.6)
	F	9	75 (2)	2.5 (0.2)	8.9 (0.7)
8	M	6	76 (3)	2.8 (0.1)	10.9 (0.7)
	F	7	77 (2)	3.1 (0.1)	13.0 (0.6)

Results are expressed as mean (SEM).
Differences in BAO were significant between men and women in groups 3, 4, and 7 ($p<0.01$), and in groups 6 and 8 ($p<0.05$). Differences in MAO were significant between men and women in group 3 ($p<0.01$), and in groups 6, 7, and 8 ($p<0.05$).

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