Peptic ulcer: a problem almost solved

For most of this century the problems of peptic ulcer were looked at chiefly as acid pathophysiology (pH), but in recent years *Helicobacter pylori* (*Hp*) has been recognised as a causative agent. Thus peptic ulcers now have defined causes and rational effective treatments, which have been well-documented in books1-8 and reviews9-17.

**Acid**

Peptic ulceration occurs when the digestive powers of gastric acid and pepsin overcome mucosal resistance18. In health, autodigestion of gastric and duodenal mucosa is prevented by protective mechanisms that fail at the ulcer site19.

In 1910 Schwartz18 defined this combat between gastric acid and the gastric mucosa (‘no ulcer, no acid’) and proposed that ulcer healing could be encouraged by decreasing acid or increasing mucosal resistance. In 1911 postprandial hyperacidity was found in 70% of patients with duodenal ulcer19, but the ranges of acidity after test meals in patients with duodenal ulcer and normal subjects overlap, so that there was no acidity threshold above which duodenal ulceration developed and therefore no target figure below which acidity had to be reduced1. Similar overlap was found after submaximal doses of gastric stimulants such as histamine.

The most important methodological advance in gastric secretion this century was the measuring of maximal acid output21,22. In Kay’s augmented histamine test, maximal histamine response (15-45 minutes after the agonist) was twice normal (45.9 vs 23.1 mmol/h) in men with duodenal ulcer but he found no threshold22. However, when peak acid output (the highest 30 minutes of secretion in the hour) was measured (Fig 1), it confirmed the double normal maximal acid output (42.0 vs 21.3 mmol/h) and no patient with duodenal ulcer was found who secreted less than 15 mmol/h23,24. This threshold has been confirmed by almost every other study in the past 30 years1.

In 1952 Card’s group assumed that each parietal cell had a maximal acid output so that the total acid output of the stomach after intravenous histamine could be related to the total parietal secretory cell mass. Card and Marks then showed that reduction in maximal acid output after partial gastrectomy was correlated with the absolute number of parietal cells removed25. There has been only one autopsy study in which parietal cells in the stomach were counted26, when these data were unscrambled (Fig 2) the parietal cell mass graph strongly resembled the peak acid plot and there was a threshold of 1,000 million (109) parietal cells below which duodenal ulcer has not been seen6. Figure 3 summarises the secretory situation of peptic ulcer and suggests that any treatment (physical, surgical or pharmacological) that reduces maximal acid output below 15 mmol/h would permit duodenal ulcers to heal (but re-ulcerate if the acid rose above this threshold). However, this model offered no explanation for the cause of hypersecretion.

**Mechanisms of gastric hypersecretion**

Gastric secretions were at first thought to be mostly under neural control23 until the isolation of gastrin (stimulating gastric acid). In addition to the neural pathways, there are now many known hormones that stimulate and inhibit gastroduodenal secretions10.

![Figure 1](image-url) Diagnostic discrimination of measurements of peak acid output. (Reproduced from reference 9 by permission of Butterworths.)
Neural

Patients with duodenal ulcer have abnormally high levels of muscarinic receptors in the body of the stomach, and this over-expression of receptors on the parietal and chief cells may induce gastric acid and pepsinogen hypersecretion, possibly through vagal stimulation27.

Endocrine

Clear evidence for an endocrine role in duodenal ulcer disease came from the Zollinger-Ellison syndrome of intractable peptic ulcer disease associated with gastric acid hypersecretion and a non-insulinoma pancreatic islet cell tumour. The syndrome could be controlled either by total gastrectomy abolishing gastric acid hypersecretion, or by removal of the tumour which must therefore have contained a hormone, later proved to be gastrin28.

Patients with duodenal ulcer have higher than normal basal and postprandial serum gastrin levels. These patients have a greater functional G-cell mass and about twice normal G-cell population which could, via hypergastrinaemia, stimulate the parietal cells to secrete more acid and increase the parietal cell mass29.

In health, postprandial increases in acid and gastrin secretion are halted by inhibition of antral gastrin by the acidification of the gastric antrum. This negative feedback system is deficient in duodenal ulcer disease, where the abnormally high and longer lasting postprandial rises in acid and gastrin cannot be inhibited experimentally by acidifying the antrum to pH levels which do inhibit gastric acid and gastrin postprandially in normal subjects30. Postprandial acid inhibition by intraduodenal fat, gastric antral distension and feedback inhibition of gastric emptying (pyloric competence) are also deficient in duodenal ulcer disease31.

