Extended Intestinal Metaplasia. A Survey of 1392 Gastrectomies from Dwellers of the Pacific Basin

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Abstract. Background: To assess the extent of gastric intestinal metaplasia (IM) in gastrectomy specimens in populations of the Pacific basin having different incidence of gastric carcinoma. Materials and Methods: One thousand three hundred and nine-two gastrectomies were investigated: 1088 had a gastric carcinoma and 304 miscellaneous gastric diseases. Twenty-one thousand three hundred and fourteen histological sections were reviewed under low-power (4X). IM was either spotty (SIM) or extended (EIM= encompassing one or more entire low-power fields/section). Widespread IM (WIM) was regarded as EIM if present in ≥5 histological sections. Results and Conclusion: The percent of gastrectomies harboring a carcinoma increased significantly with increasing age more notably in those with diffuse carcinomas (DC) than in those with intestinal carcinomas (IC). The percent of gastrectomies with EIM was significantly higher in specimens with IC than with DC, particularly among elderly patients, and in specimens from countries with a high cancer incidence. The percent of gastrectomies with SIM was higher in specimens having IC than in those having DC. Migration per se did not influence the frequency of specimens with EIM in elderly Japanese patients: Japanese migrants to Hawaii had a similarly high frequency of EIM as those dwelling in Japan. Japanese patients with a gastric carcinoma showed atypical mitoses in areas with EIM far from the tumor, suggesting that cellular mutation(s) play a role in the evolution of EIM towards gastric dysplasia and carcinoma in that ethnic group. The drawback of gastric biopsies in assessing the extent of gastric intestinal metaplasia and, thereby, estimating possible cancer risk in long-term studies has been stressed.

Gastric carcinoma is a leading cause of cancer-related death in many countries bordering the Pacific basin (1,2). Although the cause for the development of gastric carcinoma remains poorly understood (3), recent events indicate that H. pylori infection (4,5) may induce alterations in the mucosal microenvironment resulting in histological changes such as chronic gastritis, intestinal metaplasia (IM), dysplasia and finally carcinoma (6).

Many workers claim that gastric cancers originate in islands of IM (7,8). For some, the precancerous potential of IM is related to the histochemical components of the mucins contained in columnar and goblet cells (7,8). They maintain that Type III IM (having distorted glands with cellular atypia showing goblet cells secreting sialomucins and/or sulphomucins and columnar cells secreting sulphomucins predominantly) carries an increased cancer risk, even when found in small islands in gastric biopsies (7,8). Others have failed to demonstrate such an association (9-11). Hirota et al. (12,13) found a positive relationship between carcinomas of intestinal type (IC) and chronic gastritis/incomplete IM as a background mucosa.

Surprisingly, little attention has been given to the possibility that the risk of cancer development may correlate with the extension of IM in the gastric mucosa. To explore the extension of IM some authors studied the gross appearance of the gastric mucosa treated with alkaline phosphatase(14,15). The colorimetric mapping was matched with histology and false-positive and false-negative results...
were recorded (14,16). With the aid of morphometry (17,18) and image analysis (19-22), we evaluated the extension of IM in sections from entire gastrectomy specimens. It was found that IM was more widespread in specimens with carcinomas of intestinal type than in those with diffuse type or carrying a peptic ulcer. As those methods were time consuming, only a few gastrectomies were investigated for research purposes.

IM is regarded as a specific histological and histochemical change in the gastric mucosa, irrespective of its true extension in the gastric mucosa. Years ago we developed a semi-quantitative method to assess the extension of IM in routinely stained sections from gastrectomy specimens. The aim was to compare results at different hospitals.

The present work summarizes the results of a comparative study undertaken during an 18-year period at various hospitals located at the rim of the Pacific basin.

**Materials and Methods**

Between 1981 and 1998, a total of 1392 gastrectomies were reviewed at various hospitals of the Pacific basin (22-27). Of those, 1088 had a gastric carcinoma and 304 miscellaneous gastric diseases (peptic ulcers, leiomyomas, leiomyosarcomas, lymphomas, or carcinoids).

