

## A Comparative Study between the Gastric Mucosa of Chileans and Other Dwellers of the Pacific Basin

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A total of 3,289 sections of 120 gastrectomy specimens from Chile were reviewed. Intramucosal cysts were found in 61.7% of the specimens, ciliated-metaplastic cells in 33.3%, large vacuolated cells in 20.8% and extensive intestinal metaplasia in 51.7%. The frequency of these non-neoplastic changes was significantly higher in specimens with early adenocarcinoma of intestinal type than in those with early adenocarcinoma of diffuse type or having a peptic ulcer. Similar results have been recorded in other inhabitants of the Pacific basin, but not in inhabitants of the Atlantic basin. Interestingly, the gastric cancer incidence in the various populations studied in the Pacific basin is much higher than in those studied in the Atlantic basin. Environmental factors acting in Chile appear to have induced those non-neoplastic changes in the gastric mucosa. The question arises as to whether environmental factors (promoters?) acting in Chile (as well as in Japan, in Hawaii and in New Zealand) have favored the necessary non-neoplastic mucosal conditions required for the subsequent development of gastric adenocarcinoma (in particular of intestinal type).

Key words: Gastric carcinoma — Environmental factors

Though the causes of gastric carcinoma remain unknown, considerable evidence has accumulated which suggests that this disease is caused or mitigated by environmental factors. According to Pfeiffer,<sup>1)</sup> the comparative study of population responses may provide clues which would aid the identification of the incriminating etiologic factor(s) of gastric cancer.

In previous publications we reported the occurrence of non-neoplastic changes in the gastric mucosa of populations at risk to develop gastric carcinoma, i.e., in Japanese living in Japan<sup>2,3)</sup> or migrating to Hawaii<sup>4,5)</sup> and in Maoris of New Zealand.<sup>6)</sup> Those mucosal changes were also present in low risk populations living in the same geographic regions, i.e., in Caucasians migrating into the Pacific basin either to Hawaii<sup>7)</sup> or to New Zealand.<sup>6)</sup> The non-neoplastic changes seen were intramucosal cysts,<sup>2)</sup> extensive intestinal metaplasia (IM),<sup>8)</sup> atypical mitoses in IM,<sup>9)</sup> ciliated metaplasia<sup>3,4)</sup> or pyloric cells with large or small mucus-negative vacuoles.<sup>4)</sup> These mucosal changes were seldom found in countries with a rapidly decreasing or low incidence of gastric carcinoma, such as Sweden,<sup>10,11)</sup> Norway,<sup>12)</sup> and the east coast of Mexico<sup>13,14)</sup> or the USA<sup>15)</sup> (i.e., in dwellers of the Atlantic basin).

For the present work, gastrectomy specimens from a Chilean population were investigated. The reason for our decision was that, in contradistinction with east coast populations of the American continent (Mexicans<sup>13)</sup> and US North Americans<sup>14)</sup>, Chileans have a high mortality

from gastric carcinoma<sup>16)</sup> (only surpassed by the Japanese).

### MATERIALS AND METHODS

Hematoxylin and eosin-stained sections from 120 gastrectomy specimens seen during a ten-year period at the Department of Pathology, Instituto Chileno-Japonés, Hospital San Borja Arriarán and Pontificia Universidad Católica were reviewed.

**Evaluation** The occurrence of intramucosal cysts and of IM was evaluated at low magnification (using a 4× objective). Pyloric cells having either cilia, large or small mucus-negative vacuoles were counted at high magnification (100× oil-immersion objective). One hematoxylin and eosin-stained section was de-stained and subsequently treated immunohistochemically with Monoclonal Tubulin B (Sigma-Aldrich, Sweden) to reveal cilia.<sup>17)</sup> IM was divided according to the degree of mucosal extension into two main groups as reported elsewhere.<sup>5)</sup> Group I included gastrectomy specimens having up to 5 areas of IM (area = "spot" with IM in one microscopic field, using a 4× objective) in at least one of the sections and group II included gastrectomy specimens having from one area of IM in all fields in at least one of the sections to those specimens having IM in one or more entire low-power fields in at least 4 sections/gastrectomy. Group I was regarded as having low IM and group II as high IM.

