CORRESPONDENCE

Re: *Helicobacter pylori* and Atrophic Gastritis: Importance of the cagA Status

Epidemiologic, biological, and clinical evidence have emerged to suggest that the etiology of both epithelial and nonepithelial gastric tumors involves infectious agents (*1,2*). Kuipers et al. (*3*) have recently added interesting data to support this hypothesis; in particular, they have stressed the possible relevance of the *Helicobacter pylori* cag-A-positive strains in the etiology of the subset of mucosal lesions most closely related to gastric carcinogenesis (*4*). These data expand on their previous observations and appear to be particularly relevant to the selection of patients with the highest risk of gastric cancer. Assuming that the described association is real, such patients deserve particular effort to eradicate cag-A-positive *H. pylori* infections.

However, the latest report from Kuipers et al. (*4*) prompts the following comment, which is based on data in the literature and our own experience (*5,6*). In the "Subjects and Methods" section of their report (*4*), they state that the three biopsy samples taken from each of 58 patients at the time of their recruitment in the study came only from the corpus mucosa, and that five biopsy samples were taken from each of the same patients at the time of follow-up endoscopy, with care taken to sample the same (oxyntic) area considered at initial endoscopy. In the section of their report that deals with histologic examination, the authors specified that "each item was scored separately for both antrum and corpus," but the "Results" section provides no data regarding the potentially different histologic statuses of oxyntic and mucus-secreting areas.

In our experience, the sampling method described above (that excludes the antral and/or angular sampling) may result in a decreasing sensibility of histology in the identification of atrophic-metaplastic lesions. Pathologic studies have consistently demonstrated that *H. pylori*-associated lesions (including both inflammatory and atrophic-metaplastic lesions) are localized to the antrum in the early stages and that they spread to the rest of the gastric mucosa only later (*7*). This assumption is supported by our own findings regarding inflammatory and atrophic-metaplastic lesions in a series of 181 consecutive dyspeptic, untreated, nonulcer patients (95 who were *H. pylori* positive [mean age, 54 years] and 86 who were *H. pylori* negative [mean age, 41 years]), considering two biopsy samples of corpus, angular, and antral mucosa (Table 1). Among *H. pylori*-positive patients, we found a statistically significant higher prevalence of inflammatory ($P<.001$) and atrophic-metaplastic ($P<.001$) lesions in the angular and antral samples compared with the samples taken from the oxyntic area (unpublished data). Such observations further support our doubts about the risk of missing atrophic lesions when the sampling method adopted by Kuipers et al. is used during base-line and follow-up endoscopies. The same doubts may have been experienced by Kuipers et al. (*4*) when they found that in four (29%) of 14 patients, none of the five samples taken at the follow-up endoscopy exhibited the atrophic-metaplastic lesions detected in the base-line samples. In this context, it is worth pointing out that their exclusion of the histologic data on the mucus-secreting area makes it impossible to evaluate the elective mucosal target of *H. pylori*-associated lesions linked to the morphogenesis of epidemic gastric cancer. This intestinal-type cancer represents the end point of a multistep process that starts with atrophic-metaplastic lesions, the antral location of which coincides with the typical location of the neoplasm (*8*). Considering the difficulties related to long-term follow-up studies [hence the relevance of the recent study by Kuipers et al. (*4*)], we would rather consider the increasing prevalence of atrophic-metaplastic lesions detected in the corpus samples as an excellent reflection of the likelihood of more severe damage to the antral mucosa. To avoid any confusion, however, we would like to conclude with a somewhat obvious (but nonetheless relevant) practical message for gastroenterologists and pathologists who deal with precancerous, *H. pylori*-associated gastric pathology: When conducting a clinicopathologic examination of *H. pylori*-associated precancerous lesions, particular attention should be devoted to the endoscopic sampling of the distal stomach (antral and angular mucosa), since this is where we should look more carefully for any premalignant lesions, which, unfortunately, often lack endoscopic relevance (*9,10*).

Table 1. Inflammatory and atrophic-metaplastic lesions in *Helicobacter pylori*-positive (HP+ve) and -negative (HP–ve) patients*

	Sample	Hp+ve (95 patients)	Hp–ve (86 patients)
IL	Antrum	84	5
	Angulus	85	4
	Corpus	52	4
AG + IM	Antrum	15	3
	Angulus	36	4
	Corpus	1	2

*Inflammatory lesions (IL) and atrophic gastritis + intestinal metaplasia (AG + IM) were scored as present or absent. Atrophy was never detected without coexisting IM.

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Note

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Response

We appreciate the valuable comments of Dr. Rugge and colleagues about our report concerning the presence of cagA serum antibodies and the incidence of atrophic gastritis. They address the distribution of *Helicobacter pylori*-associated atrophy. Multifocal atrophic gastritis (MAG) primarily affects the border zone between the antrum and body of the stomach. This zone includes the angulus (*1*). With aging, MAG can appear both in the antrum and the corpus, and previous data suggest that the progression occurs at approximately the same rate in both sites (*2*). In the corpus, atrophy is easily recognizable by a loss of specialized cells, but in the antrum, the diagnosis of atrophy may be more difficult. The antral mucosa is characterized by a more irregular distribution of glands and pits and contains more connective tissue than does the corpus mucosa. In addition, the border of intestinal-type mucosa can be proximal to the pylorus, which could suggest intestinal metaplasia in antral biopsies. For historical reasons, we focused on the results of corpus histology for determining the progression of MAG. We agree that this approach is conservative and that focusing on antral histology might have increased the reported incidence and prevalence of atrophy and metaplasia in our population. Yet, the observation by the Padova group of MAG lesions in the corpus of only one (1%) of 95 *H. pylori*-infected persons with a mean age of 56 years is remarkably low and may be due, in part, to the sampling of only two corpus specimens. This low prevalence and the striking difference with their findings in the distal stomach is not consistent with previous literature. In Finland and Colombia, MAG in the corpus was present in 30% and 32%, respectively, of a general population of comparable age, irrespective of their *H. pylori* status (*1,2*). In these studies, the prevalence of MAG in the antrum was about 10% (*2*) to 30% (*1*) higher. In The Netherlands, during an 11-year follow-up of an *H. pylori*-infected population (mean starting age, 49 years), we observed an increase in the prevalence of MAG in the corpus from 24% to 45% (*3*). At the end of this follow-up, the prevalence of intestinal metaplasia in the corpus was 22% compared with 26% in the antrum.

During follow-up, we observed development of atrophy in 16 subjects compared with the apparent loss of such lesions in four other subjects. A similar ratio of disease progression to regression has been reported by others (*4,5*). As discussed previously (*3*), this is likely to be due to a sampling effect. Rugge et al. suggest that this ratio would not have been observed in antral biopsy specimens. We are not aware of follow-up data that support this hypothesis.

In conclusion, we fully agree with Dr. Rugge and colleagues that complete histologic examination of the stomach of an individual patient should include biopsy specimens from the antrum, angulus, and corpus, as has been proposed before (*1*). The literature on the distribution of MAG supports the adequacy of our study design to investigate its incidence. Therefore, we believe that our findings enable a correct, although probably conservative, interpretation of the importance of *H. pylori* and associated cagA status in the incidence of MAG.

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