The presence of gastric spirochaetal organisms was first documented over a century ago. Though repeatedly reported in the medical literature, it was felt that these spiral bacteria were merely contaminants and the reports were generally ignored by the medical community. On 22 October 1982, at a meeting of the Royal Australian College of Physicians, successful culture of these 'Campylobacter-like organisms' from gastric biopsy specimens was reported for the first time. Moreover, it was shown that their presence was associated with gastritis and, possibly, with peptic ulceration. The subsequent discovery of the pivotal role of Helicobacter pylori in a wide range of conditions has revolutionised our understanding of gastroduodenal diseases. Improvements in diagnostic and therapeutic options, combined with the gradual acceptance of the aetiological role of an infective agent in peptic disease, have led to a remarkable change in the management of gastroduodenal conditions in the past decade.

Recent years have seen great advances in many fields of medicine, but in few have they been more remarkable than in upper gastrointestinal diseases. The discovery of Helicobacter pylori and the acceptance of its role in gastric pathophysiology represents a fundamental change in our understanding of gastroduodenal disease. It is now acknowledged world-wide that type B gastritis, duodenal ulceration, gastric ulceration, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma are, in part, infectious diseases. Antibiotic-based regimens are now the recommended treatment for peptic ulceration. In the foreseeable future, it may be possible to offer prophylaxis against these conditions by means of an oral vaccine.

Pre H. pylori era

While the complications of peptic ulcer disease are mentioned in records of ancient and medieval medicine, the first description of gastric ulceration was reported in 1586 by an Italian physician, followed by an autopsy report of duodenal ulceration by Johannes von Muralt in Switzerland in 1688. In 1761, erythema and erosions of the stomach...
and duodenum were described in patients with heartburn and upper abdominal pain.

During the eighteenth and nineteenth centuries, understanding of the function of the upper gastrointestinal tract gradually increased with the description of the digestive properties of gastric secretions and hydrochloric acid in the stomach. In 1825, William Beaumont, an American army physician, reported his famous series of in vivo gastric function experiments in a patient who developed a gastro-cutaneous fistula following a gunshot wound.

The symptomatology of peptic ulceration was first described in detail in 1857. At this time, gastric ulceration was a common autopsy finding, especially in females, while duodenal ulceration was rarely reported.

With the ability to clinically diagnose upper gastrointestinal conditions, gastric surgery developed during the second half of the nineteenth century. Theodor Billroth described gastroduodenostomy and gastrojejunostomy in 1881. In the same year, the first potentially usable endoscope was reported. In 1897, using bismuth subnitrate as a contrast material, the ability to diagnose peptic ulceration radiographically was reported.

Duodenal ulceration, rarely reported in the nineteenth century, began to increase dramatically in prevalence in young and middle-age males and, by 1900, was more common than gastric ulceration.

The treatment of peptic ulceration changed after the pronouncement of the dictum ‘no acid, no ulcer’ in 1910 by the Croatian, Karl Schwarz. Antacids were recommended in the treatment of peptic ulcer in 1915. In the modern era, the first substance to show promise in peptic ulcer disease was stilboestrol in 1960, followed by carbenoxolone in 1962. In 1966, the gastric histamine receptor was described followed shortly by the first H₂ receptor antagonist. The advent of this class of drugs dramatically improved the management of peptic ulceration, allowing symptom