Somatostatin inhibits both endocrine and exocrine cells, so a deficiency of this paracrine D-cell peptide could increase secretion of parietal, chief and G-cells of the stomach. D-cells are deficient in the antrum of patients with G-cell hyperplasia, the antral concentration of somatostatin is only half normal in patients with duodenal ulcer32, and patients’ meal-stimulated acid and gastrin are less inhibited than normal by somatostatin33.

Gastrin stimulates the parietal cell directly but mostly by increasing the release of histamine from enterochromaffin-like cells (ECL) in the body of the stomach. High secretion of acid is related to increased formation and turnover of histamine, which stimulates Fig 2. Estimated total parietal cells in stomach obtained at post mortem. (Reproduced from reference 9 by permission of Butterworths).

![Figure 2](image)

**Fig 2.** Estimated total parietal cells in stomach obtained at post mortem. (Reproduced from reference 9 by permission of Butterworths).

Fig 3. Postulated parietal cell mass, peak acid output and the secretory situation of peptic ulcers. (Reproduced from reference 9 by permission of Butterworths).

![Figure 3](image)

**Fig 3.** Postulated parietal cell mass, peak acid output and the secretory situation of peptic ulcers. (Reproduced from reference 9 by permission of Butterworths).
the parietal cell H₂ receptor. Increased release of histamine may be due to increased muscarinic vagal stimulation, decreased inhibition of the ECL cell by D-cell somatostatin or decreased inactivation of histamine itself. The gastrin-releasing peptide bombesin stimulates an excessive release of antral gastrin and gastric acid in patients with duodenal ulcer. Bombesin also inhibits acid secretion in normal subjects but not in most patients with duodenal ulcer, probably a somatostatin-mediated effect.

By the late 1970s endocrine and paracrine pathways for gastrin and gastric acid secretion in health, and hypersecretion in duodenal ulcer disease, had been elucidated. Patients were reasonably advised to stop smoking cigarettes and some were given mucosal protectants or procedures to lower acid secretion.

Mucosal protectants

Carbenoxolone, derived from liquorice, was the first drug to increase the rate of healing of gastric and duodenal ulcers in controlled trials, but is little used today because of its mineralocorticoid-like effects. Sucralfate is a basic aluminium salt of sucrose octasulphate introduced in 1968. It is thought to form an adherent complex in the ulcer base and act as a barrier to acid, pepsin and bile. Bismuth, which decreases proteolysis and may stabilise mucus, has been used for 200 years and there are many preparations, the most studied being colloidal bismuth subcitrate (De-Nol). Each of these drugs is as effective as an H₂ antagonist in ulcer healing, but they are not licensed for maintenance because of possible side-effects. Some ulcers healed by bismuth are slower to recur than after acid inhibitors, probably because of its suppressant effect on H. pylori (see below). Prostaglandin E in gastric mucosa may inhibit acid production or stimulate secretion of bicarbonate and mucus, and analogues in doses too low to inhibit acid have speeded the healing of duodenal ulcers by a cytoprotective effect. Prostaglandin analogues can be co-prescribed with non-steroidal anti-inflammatory drugs (NSAID) to prevent gastric ulcers.

Acid-lowering treatments

Physical damage

For more than 100 years operations have reduced delivery of gastric acid onto the duodenal bulb either by diversion (gastrojejunostomy), resection of most of the parietal cell mass (partial gastrectomy) and/or resection of part or all of the antrum containing gastrin-secreting G-cells (antrectomy), or by vagal denervation. The percentage reduction of maximal acid output is correlated with their efficacy, defined as non-recurrence of duodenal ulcer (Fig 4). Dragstedt should be doubly honoured: his acid-lowering vagotomy in 1942 was a surgical triumph of applied physiology and in his first paper in 1917 (Fig 1) he grew bacteria from ulcers and attributed them to an infection. Duodenal ulcer disease has been treated by gastric irradiation or gastric freezing to damage gastric mucosa and to decrease acid.

Acid-reducing drugs

Gastric acid can be neutralised by antacids and decreased by blocking the receptors (histamine, acetylcholine muscarinic) on the parietal cells or inhibiting the intracellular enzyme synthesising hydrochloric acid (H⁺ K⁺ ATPase). Antacids have been used for thousands of years. Controlled trials have not shown occasional doses to relieve episodes of pain in patients with peptic ulcer. Larger regular doses do increase the rate of healing of duodenal ulcer.

