Hypergastrinemia—a Risk Factor for Myocardial Infarction?

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We determined gastrin and pepsinogen I in serum samples obtained in 1968–69 from 256 women (175 women 54 years old and 81 women 60 years old when sampled). The concentration of gastrin in serum was significantly (p <0.01) and positively correlated with the incidence of myocardial infarction during a 12-year follow-up, with age taken into account as a background variable in multivariate analysis. It was not correlated with overall mortality or with the 12-year incidences of angina pectoris, electrocardiographic changes indicating ischemic heart disease, or stroke. The correlation with myocardial infarction was independent of smoking, systolic blood pressure, indices of obesity, concentrations of blood glucose during fasting and of serum triglycerides and cholesterol, and of the presence of diabetes mellitus at screening or during follow-up. Serum gastrin was significantly (p <0.05) related to body mass index (positive age-specific relation) and to smoking (negative age-specific relation). These findings may provide a new aspect to analysis of risk factors for myocardial infarction.

Additional Keyphrases: longitudinal population study of women cardiovascular disease chronic atrophic gastritis achlorhydria bacterial metabolism smoking serum cholesterol serum triglycerides diabetes mellitus obesity blood pressure gastrointestinal disease

Chronic atrophic gastritis, a common condition in the elderly (1), is not considered to have any medical consequences in most cases, but pernicious anemia, benign or malignant gastric neoplasia, gastric ulcer, iron deficiency (2, 3), and bacterial overgrowth (4) may occur. The condition is often dichotomized as antrum-sparing gastritis (type A) or antral gastritis (type B), although the validity of this discrimination has recently been questioned (5, 6). The two forms have been described as having differing symptomatologies, differing prevalences of autoantibodies against parietal cells and against intrinsic factor, and differing prevalences of increase in the circulating concentration of gastrin. The relative prevalence of the two forms varies between different reports, antrum-sparing gastritis being found in 62 to 95% of the patients (7, 8). Some cases of antral gastritis may actually represent a pangastritis (6). Normally, and in antrum-sparing gastritis, there is usually a negative relationship between serum gastrin concentration and gastric secretory capacity for hydrogen ion, but hypergastrinemia may be present in individuals with normal gastric acid output, in particular in cases of diabetes mellitus (9) and rheumatoid arthritis (10), in the presence of antiparietal cell antibodies (11), and in renal failure. During an analytical and clinical evaluation of a radioimmunoassay for gastrin we found a high prevalence of increased gastrin concentration in serum of elderly men and women (12). The longitudinal prospective study of women, which was started in Gothenburg in 1968–69, offered us an opportunity to evaluate the long-term consequences of hypergastrinemia. As described in an accompanying report (13), we analyzed gastrin and group I pepsinogens (pepsinogen I) in frozen serum samples from women who were 54 or 60 years old when they participated in the first study, and in a hypergastrinemic and a reference group after six and 12 years. The clinical follow-up showed an unexpectedly high morbidity from myocardial infarction in subjects with serum gastrin concentration ≥400 ng/L. These findings form the basis of the present communication.

Study Population and Methods

Study Population, Blood Sampling

Procedures used in this longitudinal population study of randomly selected women are summarized in an accompanying paper (13). In brief, women from five different age strata (38–60 years) were first studied in 1968–69 (14, 15) and then six (16) and 12 (17) years later. Participation rates were high. We obtained information on participants through clinical examinations and laboratory investigations, and on nonparticipants by interviews. The present study reports findings from the two oldest age strata, those 54 and 60 years old in 1968–69. Serum obtained after an overnight fast was kept frozen since the initial study at −22 to −28 °C in a cold-storage building without defrosting, ensuring minimal water loss.

Serum Gastrin Assay

In 1984 we measured the gastrin concentration of the serum samples kept frozen since 1968–69, 1974–75, and 1980–81, using a noneselective antigastrin antiserum, i.e., one that does not discriminate between gastrin-17 and gastrin-34 (12). One nanogram of the calibrator (nonsulfated gastrin-17) corresponds to 0.48 pmol and to 0.95 milli-int. unit of the Research Standard A (68/439, National Institute for Biological Standards and Control, London, U.K.). In the clinical evaluation of the method used (12), we found atrophic gastritis or achlorhydria (or both) in all patients whose concentration of gastrin in serum exceeded 400 ng/L, except in those with a history of gastroduodenal ulcer. In the present study all serum samples obtained from individuals having such an increase in gastrin concentration were also analyzed with assays stated to be specific for gastrin-17 and gastrin-34 (Immuno Nuclear Corp., Stillwater, MN 55082).

