Peptic ulcers can now be cured without operation

J H Baron DM FRCP FRCS
Senior Lecturer and Consultant

Department of Surgery, Royal Postgraduate Medical School, London

Duodenums exposed to above threshold gastric acid secretion may ulcerate if infected with *Helicobacter pylori*. Duodenal ulcers can be healed by suppressing acid secretion medically or surgically; their recurrence can be prevented by lifelong antisecretory drugs or by an elective vagotomy. However, duodenal and gastric ulcers can now be healed, and recurrence prevented, without operation by eradication of *H. pylori*.

The pathophysiology of duodenal ulcer and its treatment by medical and surgical acid inhibition is reviewed and the pathogenesis of duodenal ulcer and its cure by eradication of *Helicobacter pylori* is described. I express my indebtedness to all who have helped me over the years. There are few citations; references will be found in books *(1–5)*, reviews *(6–11)* and recent articles *(12–20)*.

Pathophysiology

Acid

John Hunter taught that the stomach secreted acid which 'animalises the food': 'the acid is increased in some diseases and in others the disposition to form it may be destroyed . . .' *(6)*. In 1910 Schwartz postulated a combat between the autodigestive power of gastric juice *versus* mucosal resistance. Ulcer formation was likely if the former increased or the latter decreased, and thus ulcer healing could be achieved by decreasing the acid or

increasing mucosal resistance. Two years later Moynihan reported that J C Adams had found 70% of patients with duodenal ulcer had hyperchlorhydria or hyperacidity. However, the ranges for maximum acidity after test meals in normal subjects and in patients with duodenal ulcer overlapped completely *(1)*. In the absence of a threshold of acidity there was no appropriate target figure for acid and patients with duodenal ulcer could not be managed successfully.

In 1953 Kay introduced the augmented histamine test to measure maximum histamine response. Peak acid outputs in response to maximal doses of histamine (and later of histalog or pentagastrin) in patients with duodenal ulcer are about twice normal. I found that patients with duodenal ulcer always secrete more than 15 mmol/h (Fig. 1). This functional discrimination parallels morphology (Fig. 2) with a threshold parietal cell number of 1×10^9 below which duodenal ulcers were not seen post-mortem. It was then possible to plot parietal cell mass and peak acid output on two vertical axes (Fig. 3). Patients with duodenal ulcer also secrete excess pepsin because of a double normal chief cell mass.

