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## Pathogenesis of duodenal ulcer disease: the rest of the story

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Although several duodenal ulcer disease-specific abnormalities in gastric function have been described (e.g. exaggerated gastrin releasing peptide-stimulated acid secretion and an abnormal sensitivity of the parietal cells to gastrin), none has withstood careful examination. We describe here the critical nature of the duodenal acid load in precipitating and washing out bile salts, which inhibit the growth of *Helicobacter pylori* (*H. pylori*) in the development of duodenal ulcer disease. The risk of duodenal ulcer is enhanced by infection with pro-inflammatory *H. pylori* (e.g. with an intact *cag* pathogenicity island). Progressive damage to the duodenum promotes gastric metaplasia, resulting in sites for *H. pylori* growth and more inflammation. This cycle results in an increasing inability of the duodenal bulb to neutralize acid entering from the stomach until changes in duodenal bulb structure and function are sufficient for an ulcer to develop. Cure of the *H. pylori* infection results in a sustained fall in duodenal acid load as well as a marked (and continuing) reduction in inflammation, which results in the cure of chronic ulcer disease.

**Key words:** *H. pylori*; peptic ulcer disease; acid secretion; duodenal acid load.

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Humans have long been fascinated with their stomachs. Archaeological findings, ancient works of art and ancient medical writings show that the civilizations of the Sumerians, Assyro-Babylonians, Chinese and Egyptians, as well as the more enigmatic Etruscans, Greeks and Romans, were all concerned with the pharmacological and empirical treatment of gastric problems. For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality. Although the pathophysiology of ulcer disease has not yet been clearly elucidated, scientists have moved away from assigning acid the dominant role in ulcer causation and now recognize distinct and identifiable causes. The two most common causes of peptic ulcer are infection with the bacterium *Helicobacter pylori* (*H. pylori*) and the use of non-steroidal anti-inflammatory drugs (NSAIDs).<sup>1-3</sup>

Although *H. pylori* is now accepted as the cause of gastritis and the gastritis-associated diseases, gastric ulcer, duodenal ulcer, gastric carcinoma and primary gastric lymphoma, the exact role of the infection in the pathogenesis of these diseases remains unclear. The advent of H<sub>2</sub>-receptor antagonists, radio-immunoassay and the ability to measure meal-stimulated acid secretion in vivo have all combined to provide

increasingly detailed information regarding gastric secretion in health and disease. The relationship between enterochromaffin-like cells, G-cells, D-cells and parietal cells continues to be explored, resulting in a huge amount of data relating to neurohumoral interactions between nerves, especially the vagus, G-cells, D-cells, enterochromaffin-like cells, oxyntic cells and different peptide messengers.<sup>4</sup> While our understanding of the interplay between various receptors and the endocrine, autocrine and paracrine influences on gastric secretion has been greatly expanded, and despite many attempts and many false leads, no disturbance of gastric physiology has proved to be specifically related to duodenal ulcer disease. Candidates have included elevated serum pepsinogen levels, a large parietal cell mass, the accelerated gastric emptying of solids, a reduced inhibition of acid secretion with antral acidification, an exaggerated acid and gastrin response to meals or the infusion of bombesin or gastric-releasing peptide (GRP), and abnormalities in duodenal bicarbonate secretion in response to the instillation of acid, as well as differences in the distribution and severity of gastritis.<sup>5</sup>

Although there is a considerable body of new information regarding the pathogenesis of duodenal ulcer, it is still impossible to answer fundamental questions such as why ulcers are focal (Table 1). This article seeks to review what is known about *H. pylori* and duodenal ulcer disease and then to speculate on the answers to these questions.

**Table 1.** Unanswered fundamental questions regarding duodenal ulcer disease.

<p>Why does a duodenal ulcer develop?          Why is it focal?          Why does it tend to recur in the same location?          Why does ulcer disease not become a problem until years after acquisition of the <i>H. pylori</i> infection?          Why does cure of the infection lead to an immediate cure of the ulcer disease?</p>
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## HISTORY OF SEARCH FOR A DYSREGULATION THAT WOULD EXPLAIN DUODENAL ULCER DISEASE

Prior to the *H. pylori* era, the main focus of research was the search for a specific dysregulation of acid gastric secretion that would explain duodenal ulcer disease. None was forthcoming.