![Fig 4. Non-recurrence of duodenal ulcer and percentage reduction of maximal acid output (MAO) after gastric operations. = partial gastrectomy; = partial gastrectomy and truncal vagotomy; = antrectomy and truncal/selective vagotomy; = selective vagotomy; = truncal vagotomy 'complete'; = proximal gastric vagotomy; = antrectomy; = truncal vagotomy 'incomplete'; = gastrojejunostomy/pyloroplasty). (Reproduced from reference 15 by permission of Yale Journal of Biology and Medicine).](image-url)
Antimuscarinic acid inhibitors were at first non-subtype specific, such as atropine and its synthetic analogues. By reducing acid output they enhanced healing and reduced recurrence of peptic ulcers, although side-effects limited dosage and patients varied in the reduction of acid output achieved by a maximum tolerable dose of the anticholinergic drug.

H₂ blockers

Classical antihistamines block H₂ receptors. In the augmented histamine test an H₂ antihistamine prevented the side effects of histamine but not the acid secretion mediated by the H₂ receptors of the parietal cell. H₂ receptor blockers (cimetidine, ranitidine, etc) markedly reduce gastric acid, both basal and in response to all stimuli, and therefore heal about 80% of duodenal ulcers in four to six weeks and almost all after three months, while maintenance therapy will keep about 80% of duodenal ulcers in remission for as long as the drug is taken. Gastric ulcers behave similarly.

Proton pump inhibitors

Proton pump inhibitors (PPI) acting on the H⁺ K⁺ ATPase in the parietal cell are the most powerful anti-secretory agents available and will heal almost every peptic ulcer. The healing rate of duodenal ulcer is strictly proportional to the inhibitory capacity of the acid inhibitory drug (Fig 5), as is non-recurrence of duodenal ulcer after acid inhibitory operations (Fig 4).

By the 1980s drugs based on pathophysiology could heal or suppress peptic ulcers, but patients were not cured of their disease because the fundamental pathogenesis of gastric and duodenal ulcers had not been discovered.

Pathogenesis of peptic ulcer

The accepted associations with peptic ulcers were smoking (possibly via acid hypersecretion and bile reflux), familiality (probably genetic), and antral gastritis of unknown cause. Duodenal ulcers were associated with early urbanisation and duodenal gastric metaplasia. Gastric ulcers were associated with body atrophic gastritis and with NSAID.

Gastritis is now classified under the Sydney system in three categories (acute, chronic and special forms), topographically (antrum and/or body), and morphologically by five histological variables. Children and healthy adults with healthy stomachs have minimal inflammation of gastric mucosa and no decrease of parietal cells or acid output with increasing age. With age, acid and parietal cells decrease in most populations, due to atrophic gastritis of the body mucosa, and replacement of secretory cells by non-exocrine pyloric type mucosa spreading cephalad, but this is now attributed to long-standing infection rather than just to age.

Gastric ulcers usually develop in antral type mucosa immediately caudad to the mass of secretory cells of body mucosa. However, gastric ulcers are found in different sites, from prepyloric to high fundic, and usually on the lesser curve. Nevertheless Oi has shown that in stomachs with gastric ulcers, the junction of body/antral mucosa occurs just cephalad to the ulcer whatever its site, and gastric ulcers hardly ever occur in body secretory mucosa. Thus the stomach does not

![Graph](image_url)

Fig 5. Correlation of suppression of 24 hour intragastric acidity and rate of healing of duodenal ulcer after 4 weeks. (Reproduced from reference 52 by permission of Gut).
normally digest itself. The secretory stomach digests the non-secretory stomach at the unstable junction, possibly in an area of potential end artery ischaemia. Patients with gastric ulcer have normal acid outputs (Fig 1) and parietal cell numbers (Fig 2) but there is a gradient of acid associated with prepyloric > incisural > body ulcers determined by the residual parietal cell mass in the body following the pattern of gastritis1. It was assumed that gastric ulceration, and indeed carcinoma, developed on the background of atrophic gastritis of cause unknown.

