Serum Pepsinogen I and Gastrin in Relation to Extent and Location of Intestinal Metaplasia in the Surgically Resected Stomach

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A study of 177 patients undergoing distal subtotal gastrectomy indicates that a preoperative serum pepsinogen I (PG I) level below 20 ng/ml predicts the presence of gastric carcinoma and the degree of intestinal metaplasia of the gastric antrum. The serum gastrin level was not predictive of carcinoma or of the degree of intestinal metaplasia. Of the 15 patients with a low serum PG I level, 13 had carcinoma and 2 had atypical polyps. The PG I level in a stored serum sample from 4 of 30 patients fell from normal to abnormal over a period of 8–9 years. Each of these converters had invasive carcinoma of the stomach. This suggests that persons showing a fall in serum PG I to abnormal levels during serial analyses should be evaluated for the possibility of gastric carcinoma.

Intestinal metaplasia may be defined as the replacement of antral or oxyntic mucosa by mutant glands (1, 2) that have the histological and histochemical (3, 4) characteristics of small intestine. Gastric ulcers and cancers frequently occur in the metaplastic antrum, especially in populations at high risk for this tumor (5, 6). Intestinal metaplasia may accompany antral atrophic gastritis (type B gastritis) or atrophic gastritis of the oxyntic mucosa (type A gastritis) (7).

We have previously reported a low serum pepsinogen I (PG I) level to be highly specific, but relatively insensitive, to the presence of intestinal metaplasia of the antrum in individuals of Japanese ancestry (8). In that study the extent of intestinal metaplasia was determined by histological examination of endoscopic biopsies taken from those parts of the stomach known to be at maximal, intermediate, and minimal risk of developing this change (3). The present study was undertaken to relate the PG I and gastrin levels with the extent and location of intestinal metaplasia in surgically resected stomachs, as determined by gross alkaline phosphatase mapping technique (3), and to assess the relation between the PG I level and the histology of gastric cancer. A parallel prospective study of the relationships among PG I, histology, and the stage of gastric cancer is reported separately (9).

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MATERIALS AND METHODS

Subjects. A fasting preoperative blood sample was obtained on the morning of surgery from 177 patients who had an elective partial gastrectomy at the Kuakini Medical Center over a two-year period ending in May 1979 (Table 1). Of these, 59 had gastric cancer, and 110 had

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TABLE 1.

Patient age	Carcinoma*			Duodenal ulcer			Gastric ulcer			Other			Total		
	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
<39	1	1	2	7	1	8	5	6	11				13	8	21
40-49	4	3	7	3	2	5	8	3	11	1		1	16	8	24
50-59	4	5	9	5	2	7	19	9	28	1	1	2	29	17	46
60-69	9	6	15	8	2	10	8	7	15	2	1	3	27	16	43
70-79	14	5	19	2	1	3	2	5	7	1	1	2	19	12	31
80+	6	1	7				1	4	5				7	5	12
Total	38	21	59	25	8	33	43	34	77	5	3	8	111	66	177

*M = male; F = female; T = total.

ulcer disease (77 gastric, 33 duodenal). The remaining 8 had a partial gastrectomy for other reasons: incidental to Whipple procedure (1), lymphosarcoma (1), adenomatous polyps with atypia (2), hyperplastic polyps (3), Menetrier's syndrome (1).

The patients in this series were derived from several races: Japanese, 130 (73.4%); Hawaiian, 16 (9%); Caucasian, 14 (7.9%); Chinese, 3 (1.7%); Korean, 5 (2.8%); and Filipino, 9 (5.1%). Gastric carcinoma was diagnosed in 49 (38%) of the Japanese patients, 5 (31%) of the Hawaiian patients, 2 (40%) of the Koreans, and 3 (21%) of the Caucasians. None of the Chinese or Filipino patients had cancer. This racial distribution reflects the predominantly Japanese patient population of the Kuakini Medical Center. The distribution of carcinoma among the non-Japanese is consistent with community experience.