The threshold model predicted that any treatment (physical, surgical or pharmacological) that lowered acid output below 15 mmol/h would allow duodenal ulcers to heal, and to stay healed unless acid returned to above the threshold. This model, like any other conceived and refutable scientific hypothesis, has now been tested and not refuted. In my analysis of 100 years of acid-lowering operations, reductions in basal and maximal acid output paralleled the efficacy (in preventing recurrence of duodenal ulcer) of the particular vagal denervation, gastric resection or combination (Fig. 3). Similarly, the proportion of duodenal ulcers which heal after medical treatment is strictly correlated with the percentage reduction of gastric acidity *(13)* (Fig. 4). All duodenal ulcers should heal in 4 weeks if intragastric pH is kept above 3 for more than 18 h/day.
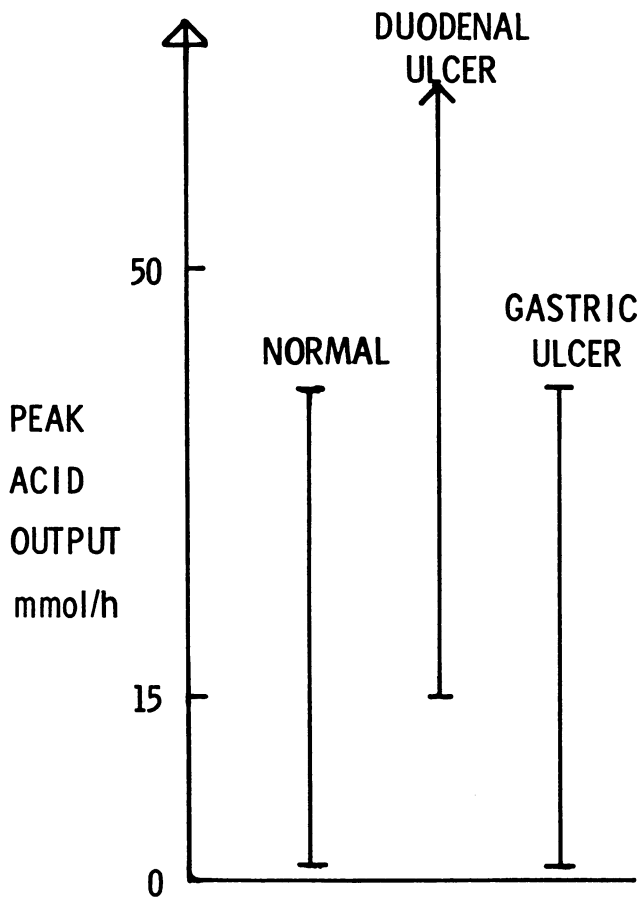
Figure 1. Diagnostic discrimination of measurements of peak acid output. (From Baron *(11)*.)
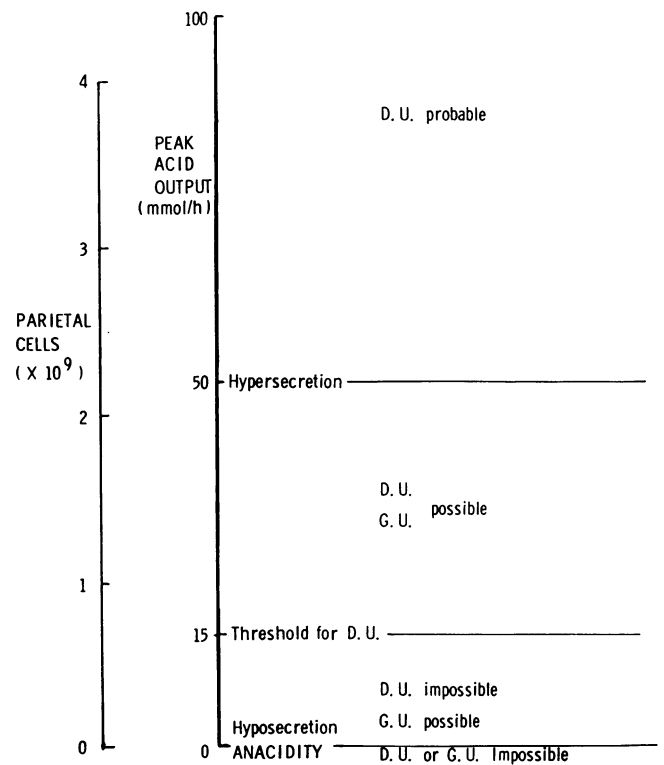

Figure 2. Postulated parietal cell mass, peak acid output and the secretory situation of peptic ulcers. (From Baron *(12)* by permission of Butterworths.)

Most duodenal ulcers will not return if maintenance therapy is started and continued indefinitely. However, if this maintenance treatment is stopped duodenums will reulcerate because the natural history of the disease has not been altered. Thus far the pathogenesis of duodenal
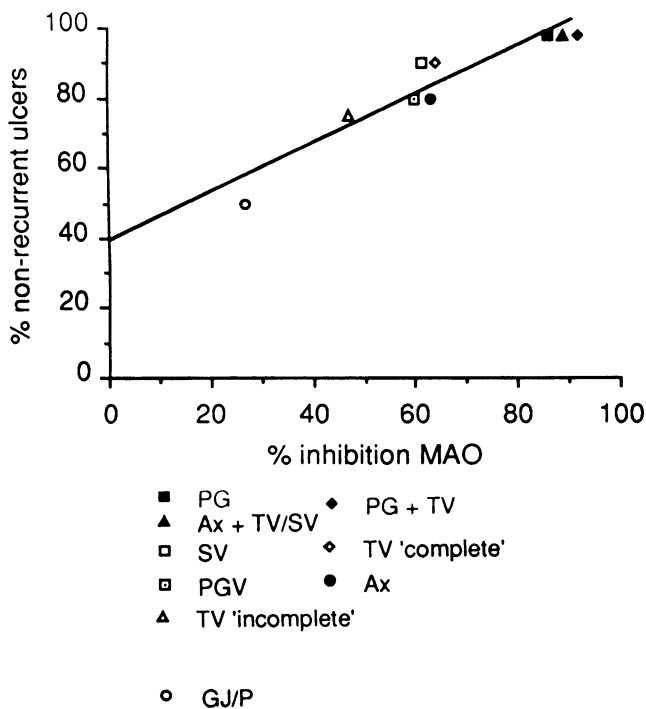