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**Table** Key dates in history of *H. pylori*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>1893</td>
<td>Gastric spiral bacteria are reported for the first time in the stomachs of dogs</td>
</tr>
<tr>
<td>1906</td>
<td>Spirochaetes are demonstrated in the human stomach</td>
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<tr>
<td>1924</td>
<td>Urease activity in the stomach is reported</td>
</tr>
<tr>
<td>1950</td>
<td>Urease in patients with gastric ulceration neutralises gastric acid via the production of ammonia</td>
</tr>
<tr>
<td>1975</td>
<td>Gastric spirochaetes and gastritis present in 80% of gastric ulcers</td>
</tr>
<tr>
<td>1983</td>
<td>Campylobacter-like organisms associated with gastritis and possibly peptic ulceration - beginning of modern era</td>
</tr>
<tr>
<td>1984</td>
<td>Temporal relationship between acquisition of <em>H. pylori</em> infection and development of gastritis</td>
</tr>
<tr>
<td>1987</td>
<td>Eradication of <em>H. pylori</em> leads to long-term cure of duodenal ulceration</td>
</tr>
<tr>
<td>1989</td>
<td>The genus <em>Helicobacter</em> is suggested</td>
</tr>
<tr>
<td>1994</td>
<td><em>H. pylori</em> classified as a grade I (definite) carcinogen</td>
</tr>
<tr>
<td>1994</td>
<td>The infection should be eradicated in patients with peptic ulcers</td>
</tr>
<tr>
<td>1997</td>
<td>European consensus report on the management of <em>H. pylori</em> infection</td>
</tr>
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</table>
control and a reduction in the rate of complications. Shortly after, the presence of a potassium-stimulated adenosine triphosphatase (H⁺/K⁺-ATPase) pump was demonstrated. Six years later, the first commercially available proton pump inhibitor was reported. While these drugs were effective inhibitors of acid secretion with the ability to heal ulcers, relapse of ulceration after cessation of treatment was frequent resulting in the need for long-term maintenance treatment.

**Gastric spiral bacteria**

The presence of gastric spiral bacteria was first reported in 1893. Bizzozero, an Italian pathologist, described spiral bacteria in the canine stomach. In 1896, Salomon reported similar findings in the stomachs of cats and mice.

Spiral bacteria were demonstrated, for the first time, in the human stomach in 1906. This initial report concerned patients with gastric carcinoma. Nine years later, spiral micro-organisms in the stomachs of patients with gastric and duodenal ulceration were reported. It was felt, however, that these organisms were contaminants from the oral cavity.

At this time, the presence of urease activity in the human stomach was documented. It was thought that this urease activity originated in gastric mucosal cells and was not associated with the presence of bacteria.

In 1938, spirochaetes were found in 43% of 242 autopsy stomachs using a haematoxylin and eosin stain. The following year, spirochaetes were reported in 37% of 35 gastric resection specimens from patients with gastric ulcer or carcinoma. In 1954, however, a study of 1000 gastric biopsy specimens failed to confirm these findings and interest in gastric bacteria lapsed.

In 1950, Fitzgerald and Murphy studied urease in the resected stomachs of patients with gastric ulceration. They suggested that urease activity protected the gastric mucosa by mediating a reaction between urea and hydrogen ions, thus neutralising gastric acid via the production of ammonia. In addition, they administered urea to ulcer patients and demonstrated that this resulted in a neutralising of gastric acid. Nine years later, it was demonstrated that gastric urease activity diminished after administration of tetracycline. The bacterial source of gastric urease was confirmed in 1968, when the absence of urease activity was demonstrated in the stomachs of germ-free animals.

In 1975, bacteria were reported in association with gastritis in 80% of gastric resection specimens from patients with gastric ulceration. Moreover, persistence of gastritis and the bacteria was demonstrated.
after carbenoxolone-mediated ulcer healing. Interest in the role of gastric bacteria in the pathogenesis of ‘peptic’ conditions was rekindled in 1979 when spiral bacteria were described on the luminal surface of epithelial cells of gastric ulcer patients. Three years later, the beneficial effect of bismuth on duodenal mucosa in patients with duodenal ulceration was demonstrated.

1983–1987

The modern era began in 1981 when a second-year medical internist, Barry Marshall, began a clinical research project with Robin Warren, a histopathologist, in the Royal Perth Hospital, Western Australia (Fig. 2). Warren had stained gastric biopsy specimens with the Warthin-Starry stain and noted the presence of mucosal bacteria. Marshall treated an elderly Russian patient with gastritis and gastric bacteria with tetracycline and noted clearance of the infection and improvement of the gastritis. Subsequent attempts to culture these bacilli were unsuccessful until April 1982. During the Easter weekend, the plates were unintentionally incubated for 5 days and colonies were visible. The
association of these bacteria with gastritis was first presented at the Royal Australian College of Physicians on 22 October 1982 and published in letter form in 1983. These ‘Campylobacter-like organisms’ were called Campylobacter pyloridis, since they were micro-aerobic, curved, Gram-negative bacteria and resembled other campylobacters both morphologically and in guanine/cytosine DNA content. The presence of multiple flagellae on these bacteria, differentiating them from other Campylobacters, was also noted. For grammatical reasons, the name was changed to Campylobacter pylori in 1987. Subsequently, it was shown that C. pylori did not belong to the genus Campylobacter and a new genus name was suggested in 1989. ‘Helicobacter’ reflects the two morphological appearances of the organism, helical in vivo but often rod-like in vitro (bakter, a staff).