A subset of these patients, 30 in all, were participants in the Honolulu Heart Study of 8006 Japanese men born between 1900 and 1919 (10). They had been examined in 1968-1970, and 1971-1975, and a serum sample, obtained at random times during one of these examinations, had been stored at −20° C.

The method of patient selection and serum collection from among the patients of many staff surgeons did not permit systematic preoperative acid output analysis.

Estimation of Extent of Metaplasia. The resected stomachs were opened along the greater curvature and stained to demonstrate alkaline phosphatase activity (3). This was supplemented by histologic analysis of mucosal strips from the entire length of the lesser and greater curvatures. The extent of metaplasia was scored by summing its gross or microscopic presence in one or more zones of the stomach, as described in previous reports (3, 5). For analytic purposes these scores were divided into four groups: none, moderate (1-4), extensive (5-8), total (9-12).

The subtotally resected stomach typically includes the entire pyloric antrum, but only the distal third of the gastric corpus. Therefore, the metaplasia score is a more accurate reflection of the extent of metaplasia in the antrum than the corpus. High scores accompany type B gastritis, but low scores may accompany type A gastritis.

Examination of Stomach Cancers. Gastric carcinomas were classified histologically as intestinal, diffuse, or mixed according to the criteria of Lauren (11). Briefly stated, the intestinal type contains definite glands, the diffuse type is composed of signet ring cells with an abundant supporting stroma and mixed forms show both types of growth. Diffuse tumors predominate in younger patients and women, intestinal forms in men and older patients (5). The intestinal form is usually associated with intestinal metaplasia and the diffuse type may occur with no metaplasia. They were staged according to the (TNM) method of the American Joint Committee (12).

Pepsinogen I. A fasting blood sample was obtained from each patient before operation, and the serum was stored in coded vials at −20° C before shipment to Los Angeles in dry ice. The concentration of PG I was determined by a competitive binding, double-antibody radioimmunoassay as previously described (8). A low level is defined as a value of less than 20 ng/ml. Previous studies have indicated that there is little diurnal variation in the PG I level. For this reason comparison of the PG I level in the preoperative specimen with the level in the stored examination specimen could be made on the assumption that any difference would not be the result of different collection times.

Serum Gastrin. Serum gastrin was measured by radioimmunoassay as previously described (14). The antibody used, 1296, had specificity for the C terminal region for gastrin and had approximately 1.5 times higher affinity for little gastrin (G17) than for big gastrin (G34). Pure human G17-1 was used as the standard, and results are expressed as picograms human G17-1 equivalent. Gastrin levels in excess of 100 pg/ml were considered abnormal. Because serum gastrin levels increase in response to eating, it was not possible to assess time trends for gastrin. There was insufficient serum for gastrin analysis in 10 subjects, all of whom had PG I levels in excess of 20 ng/ml.

RESULTS

The distribution of serum PG I and gastrin levels, according to the degree of intestinal metaplasia, is shown in Figure 1. Fifteen of 177 patients (8.5%), all Japanese, had a PG I level below 20 ng/ml, and each had some form of gastric neoplasia (13 carcinoma, 2 atypical adenomatous polyps) and some degree of intestinal metaplasia. The median PG I level decreased with increasing degrees of intestinal meta-

