The saga of gastric corpus atrophy

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Historical perspective
The loss of gastric oxyntic glands (corpus atrophy) is emerging as a marker of gastric cancer risk as indicated by low Pepsinogen I (PGI) levels 1 2. There is a need to take into account the natural history and temporal dynamics of such an entity in order to better understand its significance and especially its implications for cancer prevention and screening.

Atrophy of the gastric corpus was recognized, described and illustrated by European authors in the 19th and early 20th centuries. Fennwick provided a classical description in 1870, emphasizing its clinical and physiopathologic aspects 3. He linked the loss of oxyntic mucosal function with severe anemia. Other authors confirmed those findings and identified corpus atrophy as the basic anatomical substratum of pernicious anemia, an autoimmune disease 4-6. The clinical syndrome, the anatomic lesion and their association with gastric carcinoma were prevalent in those days, especially in northern European populations. The type of adenocarcinoma then described as associated with the syndrome was typically limited to the gastric corpus and papillary in its histopathologic pattern 7.

Drastic changes have taken place in the ecology of European and other populations in which those original observations were made. Prominent among them are improvements in home sanitation and in the diet. The modern ecology is characterized by a more “sanitized” environment and by the year round availability of fresh fruits and vegetables, thanks to refrigerated storage and transportation.

These ecological changes have been associated with drastic changes of disease occurrence. Gastric carcinoma has been declining in frequency in many countries, especially North America and Europe for several decades. The classical corpus-limited gastric atrophy (illustrated in Figure 1 by Strickland and Mackay) associated with pernicious anemia 8, is no longer frequent. Corpus-limited papillary adeno-carcinoma is presently a rare event. The pernicious anemia genes have obviously not disappeared and continue to be carried by susceptible individuals. But their consequences in terms of gastric atrophy and gastric cancer may not be as common today as once thought. It has been proposed that the gastric manifestations of pernicious anemia are triggered by Helicobacter pylori infection 9.

The classical descriptions of corpus atrophy, originally associated with pernicious anemia, seem to have persisted in some modern-day pathologists and clinicians. It is time to re-asses atrophic gastritis and its association with gastric carcinoma.

The new nosologic entities
Gastric atrophy as seen today throughout the world is not a consequence of autoimmune injury but arises from other causes, among which Helicobacter pylori infection is by far the most important. Other factors that contribute to the development of atrophy include high intake of salt and nitrates, smoking and inadequate intake of fresh fruits and vegetables 10-12. Our recognition of the importance of such infection dates back only about 20 years, when Warren and Marshall “re-discovered” this infectious agent in Australia 13. Infection with Helicobacter most probably dates back thousands of years. But it was the Italian pathologist Bizzozzero who first reported and documented their presence in 1882 14. Other European investigators also recognized such infection, but their findings met with a century of universal neglect 15.

The consequences of Helicobacter pylori infection vary from one population to another. Populations of low socio-economic conditions in general display very high prevalence of infection and very early age of first acquisition 16. The outcomes of the infection, however, are drastically different. In Africa and other tropical populations living at low attitudes, the gastric infection does not lead to gastric atrophy (non-atrophic gastritis) or gastric cancer 17 18. Populations at high gastric cancer risk such as Japan, Eastern Europe and Latin America frequently display multifocal atrophic gastritis (MAG) and intestinal metaplasia, well known precursors of gastric carcinoma 19. MAG is multifactorial in etiology and may be related to differences in genotypes of Helicobacter pylori, intake of antioxidant micronutrients or coinfection with intestinal parasites that modify the im-
mune response to the infection. Recently, it has been reported that *H. pylori* infected patients being treated with proton-pump inhibitors, develop marked inflammation in the oxyntic mucosa. But it has not been shown that such gastritis leads to atrophy. As the affluence of a society improves, duodenal ulcers and non-atrophic antral gastritis become prominent manifestations of *Helicobacter pylori* infection. With continued rise in affluence, such syndromes become less frequent. These latter changes coincide with an increase in the frequency of reflux esophagitis, Barrett’s esophagus and adenocarcinoma of the lower esophagus. These entities are associated with adequate or excessive acid-pepsin secretion. It is not clear at this point if the link between absence of *Helicobacter* infection and adenocarcinoma of the lower esophagus is causal or casual.

Chronic gastritis is commonly found in endoscopic biopsies. It is not a homogeneous clinico-pathologic entity, but presents itself in at least three different entities illustrated in the sketches shown in Figure 2 published before our awareness of the role of *Helicobacter pylori* 18. The sketch on the left represents autoimmune atrophic gastritis as illustrated by Strickland and others in patients with classical pernicious anemia 8. The sketch in the center of the Figure represents non-atrophic antral gastritis as seen in patients with duodenal peptic ulcer. This entity is due to *Helicobacter pylori* infection and does not increase the risk of gastric cancer when compared with the general population 23 24. The sketch in the right side of the Figure represents multifocal atrophic gastritis (MAG), term coined by Lambert in 1972 and typically found in populations at high gastric cancer risk 25. Autopsy studies have shown that the foci of atrophy and intestinal metaplasia in such patients increase in frequency and coalesce with advancing age 19. The extent of atrophy and metaplasia...
is a good marker of gastric cancer risk: the larger the surface involved, the higher the risk\textsuperscript{[26,27]}.

The staining of gastrectomy specimens with red dye to identify alkaline phosphatase, a normal enzyme of the small intestine, absent in the normal stomach is shown in Figures 3 and 4. These stains have confirmed the absence of metaplasia in duodenal ulcer patients\textsuperscript{[28]}. Figure 3 illustrates the typical topographic distribution of the foci of intestinal metaplasia in a Hawaiian Japanese patient with MAG. There was sufficient residual oxyntic mucosa to have secreted the acid that caused the gastric ulcer located in the anterior wall of the intestinalized antrum-corpus junction. Figure 4 shows alkaline phosphatase staining in a specimen with an ulcerated gastric adenocarcinoma originating in its typical location: the incisura. The lesser curvature is extensively intestinalyzed, as are neighboring parts of the antrum and corpus.

The involvement of the antrum, even if extensive, is not easily detected clinically and may not be suspected until it is so severe that is reflected in low gastrin 17 (G17) levels in the blood\textsuperscript{[29]}. Low PG I blood levels or low PG I:PG II ratio are good indicators of extensive corpus atrophy and high gastric cancer risk. They provide good evidence that proximal extension of intestinalization to the corpus. This is the basis for establishing cut points of 70 mg/ml of PG I and a PG I:PG II ratio of 3, as originally advocated by Miki for gastric cancer screening\textsuperscript{[1]}. But in most series, less than 50% of clinically detected gastric carcinomas are associated with low PG I levels. The other 50% are probably associated with extensive antral atrophy and metaplasia\textsuperscript{[29]}. In summary, most cases of corpus atrophy associated with a high gastric cancer risk are due to multifocal atrophic gastritis generated by long-standing Helicobacter pylori infection and its modulation by its host and environmental companions. The condition evolves slowly from childhood and ultimately may replace much of the gastric mucosa in old age. The successive stages begin with non atrophic superficial gastritis that is most severe in the antrum, followed by the appearance of atrophy and intestinal metaplasia at the antrum-corpus junction in young adults, and expansion of the metaplastic process along the lesser curvature in mid-

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