

## Two Win Nobel Prize for Discovering Bacterium Tied to Stomach Ailments

By [LAWRENCE K. ALTMAN](#)

Two Australian scientists who upset medical dogma by discovering a bacterium that causes stomach inflammation, [ulcers](#) and [cancer](#) won the 2005 Nobel Prize for Physiology or Medicine yesterday.

The winners were Dr. Barry J. Marshall, 54, a gastroenterologist from the University of Western Australia in Nedlands, and Dr. J. Robin Warren, 68, a retired pathologist from the Royal Perth Hospital.

The findings by the Australians in the early 1980's went so against medical thinking, which held that psychological stress caused stomach and duodenal ulcers, that it took many more years for an entrenched medical profession to accept it.

In its citation, the Nobel committee from the Karolinska Institute in Stockholm said that Dr. Marshall and Dr. Warren "made an irrefutable case that the bacterium *Helicobacter pylori*" causes ulcers and other diseases.

"It is now firmly established that *H. pylori* causes more than 90 percent of duodenal ulcers and up to 80 percent of gastric ulcers," the Nobel committee said.

In the wake of the ulcer discovery, many scientists have been seeking unknown infectious agents as the cause of many chronic diseases. Examples include microbes that might produce atherosclerosis, the underlying basis of coronary artery disease; ulcerative colitis; regional enteritis (Crohn's disease); and rheumatoid [arthritis](#).

A famous experiment Dr. Marshall conducted on himself was crucial in linking the bacterium to inflammation of the stomach, or gastritis, and showing that it resulted from an infection.

When the two began their research, doctors could heal ulcers with drugs that blocked the production of gastric acid, believing stomach acid caused ulcers. But the ulcers often relapsed because the bacteria remained to perpetuate the inflammation that leads to ulcers and to certain cancers.

Ulcers at that time were often a chronic, debilitating disease that required major surgery and that could cause life-threatening complications from bleeding. Also, they would often erode through the stomach and lead to peritonitis.

After Dr. Marshall and Dr. Warren discovered the role of the spiral-shaped *H. pylori* bacterium, they and others conducted trials showing that [antibiotics](#) and drugs inhibiting the production of stomach acid could cure gastritis and most stomach and duodenal ulcers.

The inflammation produced by *H. pylori* can also lead to certain stomach cancers that seem to be prevented by antibiotic treatment of the bacterium. In the early 1900's, stomach cancer was a leading cause of cancer deaths in the United States. But its incidence fell significantly, for unknown reasons, before the discovery of *H. pylori*'s role. Stomach cancer remains the second leading cause of cancer deaths worldwide.

*H. pylori* is also an important player in a type of lymphoma cancer of the stomach known as MALT, for mucosa-associated lymphoid tissue. Such lymphomas usually regress when antibiotics rid the stomach of *H. pylori*. Since the late 1800's, many doctors had noted the bacterium's presence in the stomachs of patients with ulcers and gastritis, but they ignored the connection.

In the early 1980's, Dr. Warren noted the bacterium in the lower part of the stomach in about half of the patients who had biopsies. He made a crucial observation that signs of inflammation were always present in the surface lining of the stomach near where he observed the bacterium.

Dr. Marshall joined Dr. Warren in studying biopsies from a series of patients. After several attempts, Dr. Marshall succeeded in growing a bacterium that was unknown then; he named it *Campylobacter pyloridis*, believing that it was a member of the *Campylobacter* family. (It was later found to be a member of the *Helicobacter* family and renamed *H. pylori*.)

Still, many doctors were unconvinced by the findings, a point recognized by the Nobel committee, which said the award went to Dr. Marshall and Dr. Warren "who with tenacity and a prepared mind challenged prevailing dogmas."

Dr. Marshall carried on a medical tradition in experimenting on himself to test his and Dr. Warren's theory and to show that *Helicobacter* was the primary cause of gastritis, not a secondary invader.

In earlier interviews, Dr. Marshall described how at age 32, he swallowed a gastroscopy tube to allow another doctor to look at his stomach and take several biopsies. These procedures and examinations were needed to document that Dr. Marshall had no *H. pylori* in his stomach and did not suffer from gastritis or another abnormality.

Dr. Marshall waited 10 days for the areas that had been biopsied to heal and then swallowed a pure culture of *H. pylori*. A week later, he had an unusual sensation of fullness after eating supper and felt ill. Friends told him that his breath was "putrid."

Ten days after the onset of symptoms, Dr. Marshall underwent the first of an additional three gastroscopies. Biopsies obtained through them showed that he had developed gastritis or inflammation of the stomach, but he did not continue the experiment long enough to develop an ulcer. His symptoms quickly disappeared after treatment.

Dr. Marshall said that working in a "weird" and academically obscure location aided in the discovery because he and Dr. Warren could pursue their observations without interference from the prevailing beliefs.

"If I had come up through the normal gastroenterology training schemes in the United States, I would have been so indoctrinated on the acid theory that I wouldn't have been considering anything else and might have skipped over *Helicobacter*, as everyone else had done," Dr. Marshall said in a telephone interview yesterday.

He continued: "Robin is quite obsessional. Once he sees something, he's determined to see what it is. He would have found another Barry Marshall" to work with.

Dr. Marshall said that information he obtained from the National Library of Medicine, a part of the National Institutes of Health in Bethesda, Md., aided his discovery. While in training, Dr. Marshall worked in a hospital in Port Hedland, in the Australian outback about 1,000 miles from Perth.

A librarian in Perth sent Dr. Marshall bundles of references. He said he "pulled up a whole lot of literature showing that many patients with ulcers had gastritis that the ulcer experts in the 1980's had forgotten about."

One of those papers was published in 1940 by Dr. A. Stone Freedberg at Harvard. He reported identifying similar bacteria in 40 percent of patients with ulcers and stomach cancer. Then he went on to become a cardiologist, and other scientists said they could not confirm his findings. In "*Helicobacter Pioneers*," a book edited by Dr. Marshall, Dr. Freedberg wrote that in 1990, he searched for his old specimens and laboratory books at Beth Israel Hospital in Boston to check them against Dr. Marshall's new findings. But Dr. Freedberg said someone had discarded them.

When Dr. Marshall presented his first paper on the findings, he recalled yesterday, an Australian mentor told him that he was wrong. But Dr. Marshall persisted and showed the critic where he was wrong.

Researchers are trying to learn why only a small fraction of people who have *H. pylori* in their stomachs develop gastritis and ulcers. One possible explanation is that genetic differences among humans influence their susceptibility to stomach disease. Another

theory is that differences in strains of *H. pylori* may determine the bacterium's ability to produce inflammation.

Scientists recently discovered that the Mongolian gerbil is an animal model for stomach ulcers, and the Nobel committee said studies on the gerbil could provide more evidence of how *H. pylori* damages the stomach.

Dr. Marshall said that every day he reads material on the Internet that turns up on a Google search of diseases that may be linked to *H. pylori*. "There's always something new about *H. pylori* popping up every week, and I keep an open mind on all the findings," Dr. Marshall said.

Dr. Marshall and Dr. Warren will split the \$1.3 million prize to be awarded by the king of Sweden on Dec. 10, the anniversary of the death of Alfred Nobel, the Swedish dynamite inventor who created the prizes in his will.