Pepsinogen I was determined with a kit from Sorin Biomedica, 13040 Saluggia/Vercelli, Italy. The performance of these assays in our hands is reported in an accompanying paper (13).

End-Points during the Follow-up Period 1968–69 to 1980–81

Cases with a history of myocardial infarction at the time of the initial examination were excluded when the risk for myocardial infarction as an end-point was assessed. Similarly, cases with positive findings for angina pectoris or electrocardiographic changes indicating ischemic heart disease or stroke at the initial examination were excluded from the final calculations for corresponding end-points.
Nonfatal myocardial infarction. We interviewed all participants and most nonparticipants (in all, 96.9%) for chest pain during the 12-year follow-up. We also evaluated records of all women who were hospitalized because of chest pain. We based the diagnosis of acute myocardial infarction (18) on the presence of at least two of the following three criteria: (a) central chest pain of more than 15 min duration, with onset during the previous 48 h and (or) frank pulmonary edema without previously known valvular heart disease and (or) shock without suspicion of acute hypovolemia or intoxication; (b) transient rise of serum aspartate aminotransferase (EC 2.6.1.1) activity, with a maximum evident about 24 h after onset of symptoms, in combination with a less pronounced increase or lack of increase of serum alanine aminotransferase (EC 2.6.1.2) activity; and (c) typical electrocardiographic changes.

Fatal myocardial infarction. We accepted fatal myocardial infarction as a diagnosis if so stated in the death certificate. "Silent" myocardial infarction. We defined "silent" myocardial infarction as electrocardiographic changes indicating ischemic heart disease interpreted as Minnesota Code 1.1 (19, 20) but without a history of myocardial infarction.

In our analysis we used the combined incidences of nonfatal and fatal myocardial infarction. We included the incidence of "silent" myocardial infarction only when indicated.

Angina pectoris. We defined angina pectoris as a history, obtained by interview, of central chest pain provoked by hurrying or walking uphill and disappearing at rest (21).

Electrocardiographic changes indicating ischemic heart disease. Minnesota Codes (19, 20) 1.1–2, 4.1, 5.1–2 (in the absence of 3.1), 6.1, or 7.1 were used for this classification.

Stroke. We required a hospital diagnosis for stroke (22) in nonfatal cases. Criteria in fatal cases were signs consistent with a recent cerebrovascular accident at autopsy or a death certificate with stroke recorded as the major cause of death.

Mortality. Death certificates were obtained for all participants who died. Autopsy was performed in three of five fatal myocardial infarction cases, in three of five fatal stroke cases, and in 15 of 22 women who had other diagnoses in the death certificates.

Statistical Methods

We used two-tailed tests. For analysis of frequencies in morbidity and mortality we used the extension of the chi-squared procedure according to Mantel–Haenszel with one degree of freedom (23) minimizing the effect of age as a confounding factor. We calculated relative risks (risk ratios) and their confidence limits according to the Mantel–Haenszel estimation (23, 24). We tested correlation between initial gastrin concentrations and end-points by means of Pitman's nonparametric permutation test (25), and, when adjusting for confounding variables, we used an extension of Mantel–Haenszel's procedure to permutation tests (23).

Results

Distribution of Serum Gastrin Concentration

Gastrin concentrations in serum ranged between 21 and 1200 ng/L at the initial examination. The distribution was markedly skewed, as demonstrated in an accompanying paper (13), with about 80% of values below 100 ng/L. In 20 women (8%) the serum gastrin concentration exceeded 400 ng/L. From 16 of these 20 women we had obtained a serum sample in one or both follow-up studies (1974–75 and 1980–81, respectively). Only two women demonstrated a normalization of serum gastrin concentration during the follow-up (13). All samples with serum gastrin ≥400 ng/L had increased concentrations of gastrin-17, gastrin-54, or both, as measured with specific assays.

