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REVIEW

Controversies in the *Helicobacter pylori*/duodenal ulcer story

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Summary In patients with *Helicobacter pylori*-positive duodenal ulcer (DU), the organism must be eradicated to achieve rapid, stable healing. However, evidence is against much else that is commonly accepted. (1) Does *H. pylori* cause the ulcer? Evidence against includes archaeopathology, geographical prevalence, temporal relationships and *H. pylori*-negative DU patients. DU can recur after eradication of *H. pylori* infection, and DUs may remain healed after reduction of acid secretion despite persistent infection. The faster healing of ulcers when *H. pylori* has been eradicated is due to the organism's interference with neoangiogenesis and the healing of wounded epithelial cells. (2) Does *H. pylori* infection persist until pharmacologically eradicated? Studies based on current infection show that *H. pylori* infection is a labile state that can change in 3 months. High rates of gastric acid secretion result in spontaneous cure, whereas low rates permit re-infection. Hydrochloric acid, necessary for producing a DU, is strongly associated with the likelihood of an ulcer. At the start, patients owe their ulcer to gastric hypersecretion of hydrochloric acid; approximately 60% may be *H. pylori*-negative. If acid is suppressed, the less acid milieu encourages invasion by *H. pylori*, especially if the strain is virulent.

1. Aetiology of duodenal ulcer: the acid era

For most of the 20th century, the orthodox opinion about the principal cause of peptic ulcer was that the stomach, when stimulated, secreted hydrochloric acid in excessive quantity. In particular, this effect was considered to be greater in duodenal ulcer (DU) than gastric ulcer.

This position was built up through many years of experimentation. At first, the stimulus to secretion was a 'test' meal of gruel, but the difficulties of separating any gruel left in the stomach from the gastric juice secreted into the stomach resulted in a search for a suitable parenteral stimulus. Finally, i.v. histamine, as the acid phosphate, delivered by a continuous infusion appeared to be the most suitable. There accrued evidence that it could stimulate maximal acid

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response, but its side effects (flushing, headache, etc.) were unpleasant and an antihistamine (H_1 antagonist) had to be used to allow a sufficient dose to be given to achieve the maximal response. Then a variety of errors affecting collection of the gastric juice from the stomach had to be addressed. These errors included losses from the stomach into the duodenum (minimised, but not prevented, by continuous gastric aspiration), reflux from the duodenum of alkaline contents into the stomach, and spontaneous compartment formation of the stomach into pouches, probably provoked by continuous suction.

Methods were developed to correct these errors: they relied on the slow infiltration down a second channel of an inert marker such as the dye phenol red, the measurement of electrolytes, and corrections for pyloric loss and duodenogastric reflux (Whitfield and Hobsley, 1979). As a result of the use of such methods and the proof of their accuracy, it became established that the maximal secretion of hydrochloric acid by the stomach was dependent on stature and that the best (and simplest) correlate with stature was the subject's height.

Earlier work had established that patients with DU lay in two groups related to their maximal secretory capacity: those lying above the 95% tolerance limits of the normal population and those lying within the normal limits. Thus, the distinction between large and smaller amounts of acid meant that some other cause must prevail in the normal secretory group. However, no exception was found to the original dictum of Schwarz (1910), 'No Acid, No Ulcer'. Indeed, there was at the lower border of the range in non-ulcer individuals a band of secretion in which no subject with peptic ulceration lay.

The final result of making all the corrections to the measurement of gastric acid secretion was reported in 1987 (Hobsley and Whitfield, 1987). They made no difference to the broad picture described in the previous paragraph: patients with DU never had an abnormally low secretion when maximally stimulated, but only some of them had supramaximal secretion. However, there was one important further element: in each band of arbitrarily designated secretion in the normal range, the *risk* of developing a DU increased with increasing maximal acid secretion until, at greater than the 95% upper tolerance limit of the population, it became 100%. Moreover, *Helicobacter pylori* status was not assessed in these studies. This last point is important and will be referred to again later.

2. Aetiology of duodenal ulcer: role of *Helicobacter pylori*

The award of the Nobel Prize in medicine or physiology to Warren and Marshall for the discovery of *H. pylori* recognised the importance of eradicating the organism in patients with DU, a procedure that converts a chronic relapsing situation into an acute and rapidly curable one. The impression seems to have been widely accepted that *H. pylori* actually causes the ulcer and that there is little more of interest to be discovered about the condition: for example, the journal *Gut* no longer has a section of its original research communications devoted to the subject of peptic ulcer. However, we feel that this view is too simplistic and that much remains to be learned in the field of acid and DU. Papers describing measurements of gastric secretion have virtually disappeared from the medical literature. In particular, there are three important controversies in current thinking:

1. that *H. pylori* infection *causes* duodenal ulceration;
2. that virulent strains of the organism are more likely to cause duodenal ulceration than non-virulent strains; and
3. that *H. pylori* infection is a chronic infection that remains with the patient indefinitely (at least in most cases) unless eradicated by pharmacological means.

2.1. Controversy 1: the presence of *Helicobacter pylori* causes duodenal ulcer

The evidence for this causal link is that the prevalence of *H. pylori* infection in DU patients is higher than in controls, a condition noted in all studies whether in areas of high or low population prevalence of *H. pylori*, and that the treatment of *H. pylori* infection leads to healing.

Against this concept that *H. pylori* infection causes ulceration are the following points.

- There is evidence that *H. pylori* infection has been present in humankind for centuries (Falush et al., 2003; Linz et al., 2007; Yamaoka et al., 2000, 2002); however, although heartburn and indigestion have been described for thousands of years, gastric ulcers were identified only in the 18th century and DUs only in the nineteenth (Baron, 2000). Indeed, DUs only became common at the beginning of the 20th century (Baron and Sonnenberg, 2001, 2002; Kidd and Modlin, 1998). No convincing explanation can be offered for various features such as the fact that peptic ulcer disease seems to have begun around 1750, mainly in the gastric rather than the duodenal region and affecting predominantly young women; the emphasis did not change to mainly DU predominantly in men until the beginning of the 20th century.
- The prevalence of duodenal ulceration is not higher in countries with a high prevalence of *H. pylori* infection, as would be expected if it were causal (Hobsley and Tovey, 2001; Hobsley et al., 2006).
- Geographically, the prevalence of duodenal ulceration does not correspond with the prevalence of *H. pylori* infection (Hobsley and Tovey, 2001; Hobsley et al., 2006). Within countries with the same overall prevalence of *H. pylori* infection, the prevalence of duodenal ulceration may vary from region to region. This is borne out particularly in studies from India (Tovey et al., 2004), Africa (Holcombe, 1992; Segal et al., 1998, 2001; Tovey et al., 2005) and China (Ching and Lam, 1994; Wong et al., 1998).
- There is considerable evidence of duodenal ulceration occurring in the absence of *H. pylori* infection. (i) There are only three reports (Boulos et al., 2002; Bytzer and Teglbjaerg, 2001; Pest et al., 1996) in the literature of the *H. pylori* status of cases presenting with a short history of duodenal ulceration (under 6 months) compared with those with a longer history. Without exception, these reports agree that patients with a short history are less likely to be *H. pylori*-positive than those with a longer his-