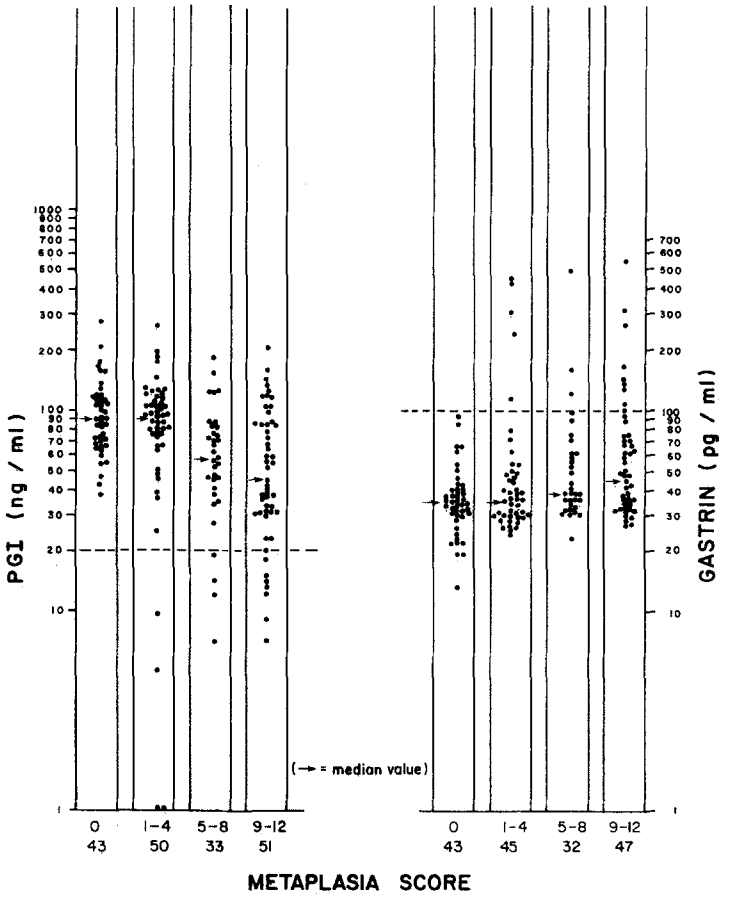

Fig 1. Distribution of PG I and gastrin serum levels in stomachs showing increasing degrees of intestinal metaplasia.

plasia, but severe antral metaplasia was on occasion associated with a high PG I level and modest degrees of antral intestinal metaplasia with a low PG I level. The incidence of a low PG I level increased with increasing degrees of intestinal metaplasia: 0% with no metaplasia, 8% with minimal metaplasia, 12.1% with moderate metaplasia and 13.7% with severe metaplasia. The median PG I level was highest (108 ng/ml) in patients with duodenal ulcer and was lowest (38 ng/ml) in those with the Lauren intestinal-type carcinoma. The median PG I level in patients with diffuse carcinoma was 92 ng/ml (Figure 2).

The serum gastrin level was more than 100 pg/ml in 16 (9.6%) of 167 patients: eleven (10 Japanese, 1 Hawaiian) had neoplastic disease (9 carcinomas, 2 adenomas), four (1 Japanese, 3 Filipinos) had peptic ulcer disease (3 gastric, 1 duodenal) and one had hyperplastic polyps. As with PG I, an elevated serum gastrin was found only in patients with intestinal metaplasia.

Of the 30 patients who had serum samples stored for 2–11 years prior to partial gastric resection, 10 had carcinoma, 17 had peptic ulcer, and 3 had gastric polyps (2 adenomatous, 1 hyperplastic) at operation. Each of the 3 patients with a low PG I level in the initial sample also had a low level in the subsequent serum sample (Figure 3). Four patients had a normal PG I level in the initial sample, and a low level in the preoperative sample. Each had an intestinal type carcinoma (two at stage 1, one at stage 3, one at stage 4) and severe intestinal metaplasia in the resected antrum. No patient with cancer had a rise in the PG I level exceeding 10% of the original value.

The incidence of a low PG I level as 24% (11 of 45) in patients with the intestinal type of gastric carcinoma and 14% (2 of 14) in those with the diffuse type. In contrast, the incidence of a high serum gastrin level was similar for both types (16% vs 14%, respectively). A low serum PG I level was found in 11 of 40 (27.5%) patients with stage 3 or 4 cancer