Clinical and Laboratory Findings in Women with Serum Gastrin Concentration ≥400 ng/L

Table 1 shows findings in women with serum gastrin concentration ≥400 ng/L (14 women out of 175 initially 54 years old, i.e., 8.0%, and six women out of 81 initially 60 years old, i.e., 7%).

Initial study. Antibodies against thyroid membranes ("anticrassommal antibodies") were found in more than half of the women, but concentrations of thyrotropin and prolactin in serum were within normal limits. One woman had had diabetes mellitus type II for a year. We saw no differences as compared with the others with respect to anemia, iron deficiency judged from serum iron concentration or current iron therapy, operative treatment of malignant disorder, goiter, rheumatic or gastrointestinal disease (operative treatment of ulcer, biliary tract disease, or appendicitis), renal disease, or use of antidepressive drugs. Of the 20 women, 19 were postmenopausal, as judged from menstrual history and corroborated by increased follitropin concentration in serum (all polypeptide hormone assays were double-antibody polyethylene glycol radioimmunoassays similar to the one used for gastrin; data not shown).

Follow-up results. The clinical follow-up revealed a high 12-year incidence of myocardial infarction (five of 20 women, 25%) and overall mortality (five of 20 women, 25%) (Table 1). Four women died from myocardial infarction. Two of the four women were autopsied, revealing a large recent myocardial infarction in one woman and one recent and one previous infarctions in the other woman. In both cases there were atheromatous changes in the coronary vessels. Of the two fatal cases not autopsied, one had had one myocardial infarction and one had had repeated myocardial infarctions before the fatal one. The nonfatal case had the characteristic chest symptoms and electrocardiographic changes as well as pattern of aminotransferase change typical of myocardial infarction. There was no overrepresentation of women who developed malignant disorders, diabetes mellitus, thyroid disease, or other autoimmune disorders during the follow-up period. One woman developed pernicious anemia. A significant (p <0.01) reduction in mean blood hemoglobin concentration was observed from 1968–69 (138 g/L) to 1980–81 (125 g/L) in those 13 women with serum gastrin ≥400 ng/L who took part in both studies. The corresponding mean figures for the rest were 137 and 133 g/L for the two times. The 12-year intraindividual changes in body mass (mean increase by 2.0 kg) and body mass index (1.6 kg · m⁻²) were not significantly different from the changes in the rest: 0.3 kg and 0.6 kg · m⁻², respectively.

Incidence of Cardiovascular Disease

Table 2 shows observed and expected numbers as well as age-adjusted risk ratios for incidences of myocardial infarction, angina pectoris, electrocardiographic changes indicating ischemic heart disease, and for stroke in women with serum gastrin concentration ≥100 ng/L and ≥400 ng/L, respectively. The 95% confidence intervals for the age-adjusted relative risks are also given. There was a significantly increased risk ratio for myocardial infarction in women who had serum gastrin concentration ≥100 ng/L (p <0.05) or ≥400 ng/L (p <0.001, also if only the four cases who were nondiabetic at screening were included; p <0.01 if only cases with serum peptopinogen <30 μg/L were included, see Figure 2). Similar results were obtained when "silent"
### Table 1. Clinical Data for 20 Women with Serum Gastrin ≥ 400 ng/L in 1968–69, as Determined in 1984 with a Nonelective Antigastrin Antiserum