Figure 3. Non-recurrence of duodenal ulcer and percentage reduction of maximal acid output after gastric operations. (From Baron *(9)* by permission of *Yale Journal of Biology and Medicine*.)
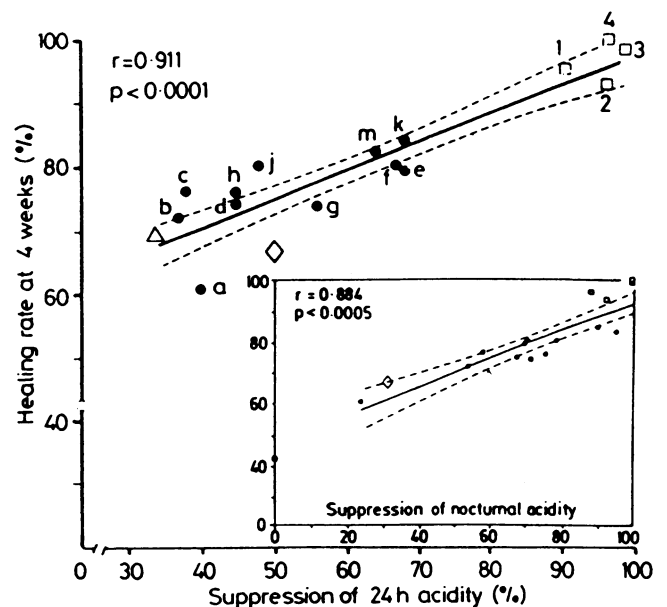

Figure 4. Correlation of suppression of 24 h (and nocturnal intragastric acidity) and rate of healing of duodenal ulcer 4 weeks. ○ placebo, △ enprostil, ◇ antacid; ● H₂ blockers, cimetidine a, b, d, f, g, j, famotidine n, oxmetidine c, ranitidine e, h, k, omeprazole: (1) 20 mg; (2) 30 mg; (3) 40 mg; (4) 60 mg mane. (From Jones *et al.* *(13)* by permission of *Gut*.)
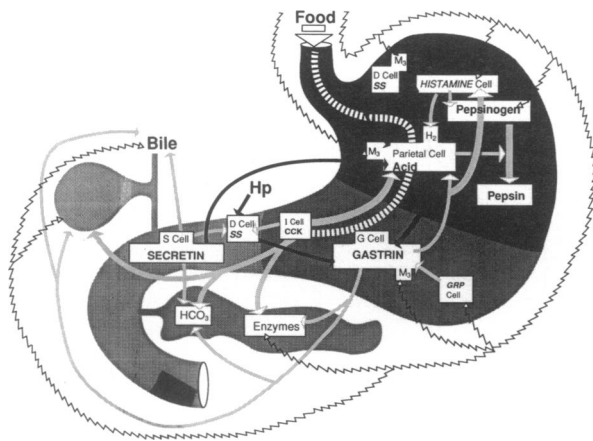
Figure 5. Regulation of gastric secretion. Names in capitals are HORMONES or *PARACRINE*. Names in lower case are gastric secretions. The vagus nerves are shown as zig-zag lines. Stimulation is indicated by open arrows and inhibition by solid arrows. Modified from Baron *(1)*. Any impairment by *H. pylori* of D cell activity will reduce secretion of somatostatin and may increase gastrin, histamine and acid.

ulcer disease had not been determined and there was no rational cure.

Mechanisms for hypersecretion (Fig. 5)

Endocrine

Patients with duodenal ulcer have higher than normal basal and post-prandial gastrin. The number of G cells in the human antra, the G cell mass, is twice normal, overlapping the normal population as with acid secretion. Gastrin is trophic and hypergastrinaemia could increase the parietal cell mass. In patients with duodenal ulcer G cells are not inhibited as much by acidic pH in the antrum in a range which inhibits gastric acid and gastrin in normal subjects.