A total of 3,289 sections obtained in the 120 gastrectomy specimens were reviewed. The mean number of

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Table I. Age and Histological Findings in Gastrectomy Specimens from Chilean Patients

Age (years)	Histology			Total
	Carcinoma of intestinal type	Carcinoma of diffuse type	Peptic ulcer	
20-59	22	19	6	47
>60	34	22	4	60
Unknown	8	4	1	13
Total	64	45	11	120

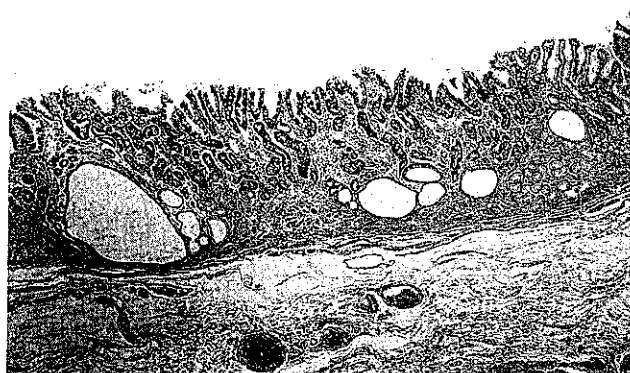


Fig. 1. Gastric mucosa in a Chilean patient. Note the occurrence of intramucosal cysts (hematoxylin and eosin,  $\times 25$ ).

sections was 27.4 sections/gastrectomy (range 5-132 sections). The sections had been obtained from the lesser curvature (antrum and corpus) and from the greater curvature (antrum and corpus). The mean number of sections for specimens with intestinal-type carcinoma was 29.1 sections, for those with adenocarcinoma of diffuse type 28.9 sections and for those with peptic ulcer, 10.7 sections/specimen.

The Spearman non-parametric correlation coefficient test was used for statistical analysis.

## RESULTS

Of the 120 specimens, 64 had an early adenocarcinoma of intestinal type, 45 had an early adenocarcinoma of diffuse type and in the remaining 11 specimens, a gastric peptic ulcer was observed.

**Age of the patients** The age distribution of the patients is shown in Table I. Of the 41 patients with early adenocarcinoma of diffuse type whose age had been recorded, 22 or 53.6% were 60 years of age or older. Of the 56 patients with early adenocarcinoma of intestinal type whose age had been recorded, 34 (60.7%) were 60 years or older (Table I). While patients with diffuse type were

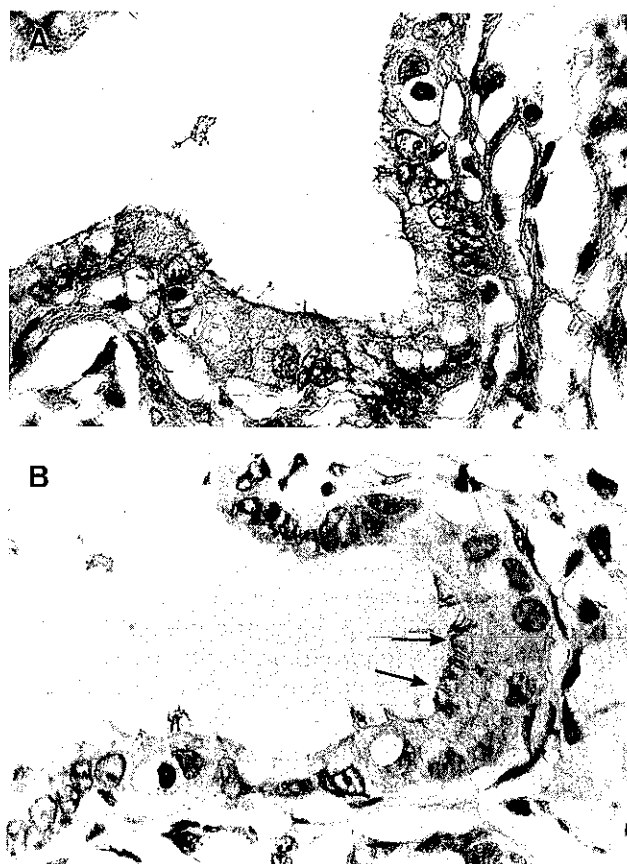


Fig. 2. A: High-power view of the gastric mucosa in a Chilean patient showing ciliated metaplastic cells (hematoxylin and eosin,  $\times 1,000$ ). B: The same area de-stained and challenged with Tubulin B (hematoxylin and eosin,  $\times 1,000$ ).

somewhat younger ( $< 59$  years), the difference was not significant ( $P < 0.6$ ).

