The 2005 Nobel Prize in Physiology or Medicine: *Helicobacter pylori* and its role in gastritis and peptic ulcer disease

Gastritis (inflammation of the stomach) and peptic ulcer disease (PUD; ulceration of the stomach or duodenum) have been a major human health problem the world over, particularly in most countries of the developed world. In USA and Australia, one in ten people might be expected to suffer from PUD during one’s lifetime; and in the developing world, the incidence of the disease seems to be still higher, although similar data are not available.

In the past, it was believed that gastritis and peptic ulcers were caused by acid, stress, spicy food, etc. and should be treated by drugs blocking acid production. However, these traditional antacid ulcer medications provided only temporary relief. This situation dramatically changed, when it was discovered that gastritis and PUD are actually caused by a bacterium (later named *Helicobacter pylori*), although some ulcers are also caused by long-term use of non-steroidal anti-inflammatory agents (NSAIDs) like aspirin and ibuprofen.

When caused due to bacteria, the patients suffering with this disease could be permanently cured by eradication of *H. pylori*, using antibacterial therapy. There is evidence that *H. pylori* infection also causes gastric cancer, the adenocarcinoma, which can be prevented by *H. pylori* eradication, although convincing evidence based on clinical trials is lacking.

It is also known now that *H. pylori* is a ubiquitous gastrointestinal organism, which infects over three billion people the world over, with the infection generally becoming less common with rise in the standard of living (Figure 1). A surprising finding, however, was that not more than 20% of people (regardless of age) who tested positive for *H. pylori* had ulcers.

The above pioneering work involving discovery of *H. pylori* and its role in the development of gastritis and PUD has been recognized by the award of 2005 Nobel Prize for Physiology or Medicine to two Australian scientists, Barry J. Marshall and Robin Warren, who retired in 1999 from his position as a senior pathologist at the Royal Perth Hospital, also located in Perth, Western Australia.

**Life of Robin Warren**

Robin Warren was born on 11 June 1937 in Adelaide, South Australia. He graduated to earn his MBBS degree from the University of Adelaide in 1961. Later, after receiving training at several places including Queen Elizabeth Hospital, Woodville, SA (1961–62), Institute of Medical and Veterinary Science, Adelaide (1962–64), and the Royal Melbourne Hospital (1964–66), he was admitted to the Distinguished Fellowship of Royal College of Pathologists of Australasia in 1967. Thereafter, for more than 30 years, he worked as a senior pathologist at the Royal Perth Hospital (1968–99).

**Life of Barry Marshall**

Barry Marshall was born on 30 September 1951 in Kalgoorlie, Western Australia, as the eldest of four children in a family with no privileged background (his father was a boiler-maker, and his mother was a nurse). Marshall studied medicine at the University of Western Australia during 1968–74 to earn the MBBS degree. Later he worked in Royal Perth Hospital, during 1977–84 as Registrar, Medicine, and during 1985–86 as NHMRC Research Fellow, Gastroenterology. In 1986, Marshall moved out to USA and worked at the University of Virginia, first as a Research Fellow and Professor of Medicine (1986–94), and later as Professor of Research in Internal Medicine (1996). In 1996, Marshall returned from USA to Perth as an internationally acclaimed medical scientist and then worked at his alma mater, the University of Western Australia in various capacities.

**Awards and recognitions won by Warren and Marshall**

Table 1. Summary of work by Warren and Marshall on H. pylori in chronological order

Noticed that inflammation of the stomach (gastritis) was associated with the presence of a bacterium (Warren).

Studied 100 patients and discovered that this bacterium was present in every patient who suffered from duodenal ulcer (Warren and Marshall).

Grew the first culture of the bacterium, which was later named H. pylori (Marshall and microbiologists from Royal Perth Hospital).

Swallowed a culture of this bacterium, and suffered acute symptoms in order to prove the hypothesis that H. pylori was the cause of gastritis (Marshall and a volunteer).

Promoted this hypothesis, despite significant scepticism from gastroenterology specialists (Marshall).

Through persistence and publication of research papers, stimulated much research and treatment trials which eventually proved that H. pylori did indeed cause gastritis and gastric ulcers (Warren and Marshall).

Benjamin Franklin Award for Life Sciences (1999), Japanese Keio Medical Science Prize (2002), and the Australian Centenary Medal (2003).