### Gastritis

Peptic ulcer disease has long been recognized to be almost invariably associated with a histological gastritis.<sup>6</sup> The different patterns of gastritis associated with duodenal ulcer and gastric cancer were first described early in the 20th century, and these observations have been repeatedly confirmed.<sup>7-9</sup> Cross-sectional and follow-up studies have shown that gastritis is localized primarily to the antrum in patients with duodenal ulcer, with a minimal tendency to progress into the gastric corpus.<sup>10</sup> This behaviour differs from the pattern of gastritis in those without duodenal ulcer (e.g. those with simple gastritis or with gastric ulcer). The natural history of gastritis in non-duodenal ulcer patients is for an extension of the inflamed area from the antrum into the corpus, resulting in acid secretion and eventually loss of parietal cells and the development of atrophy. Over time, the gradual increase in the amount and extent of gastritis leads to a decreasing acid secretion and could lead to a 'burning out' of some cases of duodenal

ulcer. The observation that therapy that reduced acid secretion, such as parietal cell vagotomy, was associated with a rapid extension of the gastritis into the corpus showed that a gastric factor (most probably acid secretion) was responsible for 'protecting' the corpus from atrophic gastritis, and also for the patterns of gastritis associated with different diseases.<sup>11,12</sup> These observations were the harbinger of studies showing that pharmacological acid suppression could also release the inhibition preventing corpus gastritis by *H. pylori*.<sup>13,14</sup> It is now recognized that anti-secretory therapy, irrespective of the nature of the inhibition, has the potential for allowing *H. pylori* to interact with the corpus mucosa, resulting in an increase in the severity of gastritis.<sup>15,16</sup> Overall, the importance of corpus inflammation and its relation to acid secretion has formed the basis of a model explaining how different diseases might result from *H. pylori* infection.<sup>15</sup>

### ***Helicobacter pylori***

In the mid-1970s, Steer, in a series of elegant studies, revived interest in a bacterial infection as a cause of gastritis.<sup>17-19</sup> In the early 1980s, Warren and Marshall were able to culture the bacterium associated with the gastric inflammation and suggested that this organism caused the gastritis.<sup>20</sup> Self-inoculation experiments by Marshall and Morris showed that the bacterium was able to cause gastric inflammation rather than simply being a commensal.<sup>21,22</sup> Finally, attempts by McNulty et al to treat the infection demonstrated that a reduction in bacterial load led to an improvement in gastritis and provided evidence in support of the hypothesis that a cure of the infection might lead to a cure of some of the gastritis-associated diseases.<sup>23</sup>

The strong link between *H. pylori* and peptic ulcer, and the observation that a cure of the infection resulted in a cure of the ulcer disease, provided strong evidence that *H. pylori* was determinant in the pathogenesis of peptic ulcer disease. Investigators began to ask whether the infection also might be responsible for some, if not all, of the previously described abnormalities in acid or gastrin secretion.

### **Secretions**

Decades before the initial description of *H. pylori*, corpus gastritis was shown also to be associated with a reduction in acid secretion out of proportion to the number of parietal cells, suggesting the presence of a substance inhibiting acid secretion that was associated with the inflammation.<sup>24,25</sup> These observations were also prophetic for what we have learned about *H. pylori* infection and acid secretion.

In 1971, McGuigan and Trudeau observed that patients with duodenal ulcer had an exaggerated gastrin release in response to meals and suggested that the trophic effect of gastrin might be responsible for the increased parietal cell mass characteristic of duodenal ulcer disease.<sup>26</sup> In the late 1980s, a number of investigators examined meal-stimulated gastrin release in relation to *H. pylori* infection. Exaggerated meal-stimulated gastrin release was shown to be related to *H. pylori* infection and reversed following cure of the infection.<sup>27,28</sup> The inability to demonstrate a relationship between gastrin secretion or acid secretion and *H. pylori* infection, and the finding that the parietal cell mass did not reliably fall following a cure of the infection, eliminated the hypothesis that the gastrin was responsible, either directly or indirectly, for the trophic effect seen in duodenal ulcer disease.<sup>29-32</sup> Overall, these observations provided the basic knowledge of studies required in order to understand how to evaluate *H. pylori*-related perturbations in gastric function (Table 2).