The carcinomas were located in the body or in the antrum. The results of IM in gastrectomy specimens from Japanese patients with carcinoma of the cardia have been published elsewhere (28).
All cases were collected during an approximately 18-year period at the respective hospitals. Sections were stained with hematoxylin and eosin (H&E).

**Histological classification of carcinomas.** Carcinomas were classified according to the predominant histological type into intestinal (IC) and diffuse (DC) carcinomas (29). Following Ming recommendations, carcinomas of mixed histologic phenotype were classified as DCs (30).

**Assessing intestinal metaplasia.** All filed histological sections were reviewed under low-power magnification (4x objective). Sections were classified into those with "spotty" IM (SIM) or extended IM (EIM) (24). Specimens with SIM were those with one or more IM islands or "spots" in one or more sections. Specimens with EIM were regarded as those showing extended IM to one or more entire low-power fields (4x objective)/section. Specimens having widespread IM (WIM) were those showing EIM in one or more entire low-power fields/section in ≥5 histological sections/specimen.

**Statistical analysis.** The non-parametric test of Wilcoxon and the ANOVA analysis were done using StatView Version 4.5 software (Abacus Concepts, Berkley, CA, USA). Statistical significance was defined as p<0.05.

### Results

**Gastric carcinomas.**

**Cancer phenotype (Table I):** Of the 1088 gastric carcinomas reviewed in the Pacific basin, 57.8% (n=629) were IC and the remaining 42.2% (n=459) DC. The difference was significant (p<0.05). The highest percent of gastrectomies with IC was found in Matsuyama (69.7%), while the highest percent of cases with DC was found in Vancouver (55.4%) and the lowest in Matsuyama (30.3%).

**Age and histological cancer phenotype (Table I).** As IM increases with increasing age (29,30), the histological cancer phenotypes in elderly patients (≥60 years of age at operation) were compared. The mean percentage of elderly patients having IC was 62.5% and for those carrying a DC, 55.1%. The mean percentage of elderly patients having IC was highest in Vancouver (84.4%) and lowest in Santiago (53.1%). For elderly patients harbouring a DC, the highest percent was found in Vancouver (69.6%) and the lowest in Santiago (48.9%).

When compared to patients at all ages, the overall mean percentage of elderly patients having DC raised by as much

### Table II. The number of gastrectomies having ≥ 5 sections with EIM extended gastric intestinal metaplasia and the total number of gastrectomies with EIM (percent in brackets). The cancer incidence (mortality rate in Chile) is also shown.

<table>
<thead>
<tr>
<th>City</th>
<th>Intestinal</th>
<th>Diffuse</th>
<th>Cancer incidence (per 10^5 males)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokyo</td>
<td>71/126</td>
<td>24/68</td>
<td>53.6</td>
</tr>
<tr>
<td>Matsuyama</td>
<td>73/115</td>
<td>17/29</td>
<td>53.6</td>
</tr>
<tr>
<td>Honolulu</td>
<td>Data non available</td>
<td>Data non available</td>
<td>11.8</td>
</tr>
<tr>
<td>Auckland-Otahuhu</td>
<td>7/74</td>
<td>0/18</td>
<td>27.9 (Maories)</td>
</tr>
<tr>
<td>Santiago</td>
<td>32/51</td>
<td>3/9</td>
<td>33.9* (62.7%)</td>
</tr>
<tr>
<td>Vancouver</td>
<td>9/45</td>
<td>2/10</td>
<td>9.2 (20.0%)</td>
</tr>
<tr>
<td>All cities</td>
<td>192/411</td>
<td>46/134</td>
<td>(46.7%) (34.3%)</td>
</tr>
</tbody>
</table>

* mortality rate

### Table III. A total of 21,314 sections (mean 19.6 sections/gastrectomy) corresponding to 1088 gastrectomy specimens reviewed in the Pacific basin.