<table>
<thead>
<tr>
<th>Serum gastrin, ng/L</th>
<th>Alcohol (Yes/No)</th>
<th>Blood pressure, mm Hg</th>
<th>Hemoglobin, g/L</th>
<th>Triglycerides, mmol/L</th>
<th>Cholesterol, mmol/L</th>
<th>Anti-M</th>
<th>Follow-up (1980–81)</th>
<th>Observation(s) during follow-up</th>
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<td>54-year-old women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>483</td>
<td>No</td>
<td>64.4, 124</td>
<td>135</td>
<td>0.6</td>
<td>60</td>
<td>Neg</td>
<td>102, 700</td>
<td>Dead</td>
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<tr>
<td>470</td>
<td>Yes</td>
<td>66.3, 148</td>
<td>141</td>
<td>1.1</td>
<td>7.2</td>
<td>100</td>
<td></td>
<td></td>
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<td>No</td>
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<td>2.0</td>
<td>7.1</td>
<td>100</td>
<td></td>
<td></td>
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<tr>
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<td>No</td>
<td>55.6, 132</td>
<td>134</td>
<td>0.8</td>
<td>7.5</td>
<td>1600</td>
<td></td>
<td></td>
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<tr>
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<td>130</td>
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<td>5.7</td>
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<td>53.2, 158</td>
<td>166</td>
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<td>8.4</td>
<td>Neg</td>
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<td>66.1, 132</td>
<td>142</td>
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<td>8.2</td>
<td>100</td>
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<td>&gt;1200</td>
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<td>136</td>
<td>0.8</td>
<td>7.3</td>
<td>100</td>
<td>59.7, 137</td>
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<tr>
<td>&gt;1200</td>
<td>No</td>
<td>70.8, 156</td>
<td>136</td>
<td>0.5</td>
<td>5.2</td>
<td>1600</td>
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<td>7.9</td>
<td>1600</td>
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<tr>
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<td>135</td>
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<td>6.3</td>
<td>1600</td>
<td>67.1, 131</td>
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<tr>
<td>&gt;1200</td>
<td>No</td>
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<td>134</td>
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<td>7.2</td>
<td>100</td>
<td>60.1, 122</td>
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<tr>
<td>&gt;1200</td>
<td>No</td>
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<td>138</td>
<td>1.2</td>
<td>6.7</td>
<td>1600</td>
<td>96.3, 105</td>
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<tr>
<td>&gt;1200</td>
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<td>70.2, 182</td>
<td>129</td>
<td>1.9</td>
<td>6.1</td>
<td>1600</td>
<td>61.3, 119</td>
<td></td>
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<tr>
<td>60-year-old women</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>490</td>
<td>No</td>
<td>69.9, 132</td>
<td>125</td>
<td>1.0</td>
<td>7.8</td>
<td>Neg</td>
<td>61.3, 145</td>
<td></td>
</tr>
<tr>
<td>702</td>
<td>No</td>
<td>58.8, 172</td>
<td>138</td>
<td>0.9</td>
<td>8.2</td>
<td>2500</td>
<td>59.5, 116</td>
<td></td>
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<tr>
<td>745</td>
<td>No</td>
<td>78.9, 138</td>
<td>146</td>
<td>1.1</td>
<td>7.2</td>
<td>100</td>
<td>73.0, 137</td>
<td></td>
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<tr>
<td>903</td>
<td>No</td>
<td>66.0, 174</td>
<td>156</td>
<td>1.5</td>
<td>5.3</td>
<td>Neg</td>
<td>86.1, 122</td>
<td></td>
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<tr>
<td>960</td>
<td>No</td>
<td>81.2, 158</td>
<td>138</td>
<td>1.6</td>
<td>8.3</td>
<td>Neg</td>
<td>86.1, 122</td>
<td></td>
</tr>
</tbody>
</table>

*Daily (D), weekend (W), or nondrinker (N). *Blood pressure of the subject in sitting position after about 5 min rest, measured with a mercury manometer. *Microsomal antibodies, reciprocal titer. *Cases not commented on were apparently healthy.

### Table 2. Twelve-Year Incidence and Relative Risk for Myocardial Infarction, Angina Pectoris, "Coronary ECG," Stroke, and Total Mortality

<table>
<thead>
<tr>
<th>End-points</th>
<th>Initial serum gastrin &gt;100 ng/L</th>
<th>Initial serum gastrin &gt;400 ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>5*</td>
<td>0.9</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>&quot;Coronary ECG&quot;</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Total mortality</td>
<td>10</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Results, adjusted for age, are given for women with initial serum gastrin concentration >100 and >400 ng/L, respectively.

*Coronary ECG, electrocardiographic changes indicating ischemic heart disease. *Figures within parentheses denote 95% confidence interval of relative risk. Statistically significantly different (*p<0.05, *p<0.001) from the number of women with concentration of serum gastrin less than the concentration stated.