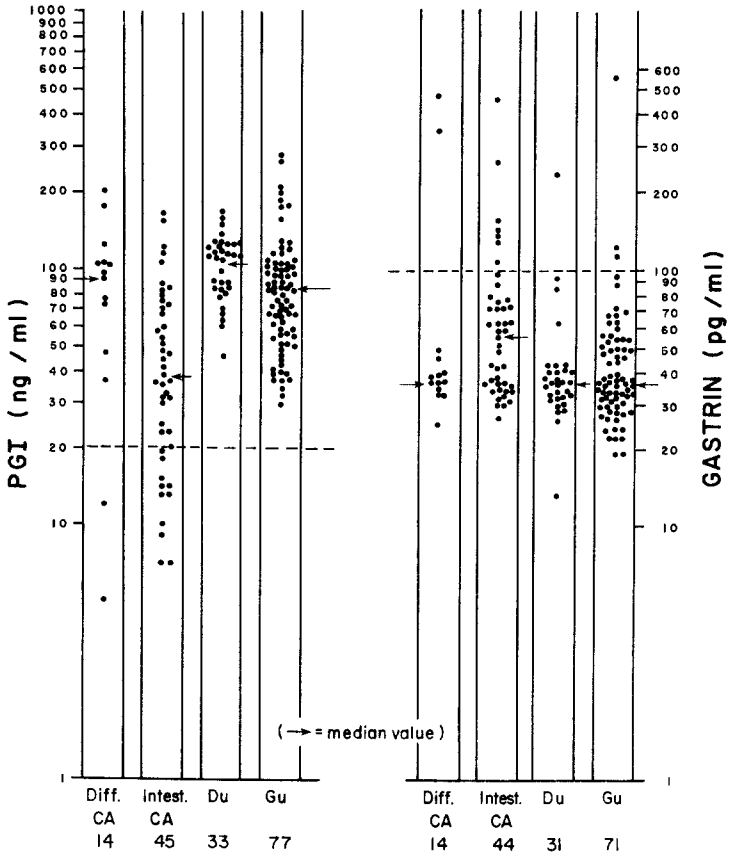

Fig 2. PG I and gastrin serum levels in patients with gastric cancer or ulcer. The carcinomas are separated into the diffuse and intestinal type.

and in 2 of 19 (10.5%) with stage 1 or 2 cancer. The two early stage tumors with low PG I levels occurred in patients who converted from normal to low levels during the period of observation. In spite of the apparent association of low PG I with high-stage, intestinal-type carcinoma, the numbers of cases are small and neither difference achieved statistical significance.

The pathologic findings in resected stomachs associated with a low serum PG I are summarized in table 2. Of 15 patients, 10 had type B gastritis and 5 had type A gastritis. Three patients with type B gastritis had little or no oxyntic mucosal atrophy (Figure 4), but each had fairly severe superficial gastritis (Figure 5). Three others, all with type A gastritis, had no identifiable parietal or chief cells in the corpus. The stomachs between these extremes showed varying degrees of oxyntic mucosal atrophy. Some had a normal number of glands that appeared shorter than usual. Others showed foci where no glands remained but had other zones where atrophic glands persisted. In cases of partial atrophy the reduction in volume of the oxyntic glands was most extensive in their deepest portions where chief cells predominate (Figure 6). Intestinal metaplasia of the oxyntic mucosa was most extensive in type A gastritis. Four of the 5 patients with type A gastritis had a high serum gastrin, as compared with 4 of 10 patients with type B gastritis.

DISCUSSION

Previous studies have shown that over 90% of patients with severe atrophic gastritis of the proximal stomach (type A gastritis) have a low serum PG I level (16). This is consonant with the finding that PG I is produced exclusively by the chief cells and mucous neck cells in this portion of the stomach (17, 18). In a previous study of indigenous and Hawaii Japanese (8), we found that low serum PG I is also highly specific for intestinal metaplasia. This study population has a high frequency of antral (type B) gastritis and is at high risk for the development of carcinoma in the pyloric antrum. A sepa-

