Commentary

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*Helicobacter pylori*, gastric acid, and duodenal gastric metaplasia

In this issue, there are two studies examining the pathogenesis of gastric metaplasia within the duodenal bulb (DGM). On page 513, Harris et al examine the relation between DGM, *H pylori* status, and gastric acid output. Their study involved healthy volunteers and duodenal ulcer patients, with and without current *H pylori* infection. Acid output was measured basally and in response to stimulation with gastrin releasing peptide (GRP) and supraphysiological doses of pentagastrin. They found a significant direct correlation between the extent of DGM and gastric acid output measured by each of the above methods. The correlation was greater for basal and GRP stimulated acid output, which are both measures of physiological regulations of acid secretion, than for supraphysiological doses of pentagastrin, which measures only the maximal acid secretory capacity. The finding of a strong direct correlation between gastric acid output and degree of DGM supports the hypothesis that DGM develops in response to an increased duodenal acid load.

Harris et al also included data on the relation between *H pylori* status and gastric acid secretion, though fuller details of this are presented in their earlier publication. Basal acid output, GRP stimulated acid output, and pentagastrin stimulated acid output were all increased in duodenal ulcer (DU) patients and this resolved, after eradication of the infection. The finding that *H pylori* infection causes increased basal and GRP stimulated acid output in DU patients is consistent with the previous studies by El-Omar et al and Moss and Calam. The fall in maximal acid output after eradication of *H pylori* in DU patients has been noted in one previous study but not in others.

Despite the fall in gastric acid secretion after eradication of *H pylori* infection, there was no statistically significant fall in the extent of DGM, though there was a trend in that direction. A recent study by Khulluru et al did observe a statistically significant 42% reduction in extent of DGM at six months after *H pylori* eradication in DU patients. In the light of these findings, a relation between *H pylori* infection, acid secretion, and DGM becomes apparent in DU patients; namely *H pylori* infection stimulates increased acid secretion and the resulting increased duodenal acid load results in the development of DGM.

In retrospect, one possible weakness in this otherwise excellent study by Harris et al is their selection of *H pylori* negative DU patients. These consisted predominantly of patients who had been cured of *H pylori* infection some years earlier and whose ulceration had persisted or recurred. Resolution of DGM as shown in their study, occurs slowly, if at all, after eradication of *H pylori* and the accompanying reduction in acid secretion. It may be inappropriate therefore to correlate the degree of DGM in these DU patients cured of *H pylori* with their current acid status. Before eradication of their *H pylori* infection their acid secretion will have been considerably higher and the degree of DGM metaplasia is therefore likely to reflect their previous high duodenal acid load. Consistent with this is the fact that two of these DU patients cured of *H pylori* had very severe DGM (100% and 72%) despite only modest acid output. Excluding the DU patients in whom *H pylori* had been eradicated shows an even stronger association between DGM and basal and GRP stimulated acid output, which are the acid measurements that show greatest resolution after eradication of *H pylori*. This is consistent with DGM being caused by longterm increased duodenal acid exposure and being slow to resolve after reduction of acid secretion.

In addition to increasing gastric acid, *H pylori* might directly stimulate the progression of DGM by inducing inflammation of the duodenal mucosa. Harris et al tried to test this hypothesis by seeing whether *H pylori* positive subjects had more DGM than *H pylori* negative subjects. They found that the degree of DGM was unrelated to *H pylori* status and therefore concluded that the mechanism by which the infection produces DGM is likely to be entirely through its acid stimulatory effects. However, as already mentioned, their *H pylori* negative DU subjects are an unsatisfactory group for performing correlations based on current status. After excluding these there are insufficient subjects of different *H pylori* status and similar acid output to test for an acid independent relation between *H pylori* status and severity of DGM. Consequently, this study does not clarify whether colonisation of DGM by *H pylori* and the subsequent inflammation contributes to progression of DGM.

On page 508, Savarino et al report their study of the relation between gastric acidity and DGM. They examined *H pylori* positive DU patients, 49 of whom had DGM and 22 of whom did not. They performed 24 hour intragastric pH in these two groups and in a group of non-ulcer controls in whom there was no information about their duodenal histology. The intragastric pH was lower in the DU patients than controls, but no difference could be detected between the patients with and without DGM. In the light of this finding, Savarino et al have come to the opposite conclusion to that of Harris et al, namely that gastric acid is not the major determinant of DGM.

How does one explain these different conclusions? The discrepancy between these results is probably explained by the different methods used to measure gastric acid status. Savarino et al measured only the acidity of the gastric juice. In contrast, Harris et al measured both its acidity and rate of secretion and were thus able to calculate gastric acid output. The strong positive correlation between DGM and gastric acid output but lack of correlation between DGM and gastric acidity shows that the rate of gastric acid secretion is probably a key factor in the development of DGM. This makes physiological sense as the amount of acid entering the duodenum will depend upon its rate of secretion by the stomach. It is worth remembering that no
matter how highly acidic gastric juice may be, it cannot exert any adverse effects on the duodenal mucosa until it passes the pylorus, and the amount doing this will depend upon its rate of secretion by the stomach.

Intragastric pH metry has the further disadvantages of being a relatively insensitive means of measuring gastric acid status in the highly acidic stomach. This is shown by Savarino et al who observed that the 24 hour intragastric pH in their DU patients differed from that in their healthy volunteers by only 0.4 pH unit. In contrast, Harris et al found that DU patients had a 400% increase in basal acid output and 300% increase in GRP stimulated acid output compared with healthy controls. This higher sensitivity of acid secretion tests versus pH measurement at low pH makes the former tests more suitable for detecting correlations between disease and high acid status.

It is interesting that the measures of acid status found to correlate most strongly with the extent of DGM – that is, basal acid output and GRP stimulated acid output are also the ones which are most markedly increased by H pylori infection in DU patients. This shows that it is the disturbance of these physiological functions by H pylori infection that results not only in the development of DGM but also in the development of actual duodenal ulceration.

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