# A Bug That Can Dig a Hole in the Stomach!

## The Discovery that Revolutionized the Treatment of Peptic Ulcer

## Nobel Prize in Physiology or Medicine 2005

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Key words
Peptic ulcer, *Helicobacter pylori*.

**Barry J Marshall and J Robin Warren from Australia received the Nobel Prize for their discovery of the role of the bacterium *Helicobacter pylori* in gastritis and peptic ulcer. Their findings challenged the prevailing dogma about peptic ulcer. Thanks to their pioneering work, peptic ulcer is no longer a chronic, frequently disabling condition, but a disease that can be cured by a short regimen of antibiotics and acid secretion inhibitors.**

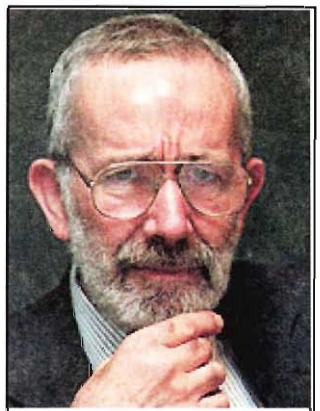
### What is an Ulcer?

Gastric secretion is highly acidic, which is essential for the digestive process. Epithelial cells that line the stomach and duodenum (proximal part of intestine) are protected from this acidic secretion. An imbalance between the acid secreting mechanism and the protective mechanism causes inflammation of the gastric mucosal epithelium, a condition which is known as 'gastritis' that can progress to form 'peptic ulcer'. Ulcer is an erosion of the epithelial layer. The term peptic ulcer includes both gastric and duodenal ulcer.

### Peptic Ulcer: Paradigm Revised

Before their pioneering discovery, the etiology of peptic ulcer was obscure. Stress, alcohol, tobacco and spicy foods were considered to be causative factors. Treatment mainly involved antacids, H2 receptor blockers like ranitidine and proton pump inhibitors like omeprazole. But the relapse rate after such treatment was very high. Surgical intervention for complications like bleeding peptic ulcers was quite common. After the discovery of

the role of *H. pylori* in peptic ulcer, antibiotics like clarithromycin that act against these bacteria were included in the treatment regimen. This revolutionized the treatment of peptic ulcer. The frequency of relapse dramatically came down and surgical interventions became rare. This discovery of Marshall and Warren has transformed our understanding of the microbiology and pathology of the human stomach. "No acid, no ulcer", a calcified dictum which had prevailed before, disappeared.



Robin Warren

Barry J Marshall

***Recipients of the 2005 Nobel Prize.***

## Discovery of an Unexpected Bug

On the 12th of June 1979 (his 40th birthday), Robin Warren, a pathologist, made an important observation that curved bacteria are present in gastric biopsies. After examination of many gastric biopsy specimens he noticed that the curved bacteria were always associated with specimens that showed signs of inflammation and that their number correlated with the degree of inflammation. Barry Marshall joined Robin Warren in 1981. Together, they studied stomach biopsy samples from several peptic ulcer patients and found these bacteria in more than 85% of cases. They were unable to find such bacteria in healthy specimens. Although there were earlier reports of the presence of such bacteria in the stomach, no one had previously associated them with any pathological condition.

Interestingly, Marshall found an article about gastric ulcer healing property of bismuth. They went ahead to test the antibacterial activity of bismuth against these newly identified bacteria trying to link the presence of these bugs to ulcers and gastritis. For this, bacteria had to be cultured. They tried different selective growth media but without any success for more than a year. Every time they incubated only for 48 hours. But one Easter weekend, Marshall left the plates for six days. This time they could see growth. They could see many corkscrew shaped bacteria under the microscope. They also observed that bismuth can kill these bacteria. But just isolation of bacteria from the specimen was not sufficient to convince the scientific community about its role in peptic ulcer. Reputed journals rejected their

findings. Their talks were greeted with skepticism in conferences and the medical fraternity ridiculed them. But they did not give up. Marshall started treating his patients with combination of antibiotics. Every time, Marshall saw his patients being cured by his treatment. But the difficult job was to convince his colleagues in the rest of the world. His attempts to induce gastric ulcer in laboratory animals in order to prove Koch's third postulate failed (Koch's postulates state that a microrganism can be associated with a disease only if it can be isolated from an animal showing the disease symptoms and can cause the same disease when reintroduced into a healthy animal).