Neural

There is no consistent evidence of any abnormal vagal or sympathetic effects on the stomach in duodenal ulcer disease.

Paracrine

The gastrin-releasing peptide (GRP) bombesin is one of the few stimulants of the release of antral gastrin which is not inhibited by antral acidification. Could patients with duodenal ulcer disease have excess neural GRP? They have excess GRP cells in their duodenal bulb. Somatostatin inhibits both endocrine and exocrine cells. The concentration of somatostatin in antral biopsies from patients with duodenal ulcer was only half the level found in normal subjects and meal-stimulated acid and gastrin was significantly less inhibited by somatostatin in patients with duodenal ulcer than in normal subjects. There was a deficiency of somatostatin-producing D cells in the antra of patients with G cell hyperplasia and in the duodenal mucosa in patients with duodenal ulcer. Perhaps duodenal

ulcer disease was due to a deficiency of D cells and of their product somatostatin leading to a relative and inappropriate hypergastrinaemia, excess G cells and stimulation of gastric acid and parietal cells.

Histamine

Gastrin primarily stimulates the enterochromaffin and possibly mast cells to release histamine which then stimulates the parietal cells to release acid. The gastric mucosa of hypersecretors contains less stored histamine than in normal subjects indicating an increased rate of formation and turnover. After complete, but not after incomplete, vagotomy the mucosal histamine returns to normal and this increase is correlated with the fall of acid output. Acid hypersecretion could be due to the release (or decrease of inactivation) of histamine.

Pathogenesis

Until recently the known risk factors for peptic ulcer were antral gastritis, familiality and smoking. Duodenal ulcer was also related to early urbanisation and gastric metaplasia.

Gastric metaplasia

The Leeds group remind us of Konjetzny's dictum "an ulcer does not develop in a healthy mucosa". Duodenal ulcer develops from duodenitis which develops specifically in abnormal mucosa, gastric metaplasia, long known to be induced experimentally by excess acid. Gastric heterotopia was never found in the duodenum when preoperative maximum acid output was less than 10 mmol/h, was rare below 20 mmol/h and was increasingly common the higher the acid output. Duodenal gastric metaplasia was also correlated with fasting pH and not seen unless pH was below 2.5. In 290 dyspeptic patients, gastric metaplasia was absent in 201 duodenal biopsies only one of which showed active duodenitis, but in those with <5%, 5–20%, and >20% gastric metaplasia there was active duodenitis in 21/39, 17/34 and 14/16, respectively (Fig. 6) *(14)*. The majority view is that gastric metaplasia is related to excess gastric acid load entering the duodenum possibly as a defensive overgrowth of Brunner's glands. A contrasting model is that heterotopic metaplastic gastric type mucosa in the duodenum contains parietal (and chief) cells, whose endogenous acid (and pepsin) production could contribute to increased acid load on the bulb, and thus ulceration.

Gastritis. In the general population acid secretion and parietal cell numbers decrease with age due to atrophic gastritis of the body mucosa and replacement of secretory cells by cephalad spread of pyloric type mucosa. In healthy subjects with healthy stomachs without atrophic gastritis there are no losses of either parietal cells or acid secretion. Patients with duodenal ulcer preserve their high secretion throughout their life; although they have antral
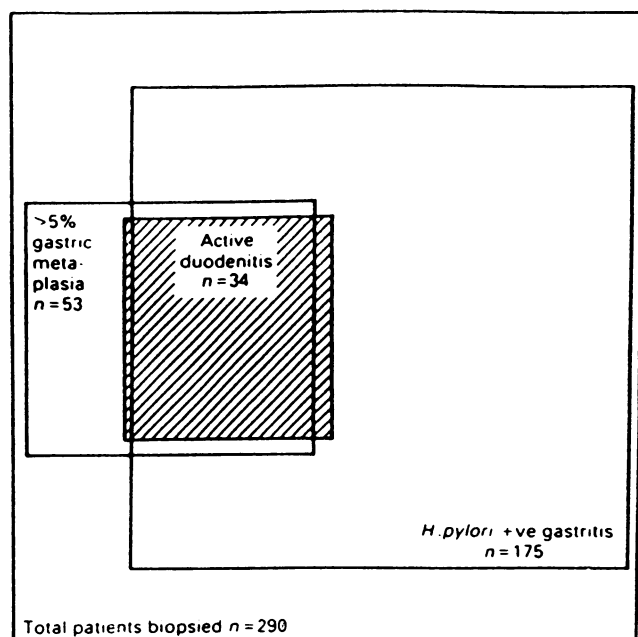
Figure 6. Active duodenitis, gastric metaplasia in the duodenum and Helicobacter-associated gastritis in 290 dyspeptic patients. (From Wyatt *et al.* *(14)* by permission of *Journal of Clinical Pathology.*)

gastritis they do not have fundic atrophic gastritis and do not lose their parietal cells.