Initial discovery of Helicobacter pylori and fruitful partnership between Warren and Marshall

In 1979, for the first time, Warren observed the presence of small curved bacteria on a biopsy of the gastric mucosa. Later in 1981, Warren met Marshall, and a fruitful partnership followed, which demonstrated the clinical significance of the bacteria (see later for details).

Initial scepticism about the discovery

In the early 1980s, Warren and Marshall were the subject of criticism and unkind jokes, since everyone was taught and believed that bacteria could not survive in the stomach’s acid environment. But Barry was aggressive in selling his message, and the stomach’s acid environment. But Barry was aggressive in selling his message, and it took them at least a decade longer than expected to convince the scientific world that peptic ulcer was caused by H. pylori.

Koch’s postulates fulfilled to establish link between gastritis/ PUD and H. pylori

Warren and Marshall’s work almost fulfilled all the four postulates of Koch (but see below). A summary of the work done by Warren and Marshall to fulfil Koch’s postulates is presented in Table 1.

Association of H. pylori with disease

Warren and Marshall commenced their research by studying a group of 100 patients who had undergone endoscopy for gastric conditions. They reconfirmed the link between gastritis and presence of the bacterium, thus satisfying the Koch’s first postulate.

Culturing of H. pylori as a new species

For culturing the bug, Warren and Marshall initially used without success, the selective growth conditions appropriate for Campylobacter. Later, in 1982, when the cultures were inadvertently left in the incubator over the Easter holidays (due to lack of laboratory staff), chance prolongation of the incubation period from the usual 2 to 6 days resulted in successful growth and isolation of the bacterium. This led to the discovery that the growth of H. pylori was much slower than other bacteria and allowed culturing of the bug, thus satisfying Koch’s second postulate.

The bug causing gastritis and PUD was initially named Campylobacter pyloridis due to its morphological similarity with members of the genus Campylobacter, and due to its isolation from the pyloric region of the stomach. The name of the bacterium was grammatically corrected in 1987 to C. pylori and, in 1989, it was renamed Helicobacter pylori (Figure 2), which became the type species of the new genus Helicobacter, which is now known to have several species that infect animals other than humans; these species can be distinguished with the help of 16S rRNA sequence.

Marshall swallowed a culture of H. pylori to prove his hypothesis

In order to satisfy the third and fourth postulates of Koch, Marshall himself and a volunteer swallowed a solution containing the bug to prove that it caused the disease. About a week later, Marshall started vomiting and showed other painful symptoms of gastritis. The biopsies revealed that he had developed both gastritis and an infection with H. pylori (Figure 3), but failed to develop an ulcer, and the disease resolved without treatment. Consequently, although this constituted highly suggestive evidence that the organism caused gastritis, it was far from conclusive, so that as late as 1995, Marshall himself conceded that all Koch’s postulates had not been fulfilled for confirmation of a causal relationship between H. pylori and PUD. A more important confirmation, however, was the eradication of H. pylori through the use of antibacterial drugs.

Association of H. pylori with gastric cancer and cardiovascular diseases?

Even before the discovery of H. pylori, an association between cancer of the stomach and chronic gastritis was observed, which suggested a possible link between Helicobacter infection and cancer. Similarly, several studies have also suggested an association between H. pylori infection and an increased risk of cardiovascular disease, although no causal relationship could be established.

How could the bug grow in acidic environment of the stomach?

The question remained as to how H. pylori could survive in the acidic environment...
Diagnosis of H. pylori

Once symptoms of an ulcer (e.g. abdominal discomfort, weight loss, poor appetite, nausea, etc.) are observed, the doctor may conduct an upper gastrointestinal (GI) series (involving X-ray of the esophagus, stomach and duodenum) or an endoscopy/biopsy. Once GI and/or endoscopy confirms the presence of ulcer, the patient is tested for H. pylori, since ulcers may also be caused by NSAIDs.

Diagnosis of H. pylori-related ulcers

Diagnosis of ulcers

Once symptoms of an ulcer (e.g. abdominal discomfort, weight loss, poor appetite, nausea, etc.) are observed, the doctor may conduct an upper gastrointestinal (GI) series (involving X-ray of the esophagus, stomach and duodenum) or an endoscopy/biopsy. Once GI and/or endoscopy confirms the presence of ulcer, the patient is tested for H. pylori, since ulcers may also be caused by NSAIDs.