### Histopathology

**Intramucosal cysts:** Intramucosal cysts (Fig. 1) were found in 74 of the 120 specimens (or 61.7%). Specimens with intestinal-type adenocarcinoma, however, showed a significantly higher proportion of specimens with intramucosal cysts (52 of 64 specimens or 81.3%) than those

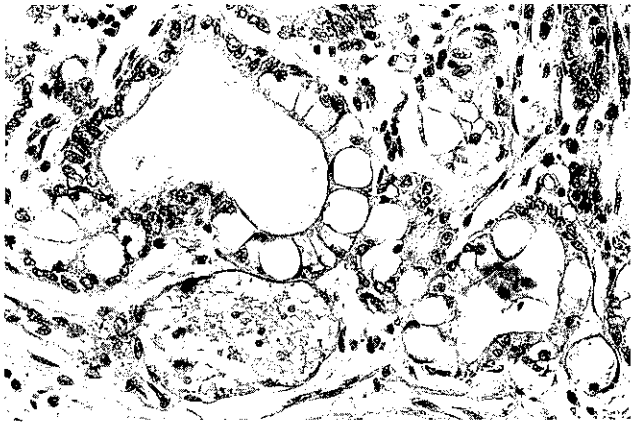


Fig. 3. Gastric mucosa in a Chilean patient with large vacuolated pyloric cells. Note nuclei near the lumen in some cells (hematoxylin and eosin,  $\times 100$ ).



Fig. 4. Gastric mucosa in a Chilean patient with small vacuoles in the subnuclear aspect of pyloric cells (hematoxylin and eosin,  $\times 100$ ).

with adenocarcinoma of diffuse type (21 of 45 specimens or 46.7%,  $P < 0.01$ ) or with peptic ulcer (1 of 11 specimens or 0.9%,  $P < 0.001$ ).

**Cells with ciliated metaplasia:** Ciliated metaplasia (Fig. 2) was present in 40 of the 120 gastrectomy specimens (or 33.3%). Specimens with intestinal-type adenocarcinoma, however, showed a significantly higher proportion of cells with ciliated metaplasia (36 of 64 specimens or 56.2%) than did those with adenocarcinoma of diffuse type (4 of 45 specimens or 8%,  $P < 0.001$ ) or with a peptic ulcer (none of 11 specimens,  $P < 0.001$ ).

**Cells with large vacuoles:** Large vacuolated cells (Fig. 3) were recorded in 25 of the 120 gastrectomy specimens or 20.8%. Specimens with intestinal-type adenocarcinoma showed a significantly higher proportion of cells with ciliated metaplasia (22 of 64 specimens or 34.4%) than did those with adenocarcinoma of diffuse type (3 of 45 specimens or 7%,  $P < 0.001$ ) or with peptic ulcer (none of 11 specimens,  $P < 0.001$ ).

**Cells with small vacuoles:** Only 7 specimens with small vacuolated pyloric cells (Figs. 4 and 5) were found in the present material (5.8%). They were present in 5 of 64 specimens with intestinal type (8%) and the remaining 2 in the 45 specimens with adenocarcinoma of diffuse type (or 4%).

**IM score:** High IM scores (see "Materials and Methods") were found in 62 (51.7%) of the 120 gastrectomy specimens. High IM scores were present in 79.7% ( $n = 51/64$ ) specimens with intestinal-type cancer, but only in 20.0% ( $n = 9/45$ ) of the specimens with diffuse-type adenocarcinoma ( $P < 0.001$ ) or in 18.2% ( $n = 2/11$ ) of the specimens with a peptic ulcer ( $P < 0.001$ ).

The higher IM scores found in patients with intestinal-type cancer than in those carrying a diffuse-type carci-



Fig. 5. Gastric mucosa in a Chilean patient with extensive intestinal metaplasia occupying the entire field at low magnification (hematoxylin and eosin,  $\times 25$ ).

noma was not due to a significant difference in age between the groups.

**Percent of sections with IM:** IM was recorded in 1,556 of the 1,867 sections (83.3%), corresponding to 64 gastrectomies carrying an intestinal-type carcinoma. This was significantly higher ( $P < 0.001$ ) than for the 45 gastrectomies having diffuse-type carcinoma, in which 580 of the 1,304 sections (44.5%) had IM, and for the 11 specimens with peptic ulcer, in which 20 of the 118 sections (16.9%) had IM.