In men the relative risk of a duodenal ulcer rose sixteenfold with superficial gastritis in the antrum and eighteenfold if it was atrophic. Long-term population follow-up in Finland showed that of patients with endoscopy negative dyspepsia in 1979, those who had normal histology of both body and antrum never developed duodenal ulcer in the following 10 years, but that 10% developed duodenal ulcer if the body mucosa was normal and the antrum showed superficial gastritis. If superficial gastritis was present both in the body and antrum, the 10-year incidence of duodenal ulcer was 7%, yet if both body and antrum showed atrophic gastritis duodenal ulcers did not develop. Here was confirmation that duodenal ulcer disease always needed a certain gastric output of acid from a certain number of healthy parietal cells; it also confirmed that for duodenal ulcer to develop there must be antral gastritis.

The mechanism of the association between antral gastritis and duodenal ulcer was long obscure. This mystery and some of the endocrine and exocrine abnormalities have been clarified recently by the identification of *Helicobacter pylori*.

Helicobacter pylori

Soon after the original isolation of *H. pylori* in 1983 by Warrent and Marshall it became clear that this bacterium was the prime cause of non-autoimmune gastritis *(15)*. Since then, *H. pylori* infection has been found in gastric antra in most patients with peptic ulcer and in areas of focal gastric metaplasia in the duodenum in almost every patient with duodenal ulcer. Presumably, *H. pylori* infects

these metaplastic islands leading to breakdown of mucosal integrity, duodenitis and then ulceration.

The Leeds Venn diagram (Fig. 5) of the duodenal biopsies in 290 dyspeptic patients emphasises that almost always active duodenitis occurs only in duodenums with gastric metaplasia; secondly, active duodenitis occurs almost without exception only in duodenums with *H. pylori* *(14)*. The two Leeds components (acid-induced duodenal gastric metaplasia + *H. pylori*) provide our current model of active duodenitis and duodenal ulceration *(14)*.

In our series, without exception, bacteria were present only in duodenal mucosa showing focal gastric metaplasia, presumably because *H. pylori* can colonise only gastric mucus. *H. pylori* were twice as common in duodenal mucosa with active (62%) rather than chronic inflammation (27%). Our incidence of *H. pylori* in single biopsies from duodenums of patients with duodenal ulcer (55%) was similar to that in other studies. However, we noted that the frequency of duodenal ulcer in patients with *H. pylori* in their duodenums (46%) was double the frequency of ulcers in the duodenums of patients with *H. pylori* in their antra, suggesting that duodenal *H. pylori* may be more closely correlated with duodenal ulceration than is antral infection with *H. pylori*.

The Sydney group took two biopsies from both the duodenal bulb and the antra of 90 patients with duodenal ulcer and of 47 non-ulcer patients. Of 71 patients with *H. pylori* in their duodenums, 98% had either active (38) or healed (32) duodenal ulcer, giving by stepwise logistic regression a relative risk for duodenal ulcer of 51 and an odds ratio of 172, whereas of 96 with *H. pylori* in their antrum only 89% has an active (43) or healed (44) duodenal ulcer, a relative risk of only 8, odds ratio 56. Superficial gastric metaplasia was almost invariable in duodenums with either active ulcer (91%) or healed ulcer (93%) but was also seen in patients without ulcer (32%) so that the relative risk of duodenal ulcer was only 6 with an odds ratio of 21. However, full-thickness gastric metaplasia of the heterotopic type was seen only in duodenums with active (5/46) or healed (1/44) ulcers. In this study age, sex, cigarette smoking and non-steroidal anti-inflammatory drug intake were not significant risk factors.