Diagnosis of H. pylori

The bug H. pylori may be diagnosed through blood, breath, stool and tissue tests. The urease test allows patients to have a diagnosis within 20 minutes of having a biopsy, and start curative therapy immediately. In non-invasive breath test, the patient is made to swallow a small amount of urea labelled with a carbon isotope ($^{13}$C or $^{14}$C), which is broken down by H. pylori to release carbon dioxide in the breath; this breath test became a popular and accurate means of diagnosing H. pylori in patients.

Treatment for H. pylori eradication?

It was shown that 80% of patients were permanently cured of their ulcer, if H. pylori was eradicated. This resulted in a complete reassessment of ulcer treatment, and became an essential part of the management of ulcer disease. Therapy for H. pylori infection consists of 10 days to 2 weeks of one or two effective antibiotics, plus either a H$_2$ blocker or a proton pump inhibitor; a stomach lining protector may also be used. Currently, eight H. pylori treatment regimens are approved, and the eradication rates range from 61 to 94%. Overall, triple therapy regimens have shown better eradication rates than dual or quadruple therapy. Longer time of treatment (14 versus 10 days) results in better eradication rates.

Dual, triple and quadruple therapy

Two weeks of dual therapy involving two drugs (an antibiotic and an acid suppressor) is generally recommended for eradication of H. pylori. However, it is not as effective as triple therapy, which involves taking two antibiotics to kill the bacteria and either an acid suppressor or stomach lining shield. Two weeks of quadruple therapy (also called bismuth-triple therapy), which uses two antibiotics, an acid suppressor and a stomach lining shield, was also found promising in several studies. Despite some problems and side effects associated with triple therapy, recent studies show that it is ideal.

Whole genome sequence and genetic variability of H. pylori

In 1997, the genome (17 megabase) of H. pylori was fully sequenced and found to have 1600 genes, of which only 750 are essential. At least 23% of all genes are unique to H. pylori, which should be specific for survival of the pathogen in the stomach. A high degree of genetic variability also exists among different strains of H. pylori, which explains why only one in six infected humans suffers from ulcers. About 60% of H. pylori strains in USA contained a particular sequence of genes, i.e. a ‘pathogenicity island’ (encoding Cag-PAI), and people infected with a strain containing this pathogenicity island were significantly more likely to develop ulcers or adenocarcinoma than those infec-

Table 2. Drugs used to treat H. pylori peptic ulcers

<table>
<thead>
<tr>
<th>Drugs used to treat H. pylori peptic ulcers</th>
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<tbody>
<tr>
<td>Metronidazole, tetracycline, clarithromycin, amoxicillin</td>
</tr>
<tr>
<td>Cimetidine, ranitidine, famotidine, nizatidine</td>
</tr>
<tr>
<td>Omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole</td>
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<tr>
<td>Bismuth subsalicylate</td>
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Table 3. FDA-approved treatment options

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Lansoprazole 30 mg BID + amoxicillin 1 g BID + clarithromycin 500 mg TID</td>
<td>10 days</td>
</tr>
<tr>
<td>Lansoprazole 30 mg TID + amoxicillin 1 g TID</td>
<td>2 wks</td>
</tr>
<tr>
<td>Lansoprazole 30 mg QD + clarithromycin 500 mg TID</td>
<td>2 wks</td>
</tr>
<tr>
<td>Lansoprazole 30 mg BID</td>
<td>10 days</td>
</tr>
<tr>
<td>Lansoprazole 30 mg BID + clarithromycin 500 mg BID</td>
<td>10 days</td>
</tr>
<tr>
<td>Lansoprazole 30 mg BID + clarithromycin 500 mg TID</td>
<td>2 wks</td>
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<tr>
<td>Lansoprazole 30 mg BID + clarithromycin 500 mg BID</td>
<td>10 days</td>
</tr>
</tbody>
</table>

*Although not FDA-approved, amoxicillin has been substituted for tetracycline in patients for whom tetracycline is not recommended. **This dual therapy regimen has restrictive labelling. It is recommended for patients who are either allergic or intolerant to clarithromycin or for infections with known or suspected resistance to clarithromycin.

The H. pylori Foundation: A source for additional information

The ‘Helicobacter Foundation’ was founded by Barry Marshall in early 1994. He chartered the Foundation in order to provide people with information on H. pylori and its effects. The Helico Site (www.helicobacter.com) is maintained by Marshall and ConcreteBob Software. An upgrade is currently under way. Readers may get additional information on this site.


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