**Table 2.** Data needed to interpret a study of acid secretion in patients with *H. pylori* infection.

Full dose response to any acid stimulant (e.g. gastrin-releasing peptide)
Pentagastrin-stimulated maximum gastric acid output
Comparison of the results with the stimulant with the maximum acid output
Histological assessment of the status of inflammation in the gastric corpus
Effect of cure of the infection of the parameter assessed

Following on the elegant studies of bombesin-stimulated gastrin and acid secretion by Hirschowitz et al<sup>33</sup>, the group in Glasgow evaluated acid secretion stimulated by the human bombesin equivalent GRP. They showed that GRP-stimulated acid secretion was exaggerated in patients with duodenal ulcer compared with uninfected patients or those with *H. pylori* infection without duodenal ulcer disease.<sup>32,34,35</sup> The results of these experiments illustrate the pitfalls that arise in attempting to identify specific dysregulations of gastric physiology relating *H. pylori* and duodenal ulcer disease without including what are now recognized as the controls needed to place the physiological observations into perspective (Table 2). For example, GRP-stimulated acid secretion has been reported to be exaggerated in duodenal ulcer patients compared with those with *H. pylori* infection without duodenal ulcer, or uninfected individuals. When the results of GRP stimulation were normalized based on the maximal acid secretion, it was recognized that the putative *H. pylori*-duodenal ulcer-specific abnormality in acid secretion was actually an upward shift of the dose-response curve to GRP and not specific for duodenal ulcer disease.<sup>36,37</sup>

Meal-stimulated acid output in patients with duodenal ulcer has been shown to increase in proportion to the pentagastrin-stimulated maximum acid output (MAO)<sup>38</sup>, and persist for longer than normal.<sup>39,40</sup> Olbe et al described elegant studies in *H. pylori*-infected and uninfected individuals with and without duodenal ulcer in which they investigated interactions between antral distention and gastric secretion stimulated by pentagastrin, as well as gastrin release stimulated by GRP.<sup>41</sup> They found that the inhibitory effect on acid secretion induced by antral distention was restored after the *H. pylori* infection was cured, the effect being independent of whether duodenal ulcer disease was present.<sup>41</sup>

None of the physiological alterations that appeared to be related to duodenal ulcer – for example elevated serum pepsinogen levels, a defective reflex inhibition of acid secretion with antral acidification<sup>42</sup> or gastric distention<sup>43</sup>, intraduodenal fat<sup>44</sup>, fasting<sup>38</sup>, an exaggerated gastrin response to meals or to the infusion of bombesin or GRP, an exaggerated acid output in response to meals or in response to bombesin or GRP infusion, and an exaggerated acid output in response to the instillation of acid – have been proved to be more than reversible epiphenomena related to the *H. pylori* infection.<sup>37</sup>

## Duodenal acid load

It has been known for decades that there is an amount of acid secretion below which duodenal ulcer rarely occurs. The dictum 'no acid, no ulcer' still holds<sup>45</sup> as the addition of 'no *H. pylori*, no ulcer'<sup>46</sup> has not invalidated it, and the large body of evidence relating to the importance of acid in ulcer disease developed over the past century cannot be ignored. The fact that the parietal cell mass is generally greater than normal in patients with duodenal ulcer and remains high after cure of the infection suggests that the

increase in the parietal cell mass pre-dates the infection and may be one factor predisposing to duodenal ulceration after *H. pylori* infection.<sup>29–31,46–47</sup> These results are also consistent with elegant studies in twins suggesting a genetic effect in duodenal ulcer disease. For example, a study of monozygotic and dizygotic twins reared either together or apart found that genetic influences on peptic ulcer are independent of the genetic influences important for acquiring *H. pylori* infection.<sup>48</sup>

In the 1940s there was a considerable interest in duodenal acid load and its role in duodenal ulcer disease, an interest that has continued intermittently until the present day. We now believe, the data being consistent with this, that the duodenal acid load is the critical determinant of the conditions necessary for allowing *H. pylori* effectively to colonize and thrive in the duodenal bulb. Gastric metaplasia is the appearance of gastric mucus-type cells replacing the normal villus surface of the duodenum. While gastric metaplasia is a non-specific response to injury (being seen in patients with duodenal Crohn's disease, for example), its extent is usually a reflection of duodenal acid load.<sup>49</sup> For example, gastric metaplasia in the duodenum can easily be induced in animals by acid produced in response to repeated injections of gastrin<sup>50</sup>, is extensive in patients with Zollinger–Ellison syndrome<sup>51</sup>, and is markedly uncommon in patients with achlorhydria.<sup>52</sup> The prevalence of gastric metaplasia is increased in patients with duodenal ulcer disease<sup>53</sup> and decreases after acid-lowering operations for this condition<sup>54</sup>, suggesting that the process is reversible, albeit slowly.