H. pylori is perhaps the most common pathogenic bacterium. Gastritis is correspondingly common, but only a small proportion of those infected manifest disease clinically. In some populations early infections are associated with atrophic pangastritis which may be subclinical or may lead to gastric ulcer or carcinoma; the loss of parietal cells in the body mucosa lowers acid output below the threshold for development of duodenal ulcer, possibly because of the absence of acid-induced gastric metaplastic duodenal mucosa. In others, *H. pylori* leads only to superficial gastritis of the body and antrum, and a duodenal ulcer may then develop by various postulated mechanisms, some bacteria-specific and some host-specific.

Classification of *H. pylori* is complex but there appears to be at least one potentially useful characteristic, the

production of a vacuolating cytotoxin. This cytotoxin is associated with the host's recognition of a 128 kDa antigen; all patients with duodenal ulcer, but only 32 of 51 controls, recognised this antigen which is produced by a cagA gene. No ulcers were found in subjects not recognising this antigen. A specific ELISA of this 128 kDa antigen has allowed measurement of serum IgG responses and shown high levels in patients with duodenal ulcer and duodenitis. Another gene, VacA, controls another cytotoxin. If H. pylori infects the duodenum only in those who have high gastric acid output, then this high output may be an underlying characteristic (eg genetic) of that stomach. Alternatively, H. pylori must itself be the cause of increased acid secretion, via endocrine/paracrine changes.

Endocrine

Basal and meal-stimulated serum gastrin were raised in subjects with H. pylori (with and without duodenal ulcer) and returned to normal after eradication of these bacteria. G cell numbers were not changed nor was the expression of gastrin messenger RNA abnormally high in antra with H. pylori. The characteristic failure in patients with duodenal ulcer of antral acidification at pH 2.5 to inhibit antral release of gastrin and gastric acid output was also seen in asymptomatic men with H. pylori but not seen in men without this infection.

Paracrine

D cell activity as measured either by D cell numbers, somatostatin concentration or somatostatin mRNA is correspondingly decreased in association with antral H. pylori infection. Eradication of H. pylori has increased D cells, decreased serum and antral gastrin and increased stored histamine compatible with decreased release of histamine.

Acid

After eradication of H. pylori there have been no consistent changes in intragastric 24 h pH nor nocturnal or peak acid output, but basal acid has decreased. Recently, bombesin or gastrin-releasing peptide (GRP)—stimulated gastrin release have been found to be abnormally high in subjects with H. pylori, with or without duodenal ulcer, and have also normalised after eradication of H. pylori (16). These data are compatible with the speculation that just as the primary pathophysiological effects of H. pylori in the antrum is decreased D cell somatostatin which stimulates in turn gastrin-releasing peptide, G cells, gastrin, histamine and acid, so also might H. pylori in the body decrease somatostatin inhibition of the parietal cell production of acid.

Management of duodenal ulcer disease by eradication of Helicobacter pylori

If the primary cause of duodenal ulcer disease is H. pylori then its eradication should heal and prevent recurrence of the ulcer.

Detection of H. pylori

Early studies used antral biopsies with histology and/or culture and/or an indirect urease test to detect H. pylori. These tests require endoscopy and absence of H. pylori in antral biopsies does not exclude infection in the body or duodenum. Even biopsies of each of these three areas are still only samples of the whole organs.

These are two alternative methods. Serology in research studies proved an effective non-invasive method, but upscaled to commercial tests have failed to show comparable specificity and sensitivity. Positive serology does not indicate current infection with H. pylori. It may take weeks or months for titres to fall after eradication.

The ideal method for detecting H. pylori, especially after treatment, is the carbon-labelled urea breath test, using ^{14}C or ^{13}C (preferably ^{13}C because it is a stable non-radioactive isotope). Conventionally, absence of H. pylori immediately after treatment is 'clearance' or 'suppression', and only a negative test 4 weeks after the end of treatment is considered 'eradication', after which H. pylori is most unlikely to reappear either from deep in the mucosa, or by external reinfection.