One evening in June1984, Marshall decided to use himself as a guinea pig; he drank the foul smelling culture of *H. pylori*. After 72 hours, he got all the clinical symptoms of acute gastritis, the precursor of ulcer. He spent days and nights vomiting and with abdominal pain. Biopsy taken from his stomach by endoscopy showed the features of inflammation and also bacteria were re-isolated from the specimen, satisfying Koch's third and fourth postulates. This confirmed the connection between *H. pylori* and gastritis. But connection between *H. pylori* and peptic ulcer was not proved as Marshall did not develop ulcers in his stomach. The connection between *H. pylori* and ulcers was eventually established from epidemiological studies which showed an increased incidence of ulcers in persons infected with the bacterium. Eventually in 1997, the Centre for Disease Control declared that *H. pylori* is the causative agent of peptic ulcer and the medical fraternity all over the world started using antibiotics for its treatment.

## About *H. pylori*

***Epidemiology:*** *H. pylori* infections occur worldwide, but the prevalence varies with socio-economic status. *H. pylori* is present in nearly half the world's population; in parts of the developing world, as many as 90 percent of the population carries the bug. The infection is acquired by oral ingestion of the bacterium in early childhood.

## Suggested Reading


[1] http://nobelprize.org/medicine/laureates/2005/index.html

[2] B J Marshall and J R Warren, Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration, *Lancet*, Jun 16, Vol.1, (8390), pp.1311-5, 1984.

[3] B J Marshall and S R Langton, Urea hydrolysis in patients with *Campylobacter pyloridis* infection, *Lancet*, Apr 26, Vol.1(8487), pp.965-6, 1986.

[4] B J Marshall *et al*, Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*, *Lancet*, Dec 24-31, Vol. 2(8626-8627), pp.1437-42, 1988.

[5] B J Marshall, *Helicobacter pylori*: past, present and future, *Keio J Med*, Vol.52, No.2, pp.80-85, 2003.

***Survival Strategies:*** The gastric mucosa is well protected against bacterial infections. After being ingested, the bacteria have to evade the bactericidal activity of the gastric luminal contents and enter the mucous layer. *H. pylori* has strategies to adapt and survive in this niche. Its capacity to produce urease which neutralizes the acidic pH of gastric mucosa helps it to dwell in that environment (*Figure* 1). Motility is essential for colonization and *H. pylori* flagella have adapted to the gastric niche. *H. pylori* can bind tightly to epithelial cells by multiple bacterial-surface components like BabA. Most strains of *H. pylori* possess the *cag* pathogenicity island (*cag*-PAI), a 37-kilobase DNA fragment containing 29 genes. Several of these encode components of a predicted type IV secretion apparatus that translocates effector proteins into host cells.

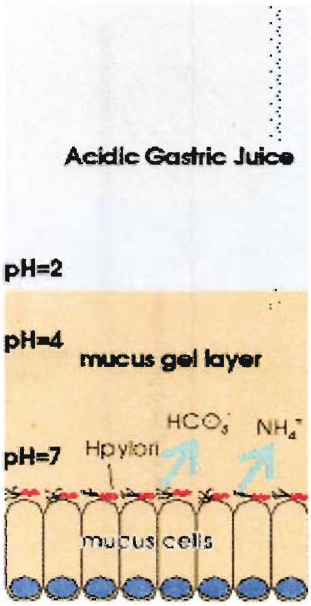



***Figure 1. Evasion of acidic pH of stomach by H. pylori*** *(Adapted from Helicobacter foundationwebsite:www.helico.com)*

***Clinical Outcome:*** *H. pylori* causes continuous inflammation in the gastric epithelium. But clinical outcome is influenced by both host and microbial factors. Inflammation of the epithelium manifests clinically as gastritis. Depending on the site of inflammation, the patient may get either gastric or duodenal ulcer (*Figure* 2). There is very strong evidence that *H. pylori* increases the risk of gastric cancer and gastric lymphoma. *H. pylori* has been classified as a type I (definite) carcinogen since 1994, mainly on the basis of large sero-epidemiologic case–control studies.