The initial description of the growth of *H. pylori* described how it was inhibited by bile.<sup>55</sup> This observation led to a conundrum, because although *H. pylori* growth is inhibited by bile, it can easily be demonstrated in areas of gastric metaplasia around duodenal ulcers, where bile is typically present.<sup>6</sup> If *H. pylori* grows in the duodenal bulb and causes duodenal ulceration, the question becomes, how can *H. pylori* survive in the duodenum? One possible explanation is that the *H. pylori* that cause duodenal ulcer disease have acquired the ability to grow in the presence of bile. That hypothesis was, however, disproved by studies showing that *H. pylori* isolated from patients with asymptomatic gastritis and from patients with duodenal ulcer disease had an identical dose-dependent inhibition of growth by bile salts.<sup>15</sup> Another possibility is that the duodenal bulb of patients with duodenal ulcer has less bile than that of normal subjects. Glycine-conjugated bile acids have a pKa of between 4.3 and 5.2, are insoluble and precipitate from solution in acid environments. It thus follows that any cause of an increase in the duodenal acid load will both promote the development of gastric metaplasia in the bulb and precipitate bile acids, allowing *H. pylori* to colonize areas of gastric metaplasia in the duodenum.<sup>37,15</sup> Any feature that increases acid secretion, for example smoking, will increase the duodenal acid load. Smoking also increases the duodenal acid load by indirectly inhibiting both duodenal and pancreatic bicarbonate secretion.<sup>56</sup>

## THE DUODENAL ACID LOAD EQUATION

The equation that determines duodenal acid load has two sides: acid secretion by the stomach and the ability of the duodenum to neutralize the acid entering it. Smoking has a strong influence on duodenal acid load and as such promotes *H. pylori* growth in the duodenal bulb. Moreover, smoking results in an increase in the frequency and severity of duodenal ulcer disease. Following a cure of the infection, smoking no longer is a risk factor for recurrent ulcer, showing that *H. pylori* infection is the critical variable.<sup>57,58</sup> Every factor that has been related to the pathogenesis of duodenal ulcer

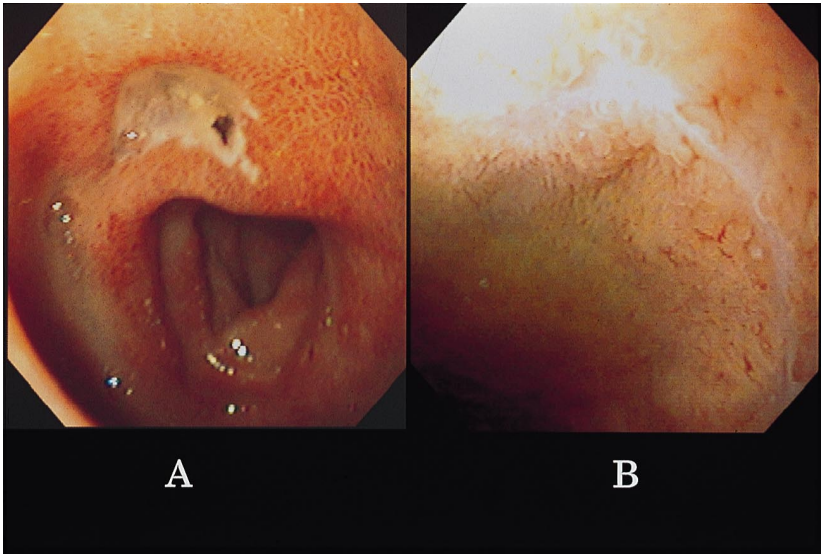
must also be considered in relation to its effect on duodenal acid load. Any event that increases acid secretion either directly (e.g. in response to gastrin or smoking) or indirectly (e.g. the failure of antral acidification to inhibit acid secretion normally) will act on the gastric (acid secretion) side of the equation. Factors that decrease the duodenum's ability to neutralize acid, such as any difference in size (smaller), shape, mucosal lining and ability to secrete bicarbonate, would act on the duodenal side of the equation to increase the effective duodenal acid load. For example, duodenal ulcers might be more frequent in patients with *H. pylori* infection and cirrhosis or with chronic pancreatitis, as they could secrete less bile or bicarbonate into the duodenum. The reduction of the duodenal acid load by anti-secretory therapy or highly selective vagotomy, stopping smoking or antacid use would result in an increase in duodenal bulb pH, which would in turn inhibit the growth of *H. pylori* and might result in the healing of duodenal ulcer disease. These data and speculations offer a possible explanation for why duodenal ulcer occurs in only some people – those with a high acid secretion – and suggests that the combination of high duodenal acid load and *H. pylori* infection is needed for the development of duodenal ulcer disease.