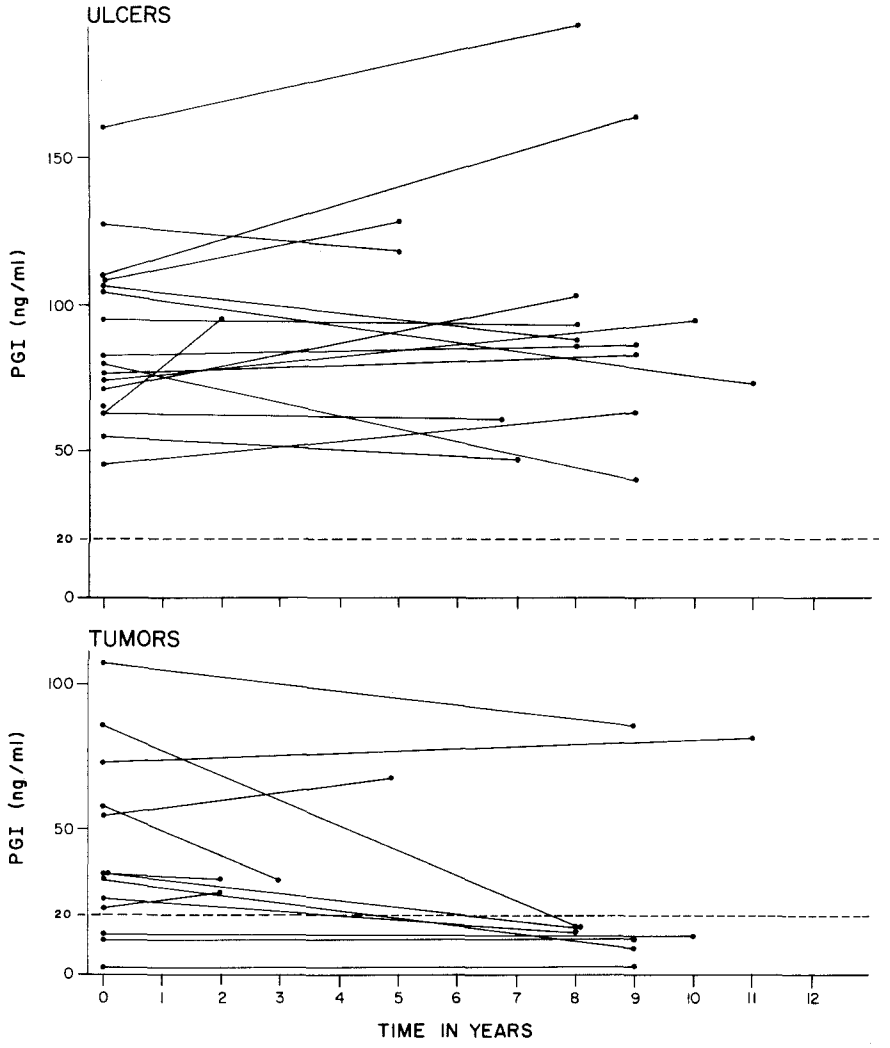

Fig 3. Time trends in serum PG I levels in patients with gastric tumors and peptic ulcer.

rate longitudinal study (9) indicates that a low PG I level is a good marker of increased risk for the Lauren intestinal-type carcinoma. Without the prior biopsy study this would have been unexpected because intestinal metaplasia of the antrum and the intestinal type of carcinoma that is characteristic of populations at high risk for gastric cancer frequently spares the oxyntic mucosa, the source of PG I (3-6). Studies of Japanese (19) and Colombians (20), two populations at high risk for antral carcinoma, indicate that intestinal metaplasia appears in the antrum at younger ages than the corpus, that it increases in frequency at each site with age, and that it is more prevalent in the antrum than the corpus at each age level. This suggests that the process either begins in the antrum and extends proximally with time or that the corpus is more resistant to mutagens acting at both sites. Intestinalization of the corpus usually appears at sites adjacent to or continuous with similar changes in the antrum (3, 4), favoring the first of these two possibilities. Whatever the mechanism, replacement of corpus mucosa by metaplastic mucosa in antral (type B) gastritis may ultimately be sufficient to reduce the PG I level to the same extent as that found in type A gastritis. The present study was undertaken to determine whether the detailed assessment of the extent of metaplasia that is possible with resected specimens would substantiate the impression gained by endoscopic biopsy. This appears to be the case. Each of the 15 patients with a low PG I had antral metaplasia, and each of these had an epithelial neoplasm (13 carcinomas, 2 adenomas). In contrast, 5 of the 16 patients with elevated gastrin levels had non-

TABLE 2.