Duodenal ulcer disease was strongly associated with antral gastritis; the relative risk in men of developing duodenal ulcer was sixteen fold if there was antral superficial gastritis and eighteen fold for antral atrophic gastritis16. Gastritis was rarely more than superficial in the body so that parietal cells (and basal and maximal acid outputs) were normal or high (Figs 1 and 2), and with increasing age hypersecretion and healthy mucosa in the body persisted. In patients with endoscopy-negative dyspepsia in 1979, who were followed for ten years, none developed a duodenal ulcer if both body and antral mucosa were histologically normal at the start of follow-up37. With antral superficial gastritis, duodenal ulcers developed in the following ten years in 10% of those with normal body mucosa and in 7% of those with superficial gastritis in the body. No duodenal ulcers developed if both body and antrum showed atrophic gastritis originally, confirming the earlier observation that a certain gastric output of acid was needed from a certain number of healthy parietal cells; antral gastritis was also an essential factor, for no clear reason.

In the duodenum ulcers are believed to develop in a metaplastic type gastric mucosa14. Such mucosa has been produced experimentally by acidification of the duodenum, either by administering gastric juice, or by secretagogues such as histamine, pentagastrin + carbachol, or tetragastrin. Such metaplasia may be a defence against excessive acid reaching the duodenal mucosa, with compensatory overgrowth of Brunner’s gland duct epithelium onto the villi14.

Duodenal gastric metaplasia in humans is correlated with gastric acid output. In hypersecretion (Zollinger-Ellison syndrome) this metaplasia is extensive and in hyposecretion (atrophic gastritis and anacidity) it is absent. The threshold for the duodenal mucosal changes has been set at a maximal acid output of 10 mmol/h, with metaplasia still rare below 20 mmol/h, commoner with higher outputs and recently shown to be positively correlated with basal and peak acid outputs58. Similarly there was an apparent pH threshold of 2.5 basally, and only with higher acidities was gastric metaplasia of variable extent seen in the duodenum59. In 290 patients with dyspepsia there were 201 without gastric metaplasia in the duodenum, of whom 200 showed no active duodenitis. In the other 89 patients active duodenitis was found in 21/39 with less than 5% gastric metaplasia, 17/34 with 5–20% and 14/16 with more than 20%50. Superficial gastric metaplasia is almost invariable in duodenums with past or present ulceration, but was seen in a third of un-ulcerated duodenums. However, full thickness gastric heterotopia was confined to ulcerated duodenums50.

Thus by 1980 peptic ulcer pathogenesis had been compartmentalised into antrum and body gastritis and inflammation of gastric metaplasia in the duodenum produced by excess acid, mediated by endocrine, paracrine and neural factors. What was missing was an exogenous prime mover.

**Helicobacter pylori**

Although a spiral bacterium had been seen in stomachs from the late 19th century and characterised this century by both light and electron microscopy, it was only in 1983 that the organism was isolated by Warren and Marshall, cultured and named successively *Campylobacter pyloridis*, *C. pylori* and finally *H. pylori*. Progress then was rapid to define *H. pylori* as the missing prime cause of non-auto-immune gastritis both in the antrum and the body of the stomach. This bacterium *in vivo* can grow only in gastric mucus through which it swims and which it may disassemble51 to adhere to gastric epithelium and promote inflammation in the stomach itself and in metaplastic gastric mucosa in the duodenum leading to active duodenitis (the precursor of duodenal ulcer).

The natural history of *H. pylori* is still poorly understood. Its mode of transmission and whether there is an animal vector are unknown. Acquisition of infection is rare in adults (less than 1% per annum in developed countries), and is thought to occur in childhood, associated with deprivation, overcrowding and presumed cross infection. Acute infection in humans (for example by inadvertent spread via gastric tubes or endoscopes) has been seen to produce an acute gastritis and hyposecretion of acid, usually self-limiting. The prevalence of infection is 5–95% and almost all those infected have asymptomatic non-ulcerated histological gastritis. Some develop increasingly severe pangastritis which may progress to gastric ulcer or carcinoma or B-cell MALT (mucosal associated lymphoid tissue) lymphomas. Others develop body-sparing antral gastritis and duodenal ulcer instead. About 95% of duodenal ulcers and non-NSAID benign gastric ulcers are associated with *H. pylori*. About half of gastric cancer is attributable to *H. pylori*.