<table>
<thead>
<tr>
<th>City in Pacific basin</th>
<th>No. sections/No. cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokyo</td>
<td>7948/345 (23.0 sections)</td>
</tr>
<tr>
<td>Matsuyama</td>
<td>5548/241 (23.0 sections)</td>
</tr>
<tr>
<td>Honolulu</td>
<td>2273/143 (15.8 sections)</td>
</tr>
<tr>
<td>Auckland-Otahuhu</td>
<td>1326/149 (8.9 sections)</td>
</tr>
<tr>
<td>Santiago</td>
<td>2987/109 (27.4 sections)</td>
</tr>
<tr>
<td>Vancouver</td>
<td>1232/101 (12.2 sections)</td>
</tr>
<tr>
<td>All cities in Pacific basin</td>
<td>21314/1088 (19.6 sections)</td>
</tr>
</tbody>
</table>
as 12.9%, and for those with IC by only 4.7%. The difference was significant \( p < 0.05 \). Thus, in this material, ICs were less influenced by increasing age than DCs.

**EIM in gastrectomies with carcinoma (Table I).** Specimens having EIM were recorded in 50.3% or in 547 of the 1088 gastrectomies reviewed. The highest percent of specimens with EIM was found in Matsuyama (59.7%) and the lowest in Vancouver (27.7%). EIM was found in 62.8% (395/629) of the gastrectomies with IC and in 33.1% (152/459) of the gastrectomies with DC. The difference was significant \( p < 0.05 \).

For cases having IC, the highest percent of specimens with EIM was recorded in Santiago (79.7%) and the lowest in Auckland-Otahuhu (39.1%). For cases with DC, the highest percent of cases with EIM was found in Tokyo (41.9%) and the lowest in Vancouver (17.9%). EIM was localized to the antrum, or to the antrum and fundus. EIM exclusively present in the fundic mucosa was not recorded in gastrectomies with carcinoma.

**EIM in the elderly patients with carcinoma (Table I).** In this material, 60.2% (389/646) of the gastrectomies in elderly individuals (≥ 60 years of age at operation) had EIM. In elderly patients with IC, 69.5% (273/393) of the gastrectomies had EIM, while in elderly patients with DC, 45.8% (116/253) had EIM. The difference was significant \( p \leq 0.05 \). For elderly patients with IC, the highest percent of specimens with EIM was recorded in Santiago (85.3%) and the lowest in Vancouver (44.7%). For elderly patients with DC, the highest percent of specimens with EIM was recorded in Matsuyama (60.8%) and the lowest in Vancouver (10.3%).

**Number of sections per gastrectomy in cases with carcinoma (Table II).** A total of 21314 sections (mean 19.6 sections/gastrectomy, range 8.9-27.4 sections) were reviewed in the 1088 specimens with gastric carcinoma seen in the Pacific basin. The highest mean number of sections/gastrectomy was recorded in Tokyo and Matsuyama (23.0 sections) and the lowest in Auckland-Otahuhu (8.9 sections).

**WIM in gastrectomies with carcinoma (Table III).** The mean percent of specimens with widespread intestinal metaplasia (WIM) i.e. having EIM in ≥ 5 sections/gastrectomy, was 43.7% (238/545). The mean percent of specimens with IC having WIM was 46.7% (or 192/411 of the gastrectomies with EIM), while the mean percent for those with DC was 34.3% (or 46/134 of the gastrectomies with EIM). The difference was significant \( p < 0.05 \). The highest percent of specimens with IC having WIM was recorded in Matsuyama (63.5%) and the lowest in Auckland-Otahuhu (9.5%). The highest percent of specimens having DC with WIM was also recorded in Matsuyama (51.5%) and the lowest in Auckland-Otahuhu (0%).

**Cancer specimens without intestinal metaplasia.** No intestinal metaplasia could be found in 12.6% (\( n = 119 \)) of the 945 specimens with carcinoma reviewed in the Pacific basin. The highest percent of gastrectomies without intestinal metaplasia was found in Auckland-Otahuhu (22.8%) and the lowest in Tokyo (8.4%).