Myocardial infarction was also included. There was no significantly increased risk ratio as far as angina pectoris, electrocardiographic changes indicating ischemic heart disease, or stroke were concerned (Table 2). There were seven cases of myocardial infarction in the 205 women with serum gastrin concentration <100 μg/L; one was fatal (data not shown).

Figure 1 shows the 12-year incidence of myocardial infarction in age-adjusted centiles of serum gastrin concentration. The relationship appeared U-shaped. Taking age into account...
account as a background variable in a nonparametric permutation test we found a significant and positive correlation between the initial gastrin concentration in serum and the 12-year incidence of myocardial infarction (p < 0.01, also when "silent" myocardial infarction was included). By similar analysis we found no significant correlation between the initial gastrin concentration in serum on the one hand and stroke (distribution also shown in Figure 1), angina pectoris, or electrocardiographic changes indicating ischemic heart disease on the other.

Concentrations of Pepsinogen I vs Gastrin in Serum

Figure 2 shows, in the 12 cases of myocardial infarction, the concentrations in serum of pepsinogen I as compared with gastrin in relationship to an area defined from the values found in the complete population sample except for outlier and borderline values (13). Two outliers were found. One case had a serum pepsinogen I level greatly exceeding the upper reference limit (115 μg/L) reported in apparently healthy individuals 20–45 years old (26). This was the single case of diabetes mellitus found in 1968–69, with the first signs of disease one year earlier. The other outlier value represents a woman, normoglycemic at screening, in whom signs of diabetes mellitus started six years later. None of these two cases had any gastrointestinal symptoms or complaints. Other "prediabetic" women—i.e., those 11 who developed diabetes during the 12 years—had serum gastrin concentrations below the 80th centile of the total population sample, as had five of six diabetic women (one diabetic woman had 131 ng/L).

Figure 1. Age-standardized 12-year incidences of myocardial infarction, stroke, and total mortality by percentiles of the serum gastrin concentration in 1968–69 (gastrin measured in 1984)

SERUM GASTRIN, PERCENTILES

MYOCARDIAL INFARCTION

STROKE

TOTAL MORTALITY

Fig. 1. Initial serum pepsinogen I vs gastrin concentration in the 12 cases developing myocardial infarction during the 12-year follow-up Shaded area covers values for the entire population sample except for outlier or borderline values (13)

There is a positive correlation between serum gastrin and myocardial infarction. The significant positive correlation between serum gastrin and myocardial infarction, the concentrations in serum of pepsinogen I as compared with gastrin in relationship to an area defined from the values found in the complete population sample except for outlier and borderline values (13). Two outliers were found. One case had a serum pepsinogen I level greatly exceeding the upper reference limit (115 μg/L) reported in apparently healthy individuals 20–45 years old (26). This was the single case of diabetes mellitus found in 1968–69, with the first signs of disease one year earlier. The other outlier value represents a woman, normoglycemic at screening, in whom signs of diabetes mellitus started six years later. None of these two cases had any gastrointestinal symptoms or complaints. Other "prediabetic" women—i.e., those 11 who developed diabetes during the 12 years—had serum gastrin concentrations below the 80th centile of the total population sample, as had five of six diabetic women (one diabetic woman had 131 ng/L).

Serum Gastrin in Relation to Possible Risk Factors for Ischemic Heart Disease

Table 3 shows, in quintiles of initial serum gastrin concentration, the mean values for initial age and initial values of systolic blood pressure, blood glucose during fasting, serum triglyceride and cholesterol concentrations, and body mass index, as well as prevalence of smokers. A significant age-specific positive association was found between serum gastrin and body mass index (p < 0.05). Smoking habits were negatively correlated to serum gastrin (p < 0.05). No other significant associations were observed.

Gastrin 17/Gastrin 34 Ratio

G17/G34 ratios ranging from 0.67 to 3.1 were observed for the five women with serum gastrin ≥400 ng/L who developed myocardial infarction (0.92 and 2.1 in the two women with markedly elevated pepsinogen I concentration, see Figure 2). These values were within the range we observed for women not developing myocardial infarction during the study period (0.11–3.9, 13).