***Diagnostic tests and Treatment:*** *H. pylori* infection can be diagnosed by non-invasive tests like urea breath test and serological tests or by endoscopic biopsy. Combination treatment of antimicrobial drugs (e.g.: clarithromycin and bismuth) and proton pump inhibitors (e.g.: omeprazole) or histamine blockers (ranitidine) for 7 to 14 days is extensively used.

## Double Edged Sword?

There is a controversy on eradication of *H. pylori* from the stomach. A recent report suggests that eradication of these bacteria may be the cause of increased incidence of adenocarcinoma

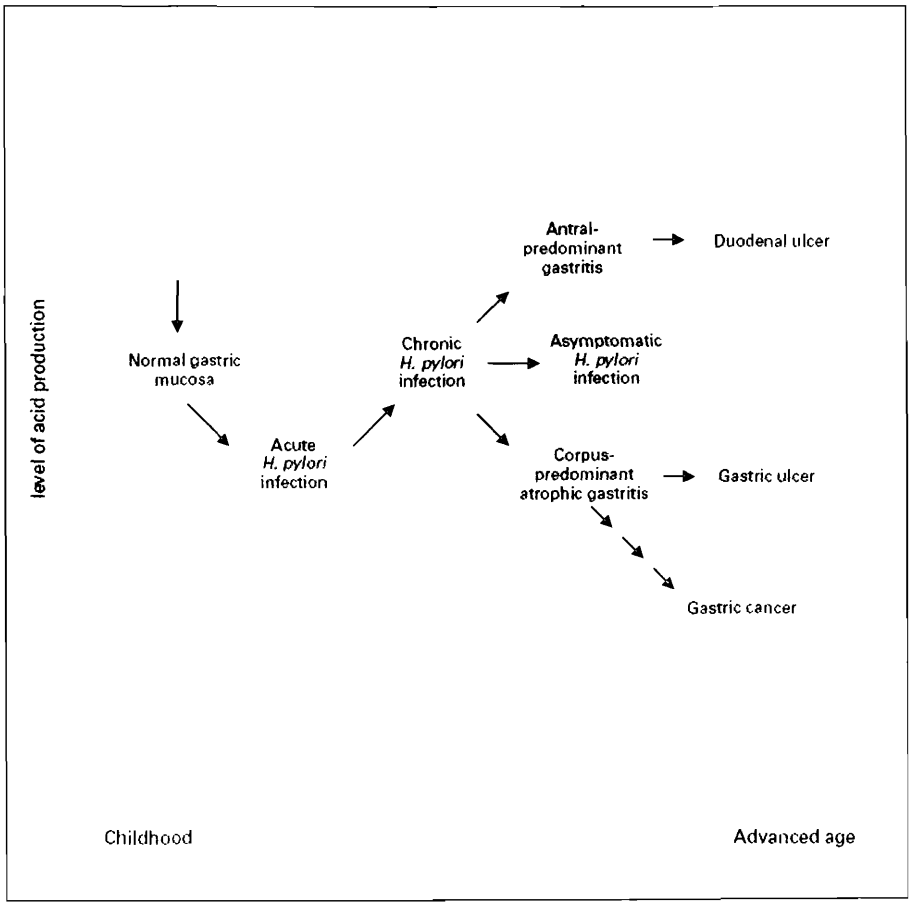



***Figure 2. Natural history of H. pylori infection.***

of oesophagus. But this relation is yet to be proven. The question of whether it is wise to eradicate *H. pylori* thus remains open.

***Epilogue:*** *H. pylori* infection is one of the most common bacterial infections in humans. In 1997 *H. pylori* genome was sequenced and this will help us to fill the gaps in our knowledge about its infection and to find novel treatments by identifying new targets for drug therapy. Vaccine strategies against this infection have been successfully implemented in animal models. As gastric immunology is poorly understood, application of these strategies in humans is difficult. A better understanding of the host-pathogen interaction is needed for the control of this infection.

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