Patient No.	PGI (ng/ml)	Gastrin pg/ml	Metaplasia score	Type gastritis	Oxyntic mucosa				
					Atrophy	Superficial gastritis	Chief cells	Parietal cells	Metaplasia
77-3566	6.9	34	5	B	0	Moderate	Normal	Normal	0
77-3292	14.7	71	10	B	0	Severe	Normal	Normal	0
77-143	7.0	141	9	B	Moderate	Severe	Reduced	Normal	0
77-49	5.3	304	2	B	Slight, focal	Severe	Diffuse CA	Diffuse CA	0
78-4972	13.9	97	8	B	Moderate	Severe	Reduced	Normal	Patchy
78-2321	17.6	108	11	B	Severe focal	Moderate	Reduced	Reduced	Patchy
78-574	13.2	62	10	B	Severe focal	Severe	Reduced	Reduced	Patchy
78-4040	19.8	61	5	B	Severe focal	Severe	Reduced	Reduced	Patchy
78-1919	13.6	35	12	B	Severe confluent	Severe	Rare	Rare	Confluent
77-3106	8.7	262	12	B	Severe confluent	Severe	Absent	Absent	Minimal
77-4435	9.5	71	4	A	Severe	Severe	Focal	Focal	Confluent
77-188	12.3	305	9	A	Severe	Severe	Focal	Focal	Confluent
78-1521	1.0	432	4	A	Severe	Moderate	Absent	Absent	Confluent
77-2971	11.6	478	10	A	Severe	Severe	Absent	Absent	Rare Foci
78-1817	1.0	456	3	A	Severe	Severe	Absent	Absent	Confluent

neoplastic disease (4 ulcer, 1 hyperplastic polyp). High serum PG I levels were encountered in some patients with extensive antral intestinal metaplasia, and low levels were found in some antrums showing only focal metaplasia. This indicates that the PG I level is not dependent upon the surface area of the metaplastic antral mucosa. All but three of the patients with low PG I had severe atrophic gastritis of the oxyntic mucosa, either as a primary disease (ie, type A gastritis) or by proximal extension of antral (type B) gastritis. Type A gastritis spares the antrum; hence it may have a low metaplasia score by our grading system. The finding of a low PG I in 3 patients without oxyntic mucosal atrophy is difficult to explain. Although each had severe superficial gastritis of the corpus, this does not appear sufficient to cause a low PG I. In the absence of acid output studies, it is not known whether these patients were hyposecretors.

Frozen sera samples, obtained at periods of 2-11 years prior to surgery were available in 30 patients. Of these, four had a normal PG I at the time of initial examination and a low preoperative specimen. Each had a carcinoma, and two patients with low-

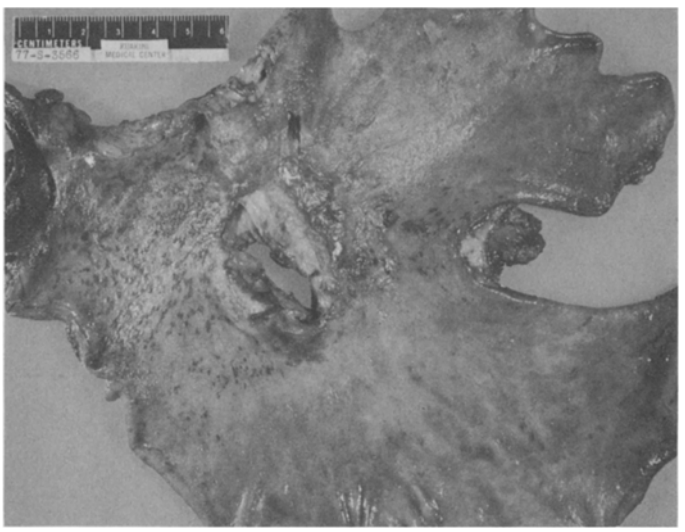

Fig 4. Gross appearance of stomach showing intestinal metaplasia throughout antrum, identified by patchy positive stain for alkaline phosphatase. The proximal two thirds of the specimen has nonmetaplastic oxyntic mucosa. There is a carcinoma in the proximal lesser curvature.