The pathway by which *H. pylori* is acquired may be related to host factors such as age, socio-economic status, host defence mechanisms, or genetic background, or there may be bacterial factors such as density of infection and differences in virulence between strains. *H. pylori* is genetically extremely diverse with more strains than almost any other bacterium, which makes it almost impossible to type. Several putative virulence factors have been identified.
(eg cag A, vac A)\textsuperscript{52}. Patients infected with the cag A +ve strains possess a pathogenicity island which is a cluster of genes that amongst them appear to encode for key virulence factors; perhaps only some strains cause severe neutrophilic gastritis and hyposecretion (and thus gastric ulcer/carcinoma) and/or duodenitis (and thus duodenal ulcer). It has been suggested that in deprived populations, whether in developed or developing countries, with high rates of infection with \textit{H. pylori} in childhood, the resulting severe gastritis in the body causes such loss of parietal cells and consequent hyposecretion that gastric metaplasia rarely develops in the duodenum\textsuperscript{53}. The duodenum is therefore not colonised by \textit{H. pylori}, so that duodenal ulcer (as opposed to gastric ulcer or carcinoma) is infrequent in these groups.

\textit{H. pylori} and hypersecretion

Thus duodenal ulcer\textsuperscript{50} involves infection by \textit{H. pylori} of metaplastic gastric type cells in the duodenum induced by hypersecretion, either an independent genetic characteristic or due to \textit{H. pylori}.

It was soon shown that basal and meal-stimulated serum gastrin was increased in subjects (with or without duodenal ulcer) and that the hypergastrinaemia was normalised after eradication of these bacteria\textsuperscript{54-58}. The specific pathophysiological feature in patients with duodenal ulcer – the failure of antral acidification to a pH of 2.5 to inhibit antral release of gastrin and gastric acid – was seen only in stomachs with \textit{H. pylori}\textsuperscript{59}.

With antral \textit{H. pylori} infection D-cell activity and somatostatin or somatostatin mRNA were decreased\textsuperscript{60-69}, and somatostatin levels and stored histamine in the body were normalised by eradication of \textit{H. pylori}\textsuperscript{62,65,69,70}. Similarly the release of gastrin by bombesin\textsuperscript{71} or GRP\textsuperscript{72} is high in subjects with \textit{H. pylori} and was also normalised after their eradication. Some studies have shown that both basal\textsuperscript{72-74} and peak acid outputs after GRP\textsuperscript{72,76} and pentagastrin\textsuperscript{74,76} fall to normal six months after eradication of \textit{H. pylori} in patients with duodenal ulcer.

Various mechanisms have been suggested to explain the endocrine changes in the stomachs infected with \textit{H. pylori}\textsuperscript{24}. Did hydrolysis of urea by bacterial urease increase mucosal pH which then interfered with the normal feedback of antral acid inhibiting release of gastrin\textsuperscript{24}? Were the endocrine changes due to inflammatory mediators such as diffusible cytokines (for example interleukins) from inflammatory cells?\textsuperscript{27} Could excessive release of plasma peptides and amino acids from gastric mucosa damaged by \textit{H. pylori} cause inappropriate hypergastrinemia?\textsuperscript{28} Surprisingly, \textit{H. pylori} produces histamine and N\textsubscript{6}-methyl histamine, known secretagogues\textsuperscript{79}.

Dragstedt’s bacterial ulcer model\textsuperscript{80} was not capable of proof in 1917 in the absence of today’s bacteriological techniques and antibacterial drugs. Not all Koch’s postulates have yet been met for the Acid + \textit{H. pylori} two component model; it has, however, been tested extensively by measuring the therapeutic efficacy of eradication of these bacteria in terms of ulcer healing, gastritis resolution and normalisation of exocrine and endocrine abnormalities.

Current management of peptic ulcer

\textit{H. pylori}, if present, should be eradicated in any patient with peptic ulcer (past or present). Ideally \textit{H. pylori} infection should be confirmed before treatment (see page 478). There is no perfect eradication regimen but detailed guidance is available on drug combinations, doses and duration\textsuperscript{69,81} and one can reasonably expect 90% eradication with the initial treatment, negligible re-infection and minimal ulcer recurrence (<2%). Certainly eradication may fail if the patient does not take all the tablets prescribed, so the clinician should explain to the patient with \textit{H. pylori} and an ulcer that the treatment has an 80–90% chance of eradicating the organism and allowing the ulcer to heal and not return, only if the patient adheres to the prescribed regime. Compliance, side-effects and cost are improved by seven day low dose regimens.