**Miscellaneous gastric diseases.** A total of 304 gastrectomies with miscellaneous gastric diseases were reviewed in the Pacific basin. The highest number of gastrectomies with miscellaneous gastric diseases was reviewed in Vancouver (\( n = 140 \)) and the lowest in Tokyo (\( n = 10 \)). No case with miscellaneous gastric diseases was reviewed in Matsuyama.

**Number of sections/gastrectomy in cases with miscellaneous diseases.** A total number of 3874 sections (mean 7.7 sections/gastrectomy, range 3.1-25.7 sections) were reviewed in the 304 specimens in the Pacific basin with miscellaneous diseases. The number of sections/gastrectomy in cases with miscellaneous gastric diseases was highest in Santiago (27.2 sections) and the lowest in Auckland-Otahuhu (6.2 sections).

**EIM in gastrectomies with miscellaneous diseases.** The mean percent of cases with EIM in miscellaneous gastric diseases in the Pacific basin was 10.9% (range 4.3%-21.7%). The number of gastrectomies having EIM in miscellaneous gastric diseases was highest in Auckland-Otahuhu (21.7%), while the lowest was in Vancouver (4.3%).

**Gastrectomies with miscellaneous diseases without intestinal metaplasia.** No intestinal metaplasia could be recorded in 39.5% (100/253 gastrectomies) of the specimens with miscellaneous gastric diseases reviewed in the Pacific basin. The highest percentage (47.9%) of specimens with miscellaneous gastric diseases without gastric intestinal metaplasia was recorded in Vancouver and the lowest (namely 0%) in Tokyo.

**Discussion**

According to the Cancer incidence in five continents (31), the world age-standardized incidence rate (ASR-W) for gastric cancer in Japan is 82.7/10^5 males (Miyagi prefecture), in Hawaii 15.1/10^5 in Hawaiian males and 21.5/10^5 in Japanese males, in New Zealand 27.9/10^5 in Maori males, but 11.0 /10^5 in non-Maori males, and in Canada 9.2/10^5 males. In Chile, the mortality rate is 33.9/10^5 inhabitants (incidence rates have not been reported). Thus, there is a wide variation in incidence in gastric cancer in the Pacific basin (including a high mortality rate in Chile).

In this survey we found that, in regions with a high incidence of gastric carcinoma (Japan, Hawaii (Japanese), New Zealand (Maoris)), or high mortality rate (Chile), the IC/DC ratio was significantly higher in Matsuyama, in Honolulu (Japanese) and
in Santiago, but not in Tokyo or in Auckland-Otahuhu (Maories). On the contrary, in regions with a relatively lower cancer incidence (Canada, and New Zealand (non-Maories)) the DC/IC ratio was significantly higher in Vancouver but not in Auckland-Otahuhu (non-Maories). When the IC/DC ratio was considered in elderly patients (≥60 years of age at operation), significant differences were observed in Auckland-Otahuhu and in Vancouver, and non-significant differences in Tokyo, Matsuyama, Honolulu and Santiago. In this study comprising only populations of the Pacific basin, we could not confirm that ICs was more frequent in countries with a high gastric cancer incidence and DCs in countries with a low cancer incidence (1,32,33).

The proportion of gastrectomies showing EIM (extended IM) was higher in Tokyo, Matsuyama and Santiago (regions with a high gastric cancer incidence and mortality) than in Honolulu, Auckland-Otahuhu and Vancouver (regions with a lower gastric cancer incidence). Considering that IM antedates the development of gastric carcinoma (12,34), the finding that EIM is more often found in gastric cancer specimens from patients from high-risk geographical zones than in those with a lower risk is noteworthy. The percentage of cases with EIM was significantly higher in specimens with IC than in those with DC in all cities investigated, indicating that EIM is mostly associated with the development of gastric carcinoma of that particular phenotype. Notwithstanding, 42% of the specimens with diffuse carcinoma in Tokyo also had EIM. This finding was more obvious among elderly patients in Matsuyama; up to 61% of their specimens with DC had EIM. Thus, the possibility that EIM may precede the development of a substantial number of DCs (particularly in high cancer incidence areas) should also be entertained.