## WHAT IS STILL MISSING THAT MIGHT EXPLAIN DUODENAL ULCER DISEASE?

No abnormality in gastric function described in relation to duodenal ulcer has proved to be ulcer specific. With exception of antrum-predominant gastritis, no structural feature has had a predictive value regarding the development of duodenal ulcer. There is really no comprehensive explanation for why duodenal ulcers appear when they do or for why they relapse. We address these questions here. The feature of antrum-predominant gastritis that associates it with duodenal ulcer is the histological reflection of a gastric corpus whose acid secretion is unencumbered. It is now recognized that it is impossible to understand secretory data without simultaneously knowing the status of inflammation of the gastric corpus. Although recent work suggests that cytokines produced in response to the infection are responsible for the inflammation-associated reduction in acid secretion, a direct effect of a bacterial product has also not been ruled out.<sup>59</sup>

Duodenal ulceration requires abnormalities in stomach and duodenal structure and function. Although there are data suggesting that acid secretion may increase after the development of duodenal ulcer disease<sup>60</sup>, the fact that maximum acid secretion does not reliably decrease after the cure of an *H. pylori* infection in duodenal ulcer patients suggests that acid secretion alone is unlikely to be the major determinant in *H. pylori* duodenal ulcer disease. Although pentagastrin-stimulated acid secretion may not decrease following a cure of the infection, the duodenal acid load falls. This change in duodenal acid load is related to the fact that the normal regulatory pathways such as the inhibition of acid secretion by antral acidification again become active. Healing of inflammation in the bulb also allows normal villus epithelium to repopulate and restore normal duodenal mucosal function (Figure 1).

The key to the development of duodenal ulceration is what happens in the duodenum. First, an adequate duodenal acid load is needed to precipitate and wash out inhibitory bile salts. The risk of developing a duodenal ulcer is also enhanced by the presence of an infection with *H. pylori* with an intact *cag* pathogenicity island, as these strains are more pro-inflammatory than *H. pylori* lacking this island.<sup>16</sup> Progressive damage to the duodenum promotes the extension of gastric metaplasia, resulting in



**Figure 1.** (A) Endoscopic photographs of a duodenal bulb with an active ulcer showing the deformity and the abnormalities in the mucosa. (B) Duodenal bulb several years after the cure of an *H. pylori* infection and healing of the ulcer showing re-epithelialization, which is associated with recovery of function.

additional sites for *H. pylori* growth and thus more inflammation. The continuation of this cycle results in an increasing inability of the duodenal bulb to neutralize acid entering from the stomach until, finally, the changes in duodenal bulb structure and function are sufficient for an ulcer to develop.

The key to understanding duodenal ulcer disease therefore relates to the combination of duodenal acid load and the degree and extent of inflammation in the duodenum. The presence of junctional tissue (where inflamed villus epithelium abuts inflamed gastric metaplasia) is likely to be a vulnerable site for breakdown.<sup>49</sup> Whether an ulcer will occur depends on the ability of the duodenum to heal and contain the inflammation.