Multivariate Analysis Including Possible Risk Factors

The significant positive correlation between serum gastrin and myocardial infarction remained when, in addition to age, we included as background variables in the multivariate analysis: smoking, systolic blood pressure, index of obesity (body mass index and waist/hip circumference ratio, 17), concentrations of fasting blood glucose and of serum triglycerides and cholesterol, or presence of diabetes mellitus at screening or during follow-up.

Mortality

The mortality from any cause in relation to initial serum gastrin concentrations is shown in Table 2. We used the same cutoff limits as for cardiovascular disease. There was no significantly increased mortality (0.05 < p < 0.10) when data on women with serum gastrin concentration ≥100 ng/L or ≥400 ng/L were compared with data for other women. Figure 1 shows overall mortality in relation to age-adjusted centiles of serum gastrin concentration. There was no significant correlation (0.05 < p < 0.10) on multivariate analysis.

Discussion

In this study special attention was given to women who had serum gastrin concentrations ≥400 ng/L, as such values usually indicate achlorhydria (12). The cutoff point of 100 ng/L corresponded closely to the 80th percentile in the present study and is often considered as the upper reference limit in clinical practice. In addition, we did a statistical analysis.
analysis with serum gastrin concentration as a continuous variable.

The finding of a correlation between hypergastrinemia in 54- and 60-year-old women and subsequent acute myocardial infarction was unexpected. One can at present only speculate upon the mechanism(s) involved. The U-form relationship illustrated in Figure 2 indicates a relationship to achlorhydria rather than to hypergastrinemia, because a significant proportion of individuals with atrophic gastritis have normal or low gastrin concentrations, either as a result of primary antral gastritis (type B) or of progression of corpus gastritis with hypergastrinemia (type A) to pangastritis. However, we made no endoscopic or gastric secretory studies in this longitudinal population study of women, so we have no direct evidence for chronic atrophic gastritis in the present study. We hoped that determination of serum pepsinogen I would be helpful in assessing the functional state of the gastric mucosa (29, 30). As reported in detail (13), however, we found several women in this study with serum pepsinogen-I concentrations by far exceeding that expected in relation to gastrin in serum. We have also found 14 women with serum pepsinogen >30 μg/L of 29 women with serum gastrin >400 ng/L in an ongoing study of nonselected 57-year-old women, as well as six patients with serum pepsinogen I values of 37 to 176 μg/L out of 19 patients with achlorhydria, the rest having values ranging from 6 to 16 μg/L (mean 8.6 μg/L). Clearly, we need more information on the diagnostic value for atrophic gastritis of serum pepsinogen I determination when applied to population samples rather than to clinical cases or relatives of patients with pernicious anemia (29, 30).

Acholorhydria and development of myocardial infarction may be directly connected, or both may be related to other factors such as senescence or autoimmune disease. We found, however, no association with clinical manifestations of autoimmunity. Alternatively, atrophic gastritis might lead to nutritional disturbance, either as a result of impaired absorption (trace elements?) or of bacterial overgrowth (anaerobic degradation or transformation of essential nutrient or component of intestinal or biliary secretions?). But we saw no evidence for nutritional deficiency associated with hypergastrinemia in our study group.

A negative relationship between smoking habits and hypergastrinemia and a positive relationship between body mass index and hypergastrinemia as observed in our study have not been reported hitherto.

It may seem surprising that an association between achlorhydria and myocardial infarction, if present, has been overlooked in the several large series of patients with atrophic gastritis reported during the years. One explanation may be that interest has been focused on development of gastric neoplasia and (or) of anemia (31). Cardiovascular disease is common in the elderly, and an evaluation of altered prevalence and mortality in study groups of elderly requires use of proper controls. Absence of age-related incidence figures and matched controls may therefore be another explanation. Furthermore, most previous studies of atrophic gastritis were not made on representative population samples—in contrast to the present one. We conclude that more information is required concerning the natural history of hypergastrinemia and that there seem to be good reasons to explore possible relationships between myocardial infarction, gastric achlorhydria, and biochemical changes related to atrophic gastritis.

References