Interestingly, 11% of the gastrectomy specimens with miscellaneous gastric diseases also displayed EIM, and nearly 13% of the gastrectomies with carcinoma had no IM. These results clearly indicate that EIM was not evoked by a growing adenocarcinoma and that some carcinomas may evolve in the absence of EIM. Whether patients with miscellaneous gastric diseases having EIM are at a future risk to develop a gastric carcinoma remains to be elucidated.

Widespread IM (WIM) was more frequently found in specimens with IC in Matsuyama (74.5%), Santiago (62.7%) and Tokyo (61.2%) than in Auckland-Otahuhu (23.3%) and Vancouver (45.0%). On the other hand, WIM was also frequently found in specimens with DC in Matsuyama (51.5%), Tokyo (34.7%) and Santiago (33.3%) but not in Auckland-Otahuhu (0%). Thus, WIM was more often recorded in populations from countries having a high gastric cancer incidence than in those with a lower incidence. Based on these findings, it is suggested that WIM may play a significant role in the ultimate development of ICs and--to a lesser degree--of DCs in populations dwelling on the rim of the Pacific basin.

To investigate the validity of the results obtained in cases with carcinoma, one important confounding factor was explored, namely the number of sections obtained/gastrectomy specimen. The mean number of sections obtained in specimens with carcinoma was highest in Tokyo, Matsuyama and Santiago and lowest in Honolulu, Auckland-Otahuhu and Vancouver. Consequently, it is possible that the higher number of sections obtained at some hospitals bordering the Pacific basin may have contributed to the detection of a higher proportion of specimens with EIM. However, the higher number of sections in specimens from cities with a high gastric cancer incidence cannot totally explain the differences found, as 63% of the specimens with carcinoma in Honolulu and 45% of those in Auckland-Otahuhu had EIM, despite a lower number of sections/specimen. Probably geographic (i.e., environmental) factors may be responsible (35,36).

It has been postulated that environmental carcinogens encourage the development of gastric carcinoma of the intestinal type (3,4,30-34). Rationally, similar environmental carcinogens may also play a role in the development of EIM before cancer ensues. As the frequency of EIM was high in Tokyo, Matsuyama and Santiago and relatively low in Vancouver, it may be speculated that local environmental carcinogens acting in the gastric mucosa of Japanese and in Chilean individuals before gastric cancer ensues are either more powerful than those affecting Western Canadians, or that the gastric mucosa in Japanese and in Chilean individuals is, for unknown reasons, more vulnerable to those factors.

Migration within the same basin did not influence the frequency of EIM in the elderly: elderly Japanese migrants developing a gastric carcinoma in Hawaii had a similarly high frequency of EIM as elderly Japanese dwelling in Japan.

Some authors claim that incomplete IM Type III carries an increased cancer risk, even when present in small islands in gastric biopsies (7,8). Other authors, however, have been unable to corroborate the prognostic significance of incomplete IM Type III (9-11). Kato et al. (37) found that incomplete IM usually occurred in the antrum whereas complete IM usually in the fundus. There was no evidence that a shift from incomplete to complete IM occurred with time.

Some authors have reported that IM may be detected in biopsies taken exclusively from endoscopically abnormal areas (38). Other authors recommend harvesting gastric biopsies from pre-established mucosal sites. In this respect, the Sydney system (39) for grading of gastritis has provided practical guidelines for optimal biopsy sampling of the gastric mucosa. Notwithstanding, using the Sydney’s recommendations, El-Zimaity and Graham (40) recently found that IM was missed in more than 50% of the biopsies from “Sydney” sites in patients with confirmed gastric IM on multiple site sampling. El-Zimaity and Graham (40) concluded that the minimal number of biopsies needed to
identify IM should probably be eight, and emphasized that current and future studies that use the Sydney system as a basis for detecting gastric IM are not likely to be reliable. Thus, it appears that sampling gastric biopsies from pre-established mucosal sites (38), or from endoscopically abnormal areas (39-42) may be both insufficient to calculate IM prevalence figures, and inadequate to estimate the possible risk of gastric IM in long follow-up studies.