A review of series of patients with a duodenal ulcer shows a wide range of acid secretion. One must therefore consider duodenal ulcer in relation to a spectrum of acid secretion. The dysregulation in acid secretion seen in Zollinger–Ellison syndrome is one end of the spectrum of ‘too much acid’. In Zollinger–Ellison syndrome, the duodenum is not allowed a rest period from acid because gastrin secreted by the tumour is not downregulated by a low antral pH. In *H. pylori* infection, the ability of antral acidification to downregulate acid secretion is defective, but the defect is minor compared with that seen in Zollinger–Ellison syndrome. The high-acid end of the spectrum in *H. pylori* duodenal ulcer is an individual with a genetically determined large parietal cell mass and minimal corpus gastritis. Such an individual would secrete sufficient acid to put a burden on the ability of the duodenum to neutralize it. One would expect that duodenal ulcer would occur in such an individual with either a *cagA*-positive or a *cagA*-negative *H. pylori*. The other end of the spectrum is an individual with duodenal ulcer and corpus gastritis such that acid secretion would be just above the threshold for

duodenal ulcer disease. In such a patient, duodenal ulceration would not be expected unless duodenal neutralization were greatly compromised (e.g. by smoking).

The ability of the stomach to secrete acid is normally balanced by the ability of the duodenum to respond with an appropriate outpouring of bicarbonate. The factors that are likely to be important in compromising duodenal function include alterations in the mucosa with inflammation, a replacement with abnormal villus architecture and gastric metaplasia, and the adverse effects of scarring on the size, shape and motility of the duodenal bulb.

A third element in compromising gastric and duodenal function relates to the host response to the *H. pylori* infection. It is entirely plausible that the greater the inflammatory response of the host to the infection, the greater the likelihood that the integrity of the tissue is compromised. Thus, one would expect that infection with *H. pylori* containing an intact *cag* pathogenicity island would be found in duodenal ulcers with either a high or a low duodenal acid load, whereas strains without an intact *cag* pathogenicity island, and thus inherently less inflammatory, would be primarily found in the presence of a high duodenal acid load (Table 3). This hypothesis has not been subjected to experimental verification, and our recent experience of challenging volunteers with *cagA*-negative *H. pylori* has shown that the degree of inflammation elicited can be very marked, suggesting that the host response to the infection may be as important or even more important than the presence or absence of the *cag* pathogenicity island.<sup>61</sup> There has been a recent study suggesting that the *cagA* status of *H. pylori* isolated from the duodenal bulb and from the stomach may differ in patients with duodenal ulceration.<sup>62</sup> This observation has not been confirmed and at the outset does not seem logical considering that *H. pylori* from the stomach are continuously shed into the bulb and in most regions of the world *cagA*-negative *H. pylori* are extremely uncommon.

**Table 3.** The interaction between virulence of the *H. pylori* and duodenal acid load shown in relation to duodenal ulcer disease.

Duodenal acid load	Virulence of <i>H. pylori</i> strain	
	High	Low
High	Duodenal ulcer	Duodenal ulcer
Normal	Duodenal ulcer	No duodenal ulcer
Low	No duodenal ulcer	No duodenal ulcer

The only instance where enhanced *H. pylori* virulence (e.g. *cagA* positive status) is important for duodenal ulcer is with normal acid secretion.

## WHY IT TAKES TIME TO DEVELOP DUODENAL ULCER DISEASE

While the presence of a high duodenal acid load promotes the development of gastric metaplasia in the bulb mucosa, it rarely leads to ulcer disease unless it is excessive (Zollinger–Ellison syndrome) or occurs without a concomitant *H. pylori* infection. It appears probable that the inflammation associated with the infection and the cycle of inflammation/gastric metaplasia/damage/scarring/production of additional sites for *H. pylori*/more inflammation, etc. finally produces a situation in which the duodenal bulb is unable to cope and the balance shifts between repair and damage. As the repair process fails, an ulcer develops, which largely destroys the original site of gastric

metaplasia but also prepares the soil for repair with new gastric metaplasia. The cycle continues and leads to chronic disease. Any factor that might enhance the aggressive factors, for example increase in duodenal acid load associated with smoking or stress, would give the aggressive factor a slight advantage, which could eventually overwhelm protective factors and result in an ulcer. In most patients with *H. pylori* duodenal ulcer, the balance is generally nearly equal, such that factors enhancing duodenal acid load will lead to ulcer recurrence (smoking more) and those which promote repair or decrease duodenal acid load (e.g. antacid use) will promote healing. Curing the *H. pylori* infection would reduce or eliminate the inflammation and allow repair to restore normal or near-normal duodenal bulb structure and function. Duodenal ulcer should thus be considered to be a dynamic interplay between factors, the key variables being related to duodenal acid load and its consequences (the ability of *H. pylori* to thrive in the bulb and damage to bulb structure and function) as well as the host's response to the infection.

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