## DISCUSSION

This investigation, carried out in consecutive unselected gastrectomy specimens from Chileans, demon-

strated the presence of particular non-neoplastic mucosal changes in a high percentage of cases. The number of specimens showing intramucosal cysts, ciliated metaplastic cells, large vacuolated cells as well as high IM scores was significantly higher in Chileans than in populations on the east coast of the American continent (i.e., Mexicans<sup>13, 14</sup>) and US North Americans<sup>15</sup>). The frequency of these changes in Chileans was also higher than for populations of another continent (Swedish<sup>10, 11, 18</sup>) and Norwegians<sup>12, 18</sup>). Interestingly, like Mexicans<sup>13</sup>) and east coast US North Americans,<sup>15</sup>) Swedish and Norwegians have a much lower frequency of gastric carcinoma than the Chileans. On the other hand, the non-neoplastic histologic parameters are similarly high in other inhabitants of the Pacific basin: Japanese living in Japan,<sup>2, 3</sup>) or migrating to Hawaii<sup>4, 5</sup>) or Maoris in New Zealand,<sup>6</sup>) all of whom have a high incidence of gastric carcinoma.<sup>18</sup>)

The above results also demonstrate that non-neoplastic mucosal changes were significantly higher in specimens harboring a gastric carcinoma of intestinal type than in those having an adenocarcinoma of diffuse type or a peptic ulcer. Why populations at high risk to develop a gastric carcinoma (such as Chileans, Japanese living in Japan or migrating to Hawaii and Maoris in New Zealand) develop those mucosal changes in association with intestinal-type carcinoma remains enigmatic. Also enigmatic is the fact that populations at a much lower risk, such as those in the Atlantic basin, seldom develop similar changes in association with intestinal-type carcinoma.

Intramucosal cysts and ciliated metaplasia were found in specimens having intestinal metaplasia. On the other hand, not all cases having intestinal metaplasia had intramucosal cysts and/or ciliated metaplasia. Further, selected gastrectomy specimens from Swedish patients having extensive intestinal metaplasia (Rubio *et al.*, unpublished) demonstrated only few intramucosal cysts and absence of ciliated metaplasia. Thus, intestinal metaplasia is not an instigator for the formation of intramucosal cysts and/or ciliated metaplasia in the gastric mucosa.

Specimens having ciliated metaplasia usually had a large number of intramucosal cysts. However, some specimens also having a large number of intramucosal cysts had no ciliated metaplasia. Why some cysts in the gastric mucosa of Chileans (and of other inhabitants of the Pacific basin) develop ciliated metaplasia remains enigmatic.

For many years it has been postulated that environmental factors are responsible for the development of gastric adenocarcinoma of intestinal type.<sup>1</sup>) The results presented here suggest that the non-neoplastic changes

may be the morphological expression of environmental influences acting in particular geographic regions. Racial differences appear to play a less important role.<sup>7</sup>) It should be mentioned that *Helicobacter pylori* was present in 85% of the gastric specimens in Mexico (Jessurum and Rubio, unpublished) and in 80% of those in Japan (Kato and Rubio, unpublished). Thus, *Helicobacter pylori* appears not to be related to the environmental influences connected with the non-neoplastic mucosal changes reported here.

According to the present concept of carcinogenesis, several steps are needed for the conversion of normal epithelial cells to so-called clinical cancer. The recognized steps are the accumulation of multiple gene abnormalities affecting DNA repair genes, oncogenes and tumor suppressor genes. But that concept does not help to explain why gastric carcinomas are more common in certain areas than in others. One explanation may be the presence in certain geographic regions of environmental offenders (promoters?) which are able to evoke non-neoplastic changes in the gastric mucosa (and the absence of similar offenders in other regions). One provocative possibility is that those environmentally induced mucosal changes may be necessary for the subsequent development of gastric carcinoma (soil theory).

In summary, the results demonstrated that the gastric mucosa in Chileans develop histological features which are similar to those present in the gastric mucosa of Asian residents of the Pacific basin, such as Japanese living in Japan or migrating to Hawaii and Maoris living in New Zealand. Similar changes were found in Caucasian migrants to islands of the Pacific basin (Hawaii and New Zealand), but not in dwellers in the Atlantic basin, such as Norwegians, Swedes, east coast Mexicans and east coast US North Americans. Environmental factors acting in Chile, Japan, Hawaii and New Zealand appear to induce those non-neoplastic changes in the gastric mucosa. The incidences of all the histologic features were significantly higher in specimens with intestinal-type carcinoma than with diffuse-type carcinoma or with peptic ulcer. The question arises as to whether environmental factors (promoters?) acting in Chile (as well as in Japan, in Hawaii and in New Zealand) have favored the necessary non-neoplastic mucosal conditions required for the subsequent development of gastric adenocarcinoma (in particular of intestinal type).

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