Eradication is rarely achieved by giving a single drug because, as with tuberculosis, suppression followed by recrudescence is almost inevitable and bacterial resistance may be induced. The first satisfactory regimen was a combination of a bismuth salt (especially triclosan bismuthate), a nitroimidazole (metronidazole or tinidazole) and an antibiotic (amoxicillin or tetracycline to which the bacteria are usually sensitive). Dual or triple therapies have been shortened from eight to four to two to one week and eradicate about 85% of metronidazole-sensitive bacteria. Clinicians need to be aware of at least the overall sensitivity in their particular populations to nitroimidazole and choose a non-nitroimidazole regime especially in patients who have previously been given these drugs frequently for alimentary or genitourinary infections. Bactericidal antibiotics such as amoxicillin and/or clarithromycin are now given together with a proton pump inhibitor (omeprazole, lansoprazole, pantoprazole) which markedly lower the drug’s minimal inhibitory concentration for killing \textit{H. pylori}. Such triple regimes achieve eradication rates of up to 90%; failure of eradication (a positive breath test) in compliant patients is usually due to nitroimidazole resistance, and if this is known or assumed, an alternative triple regime would be a PPI with both amoxicillin and clarithromycin. A quadruple regime may be necessary, with bismuth added to this triple regime\textsuperscript{84}.

After eradication, a duodenal ulcer heals rapidly and there is no need to give further acid inhibitors after the initial eradication course, nor any need for re-endoscopy to check whether the duodenal ulcer has healed if the 4-week post-eradication breath test remains negative. Should symptoms return and the breath test remain negative, some other diagnosis
must be sought but re-endoscopy may be necessary because about 5% of patients with duodenal ulcer are H. pylori negative and therefore cannot benefit from an H. pylori eradication regime. Many of these patients are taking NSAID (though may not admit it) and occasionally the duodenal ulcer is not peptic but from Crohn’s or other diseases such as neoplasia. There may be a subset of hypersecretors, usually primary but rarely associated with an endocrinopathy such as hyperparathyroidism or hypergastrinaemia (antral G-cell hyperplasia or Zollinger-Ellison syndrome) – such patients may independently and coincidentally have H. pylori but its eradication alone will not help. Most patients whose ulcers have recurred after acid-lowering operations no longer need re-operation or life-long acid inhibitors. They should be managed by eradication of H. pylori (if present).

Fewer patients with gastric ulcer have H. pylori probably because NSAID are a more common cause of gastric than duodenal ulcer. H. pylori positive patients with gastric ulcer proven benign (by endoscopy with at least eight biopsies) should be treated similarly to duodenal ulcer disease except that six to eight weeks after the initial one week period of eradication treatment they should be re-endoscoped (to check healing) with biopsy (again to exclude carcinoma and to check eradication of H. pylori). Patients presenting with perforated or bleeding ulcers should have eradication of any H. pylori, after which recurrence is rare: the H. pylori negative patients will need long term acid inhibitors. H. pylori positive patients with pyloric stenosis may respond to eradication and endoscopic balloon dilation. H. pylori negative patients with gastric ulcers will need an acid inhibitor.

Summary: Some solutions to some problems of peptic ulcer

The problems of peptic ulcer are now almost solved both conceptually and aetiopathologically, so that both acid-lowering and H. pylori eradication treatments are nowboth rational and efficacious.

The stomach does not normally digest itself, nor do stomachs ulcerate spontaneously. Ulceration usually follows attacks by humans (with NSAID), and/or bacteria (H. pylori) and rarely by primary excess of secretagogues (gastrin, histamine, calcium, parathormone). The acid pepsin from the body mucosa digests the inflamed non-parietal antral mucosa of the caudal antrum which has extended by gastritis and metaplasia into the body. Gastric juice may allow ulceration of the juxtapyloric duodenal mucosa, so that all peptic ulcers are marginal. Because nearly all peptic ulcers occur either in primary gastric mucosa in the stomach or in metaplastic gastric mucosa in the duodenum (and heterotopic gastric mucosa in Meckel’s diverticulum or the rectum) I propose that peptic ulcers are fundamentally gastric ulcers, thus resolving the age old controversy over whether gastric and duodenal ulcers were separate diseases or one disease, peptic ulcer. Most duodenal ulcers can now be cured by eradication of H. pylori with a triple regime of proton pump inhibitor, antibiotic and nitroimidazole. Immunisation85 may one day prevent or cure this infection, making peptic ulcers and gastric carcinoma less common.

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