Eradication of H. pylori

Monotherapy may suppress H. pylori but organisms reappear within days of stopping treatment, and may become resistant to a single antibiotic. The most widely used regimen is triple with bismuth, metronidazole (or tinidazole) and amoxycillin (erythromycin if patient penicillin-sensitive) or tetracycline. Bismuth may limit the development of metronidazole-resistant organisms and make them more readily eradicated by antibiotics. The standard courses were 4 weeks (17), but these are now being reduced to 1 (18) or 2 weeks, with increased compliance and decreased side-effects and cost. These regimens eradicate about 85% of metronidazole-sensitive organisms but are not recommended in patients with known metronidazole-resistant bacteria.

The newer combination is the use of an antibiotic, especially amoxycillin (19) or clarithromycin (20), whose minimum inhibitory concentration (MIC) for killing H. pylori is markedly lowered in vitro or in vivo at the high pH achieved by the addition of omeprazole or lansoprazole. Such twin therapies have achieved eradication rates over 80%. New triple therapies adding a second antibiotic to the protein pump inhibitor have achieved even higher eradication rates. Patients whose H. pylori are not eradicated by one regimen can usually be treated successfully by another.

Healing duodenal and gastric ulcers

It has long been known that a 4-week course of bismuth will heal about 80% of peptic ulcers but with frequent ulcer recurrence subsequently, although probably at a slower rate than with ulcers healed by acid inhibitors. Today's interpretation would be that bismuth suppresses H. pylori allowing ulcer healing, but as soon as the bismuth is stopped H. pylori reappears and then the ulcer

recurs. Duodenal ulcers therefore can show healing rates of 90% by any of the effective anti-*H. pylori* regimens described above. Gastric ulcers heal similarly *(20)*. Duodenal ulcers which have failed to heal with conventional acid inhibitors will heal after *H. pylori* eradication. The healing of duodenal ulcers after a course of either an H₂ blocker or proton pump inhibitor can be enhanced by adding anti-*H. pylori* drugs.

Prevention of ulcer recurrence

Eradication of *H. pylori* not only heals duodenal ulcers, but it also prevents recurrence in about 95% of patients over the period of follow-up of up to 7 years so far. This freedom from recurrence is presumably due to removal of *H. pylori* from the duodenum even though gastric metaplasia may remain because of the persistence of maximal acid output in the duodenal ulcer range.

Patients whose duodenal ulcers recur after incomplete vagotomy no longer need repeated attempts to lower gastric acid by lifelong maintenance acid inhibitors or elective revagotomy and/or antrectomy *(1)*. They can now usually be managed by the same approach as for unoperated duodenal ulcers, namely culture and sensitivity of their *H. pylori* and eradication with an appropriate anti-*H. pylori* regimen.

In about 5% of duodenal (and 25% of gastric) ulcers no *H. pylori* can be detected. In some of these patients the ulcers are due to non-steroidal anti-inflammatory drugs (which should be stopped if possible) or to inflammation (such as Crohn's disease). About 1 in 1000 are due to Zollinger-Ellison syndrome. Naturally, these patients will not respond to an anti-*H. pylori* regimen and they need specific treatment for their underlying disease or continuous acid reduction by drugs or elective operation.

Conclusions

Duodenal ulcers occur when the duodenum is exposed to both above threshold gastric secretion and infection by *H. pylori*. Lifelong acid-lowering drugs or elective acid inhibitory operations of vagotomy, antrectomy or partial gastrectomy are indeed effective treatments, but these have been superseded by simple, weeks-long, drug regimens which will eradicate *H. pylori*, will heal the ulcer, will prevent recurrence and thus cure the disease. Patients with *H. pylori* gastric ulcer can be treated similarly.

We can now suggest answers to questions which have puzzled ulcerologists since the time of John Hunter. Why does the stomach digest and ulcerate itself? Oi's data suggest that the stomach does not digest itself; the acid-pepsin from one part of the stomach (the body) digests the non-parietal pyloric mucosa existing in the other part (the antrum) or which has extended by gastritis and metaplasia, into the body. Thus, all peptic ulcers are marginal.

Is peptic ulcer one disease, or are gastric and duodenal ulcer separate diseases? I propose that peptic ulcers are essentially all gastric ulcers, occurring in gastric mucosa in the stomach or in gastric metaplastic mucosa in the

duodenum. The 'stomach' does not ulcerate spontaneously but may when attacked by secretagogues (excess calcium, parathormone, gastrin, histamine), by bacteria (*H. pylori*) or by humans (with NSAID).

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