The association with peptic ulceration, and possibly with gastric adenocarcinoma, was initially suggested by Marshall et al. Another group also described these bacteria in 1984 and the association between C. pyloridis and gastric urease activity was demonstrated shortly afterwards. The acute effects of the infection were illustrated after deliberate ingestion of a suspension of the organisms. The Australian group, having noted the historical usage of bismuth in peptic diseases, also demonstrated the inhibitory effect of bismuth salts on the organism. Reliable diagnostic techniques which facilitated epidemiological and interventional studies, such as serology, the rapid urease test, the $^{13}$C- and $^{14}$C-urea breath tests soon became available.

The initial reports of an association between an infective organism and gastroduodenal disease were greeted with some scepticism by the gastroenterology community. This was perhaps understandable given their recently acquired ability to treat such conditions effectively with acid reducing agents. A group of specialists with an interest in the
infection, the European H. pylori Study Group, was formed in Copenhagen in 1987 and this was followed by an exponential increase into the study of the role of the bacteria in gastroduodenal diseases. The group were also responsible for increasing awareness of the importance of the infection in the gastroenterology community.

**Clinical studies — clarification of role of H. pylori**

The first long-term clinical trial of treatment aimed at eradicating ‘C. pylori’ in patients with duodenal ulceration, based in the Meath/Adelaide Hospitals, Dublin was reported in 1987 (Fig. 3)\(^49\). This study revealed that eradication of the bacterium was followed by a significant reduction in ulcer relapse rates and suggested that eradication permanently cured duodenal ulcer disease. This was followed by multiple studies which confirmed this finding\(^50\)–\(^54\). A similar decrease in gastric ulcer relapse rates was also subsequently reported\(^55\)–\(^56\). The relationship between the organism and gastric adenocarcinoma and MALT (gastric mucosa-associated lymphoid tissue) lymphoma was reported in 1991\(^57\)–\(^60\). Subsequent studies assessed the role of the organism in gastro-oesophageal reflux disease\(^61\), patients receiving long-term acid suppressing medication\(^62\), paediatric populations\(^63\), and non-ulcer dyspepsia\(^64\)–\(^65\).

H. pylori was the first member of the new genus and other Helicobacters including H. mustelae (ferrets), H. muridarum (rats and mice), H. felis (cats and dogs), H. nemestrinae (pigtailed macaque), H. acinonyx
Helicobacter biology—discovery

(cheetahs), *H. rappini* (lambs) as well as *H. cinaedi* and *H. fennelliae* (in humans with gastroenteritis) have subsequently been described.

In 1994, *H. pylori* was recognised as a grade I (definite) carcinogen and the National Institutes of Health Consensus Development Conference Statement recommended that all patients who are found to have gastric or duodenal ulceration and concurrent *H. pylori* infection should receive treatment aimed at eradicating the bacterium. In 1997, it was ‘strongly recommended’ by a European consensus panel that patients with *H. pylori* infection and peptic ulcer, low grade mucosa-associated lymphoid tissue lymphoma, severe macroscopic or microscopic gastritis or recently resected early gastric cancer should receive a proton pump inhibitor-based triple therapy to eradicate the infection. In addition, it was felt that treatment aimed at eradication was ‘advisable’ in *H. pylori* positive individuals with non-ulcer dyspepsia, a family history of gastric cancer, gastroesophageal reflux disease necessitating long-term proton pump inhibitor therapy, planned or ongoing non-steroidal anti-inflammatory drug indigestion, and following gastric surgery for peptic ulcer disease or gastric cancer.

**Conclusion**

The discovery of *H. pylori* and the gradual realisation of its importance in upper gastrointestinal diseases represents one of the most important developments in medicine in the past century. Physicians are now able to cure hitherto chronic diseases with short, safe antibiotic-based treatments. It has also given rise to the potential to prevent a variety of gastroduodenal conditions. Whether this will be done by community-based screening programmes or vaccination should become clear in the next decade.

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