Aware of the limitations of gastric biopsies in assessing the magnitude of gastric IM in individual patients (43,44), we planned the present investigation in 1981. For that purpose, only gastrectomy specimens with or without (control cases) adenocarcinomas were investigated. That method had, however, several pitfalls. In fact, the size of the resected specimens varied with the topographical location of the tumor, with the size of the tumor removed and with the technique of resection used by individual surgeon within the same hospital, between different hospitals, and between different countries. In addition, the number of blocks taken from the resected specimens by pathologists at various hospitals also varied. Nevertheless, that method has permitted the comparison of the state of the non-cancerous gastric mucosa between patients dwelling in disparate geographical regions in the Pacific basin. In contrast to gastric biopsies, the method here described permitted some of the questions concerning the magnitude of gastric IM in populations at risk to be answered.

A pertinent question would be: Does EIM per se increase the gastric cancer risk or are other attributes also required? During the course of this work, we detected atypical mitoses in gastrectomies from Japanese patients (45,46). Those atypical mitoses were found in areas with EIM far from the carcinoma. Since atypical mitosis mirrors mutated cells, it is conceivable that cellular mutation(s) is important in the evolution of EIM towards dysplasia-carcinoma in the Japanese. These speculations seem to fit well with the hypothesis of gastric carcinogenesis proposed by Correa (47). According to that author mutagenic carcinogens in the microenvironment would trigger the sequence of cellular mutations leading to gastric carcinoma.

Our studies seems to add new information to the "soil" theory (48). WIM would provide the adequate "soil" for the development of many (but not all) ICs in susceptible individuals. On the other hand, many cases with DCs also displayed WIM at the time of operation. The possibility that WIM is also necessary for the ultimate evolution of a substantial number of gastric carcinomas of diffuse type should also be entertained.

It should be stressed that this work was initiated in 1981, i.e. before the discovery of the *Helicobacter pylori* by Warren and Marshall (49). In our subsequent studies that bacteria was not explored since gastrectomy sections with special stains were not available in this survey. In addition, it is known that the organism is usually absent in IM due to: a) local alterations in the pH, b) flushing of the specimens with saline after operation and, in the past, c) autolytic necrosis of the superficial mucosal cell layers – a site where the *H. pylori* usually resides – by the intense light required for photographic documentation.

Shousha et al. (50) found, in gastric biopsies from British patients, a significantly higher prevalence of IM than in those from Yemeni patients, despite the fact that the latter had a significantly higher prevalence of *H. pylori*. Our own studies of gastric biopsies in elderly Swedish patients with *H. pylori* infection (51) showed only occasionally foci of IM. Recent developments demonstrated that combined bacteria and host genotypes are required for defining high cancer risk in *H. pylori*-infected individuals (52).

Working with a transgenic mouse system, we recently found that gastric tumors (53) concurred with antral IM. Watanabe and Ito (54) also found IM in rats following abdominal irradiation. Thus, through particular alterations in the genome (transgenic mice) or under the influence of irradiation, gastric IM may evolve without the participation of *H. pylori* (55). Apparently, the relationship between the virulence of *H. pylori* and the development of IM has not yet been fully clarified. It remains to be elucidated whether *H. pylori* is able to trigger the development of EIM or of WIM in the gastric mucosa, or whether other factors, acting in the Pacific basin, are required for that evolution. In retrospect, and based on the aforementioned pitfalls in the handling and processing of resected specimens and on recent knowledge, it may be postulated that the search for *H. pylori* in this survey would have led to questionable results and to unreliable conclusions.

In conclusion, gastric intestinal metaplasia is a mucosal change that unfolds under the influence of environmental factors. The wide distribution of gastric intestinal metaplasia, namely EIM and WIM, creates the appropriate "soil" conditions for the ultimate evolution through mutations of a gastric carcinoma, most notably of intestinal type.

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Rubio et al: Gastric Intestinal Metaplasia