Fig 5. Nonatrophic, nonmetaplastic oxyntic mucosa from greater curvature of the corpus (H&E, ×120). There is a moderately severe superficial gastritis. This change accompanied a 4-cm, stage-3, intestinal-type carcinoma of the proximal pyloric antrum. The entire antrum and the lesser curvature of the corpus showed intense metaplasia.

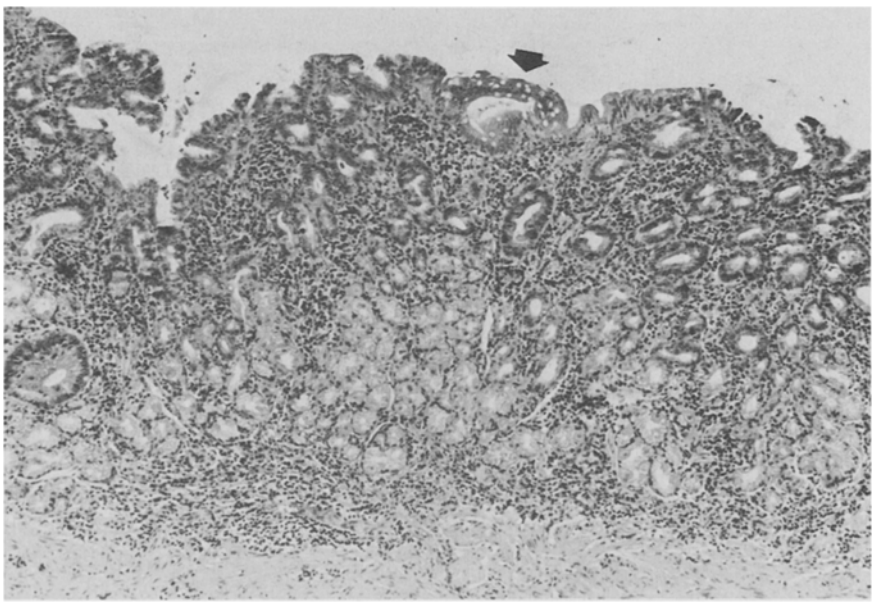

Fig 6. Atrophic mucosa from greater curvature of corpus, with occasional metaplastic glands (arrow). This accompanied a stage-1, polypoid, intestinal-type carcinoma of the proximal pyloric antrum. The superficial lamina propria is infiltrated with many lymphocytes and plasma cells. The oxyntic mucosa is thinner than usual due to a loss in the volume of the deepest portions of the glands (H&E, ×120).

stage tumors were among these converters. In a parallel longitudinal study of 7498 Hawaii Japanese men, examined from 1967 to 1970 (9), 48 patients with a stored serum sample had developed stomach cancer by 1977. A low PG I level was found in 15 (31%) of these patients, but in only 6 of 96 matched controls ($P < 0.001$). Assuming that the controls were representative of the test population, 414 of the 6434 men still alive in 1970 had a low PG I at the time of their original exam or would convert to an abnormal level in the next 20 years. The age-specific rates of gastric cancer in Hawaii Japanese men of this age group (21) suggest that 300–400 will develop the tumor over the same period. The present study indicates that 22% of these cancers will have a low PG I, suggesting that 60–80 low PG I men would develop gastric cancer in the next two decades. Taken together, therefore, these two studies indicate that a low serum PG I is a subclinical marker for greatly increased risk of carcinoma in our study population and that it merits a systematic annual screen for gastric cancer. The lack of sensitivity of the test indicates that it cannot be used as the only method to achieve early diagnosis.

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