Nobel Prize for Medicine for gastric ulcer breakthrough

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Last year's Nobel Prize for medicine was awarded in December to two Australian scientists who revealed the bacterial basis for the world's second most prevalent disease—gastritis and peptic ulcers. Ulcers were previously connected to bad diet or a stressful lifestyle—to the point that it pervaded popular culture, including in film and literature. The breakthrough paved the way for relatively straightforward treatments for a debilitating and potentially fatal disease.

The scientists, Barry Marshall and Robin Warren, confronted significant opposition to their hypothesis that peptic ulcers are caused by the spirally-shaped bacteria *Helicobacter pylori*. They collaborated for over two decades to prove their case for this simple, yet overlooked cause of the disease. The significance of their finding goes beyond the treatment of peptic ulcers, and may lead to the prevention of stomach and duodenal cancers that have been linked to *H. pylori* infection.

In Third World countries, around 90 percent of people are infected. In advanced countries, infection rates of some 30 percent are recorded, with 6.5 million cases in the US alone. High infection rates are directly linked to socioeconomic factors, in particular overcrowding, poor sanitation and poverty. Most people become infected in early childhood, but only a portion develop an ulcer in later life.

The way in which the bacteria spreads is not yet fully understood, but scientists believe it to be passed on through oral contact, as well as through water contaminated with faeces. This may explain why high infection rates are related to overcrowding and poverty.

Peptic ulcers can be a debilitating disease. Sufferers often have chronic pain and face the risk of life-threatening gastrointestinal haemorrhage or ulcer perforation. Its victims have included Napoleon Bonaparte, who died of a cancer caused by a stomach ulcer, and the author James Joyce, who died of a perforated ulcer and bled to death.

Since the disease was first recognised in the nineteenth century, peptic ulcers were thought to be caused by excessive gastric juice that corroded the lining of the stomach. Treatment therefore centred on controlling the acid build-up through anti-acid medication and reducing stress and smoking, which could elevate stomach-acid levels. An extreme treatment involved surgically severing the nerves surrounding an ulcer to stop acid build-up and further perforation of the stomach lining.

One question continued to vex the medical community: if an ulcer resulted just from acid build-up, why would it return soon after treatment? Bacteria were not considered as a possible cause as scientists thought it could not survive and grow in the highly acidic environment of the stomach. Each day the stomach is bathed in about a gallon of gastric juice, composed of digestive enzymes and concentrated hydrochloric acid that can digest food and almost all microorganisms.

As it turned out, *H. pylori* is an exception. It develops a kind of protective "cloud" that neutralises the acid. Once protected, it infects the stomach lining, causing inflammation, usually unnoticed. But in some 15 percent of cases, the inflammation leads to an ulcer—a break in the stomach's lining and can cause bleeding.

Warren, a pathologist at Royal Perth Hospital in Western Australia, made the first discovery in 1979. As he told the *Lancet*, a British medical journal: "I was just doing my day-to-day pathology. I like looking for funny things and this day, I saw a funny thing and started wondering about it." In examining a gastric biopsy in 1979, he found numerous bacteria in close contact with the stomach lining. "They appear to be actively growing and not a contaminant," he said.

Gastric histology—the study of stomach tissue—had fascinated Robin Warren for years as pathologists could only rarely examine the stomach's lining due to the destructiveness of stomach acid. He began to experiment with stains to better view biopsies under the microscope, and found that with silver *H. pylori* stained strongly. He continued his research for nearly two years before meeting up with Barry Marshall. Marshall, a trainee, needed a research project to pass a crucial medical exam.

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Marshall and Warren began working together to record the clinical details of patients with the mysterious bacteria and also to culture the organism. Regular culture methods did not work because the bacteria took longer than most to reproduce. Due to a coincidence, the growth plates were accidentally left over a long weekend. This resulted in the growth and eventual isolation of the bacteria—identified as *Helicobacter pylori*.

The next step was to demonstrate the connection between the bacteria and gastritis. The two scientists conducted a 100-patient study with 65 suffering from gastritis directly due to the presence of the bacteria. In all the patients with duodenal ulcer and 80 percent of patients with gastric ulcer, the spiral organism *H. pylori* was present.

To be scientifically sound, Marshall and Warren needed to prove that a live animal would contract gastritis when infected with the bacteria. Unfortunately, the animal models used for the test were baby piglets, and it was almost impossible to carry out an endoscopic examination on their stomachs.

Marshall then took the unusual step of using himself as guinea pig and drank a solution containing the newly-discovered bacteria. “I planned to give myself an ulcer, then treat myself, to prove that *H. pylori* can be a pathogen in normal people,” he explained in one interview. He did not develop an ulcer, but the resulting stomach inflammation was clearly surrounded by the distinctive curved bacteria.

Both scientists published their findings in the *Lancet* in 1984. A recent analysis made by *Lancet* to celebrate 90 years of the journal’s publication found that the articles by Marshall and Warren ranked second and third among its 10 most cited articles. It took many years, however, before the seemingly simple cause for ulcers was accepted.

Drug companies that make enormous profits derived from the production of antacid tablets to relieve discomfort, were particularly antagonistic to the findings. Companies like GlaxoSmithKline and Astra had an annual income of over $8 billion from the sale of ulcer treatments such as “Tagamet” and “Zantac”. In 95 percent of cases, the symptoms returned within a year.

In a 1998 interview, Marshall explained: “The livelihood of gastroenterologists and many of the drug companies depended on these drugs that were worth billions of dollars, treating millions of people with ulcers.” When the symptoms returned, people were told to try a new drug.

“A pharmaceutical company wants to sell you a drug that you take every day for the rest of your life, a cholesterol drug, a diabetes drug, they are great sellers. If they sell you a drug which cures you, you only need to take it once or for one week. So how can you make it generate as much profit? I wasn’t supported by the big drug companies. There was plenty of money going into ulcer research, but not into these bacteria,” Marshall said.

The understanding that *H. pylori* is the cause of 80 to 90 percent of gastric ulcers has revolutionised the medical treatment. One course of antibiotics is all that is necessary in most cases to kill the bacteria and stop it from re-colonising the stomach. Such treatment may also prevent the development of stomach cancer and other diseases associated with *H. pylori* infections. The incidence of stomach cancer has decreased over the last half century but still ranks as the second highest cause of cancer deaths.

Warren is now retired, but Marshall continues to research the impact of *H. pylori* in Australian Aboriginal communities. Aborigines have a higher incidence of infection compared with the Australian population as a whole, largely due to poverty, lack of sanitation and overcrowding. The infection is a significant contributor to the poor state of health of Aboriginal people who are at high risk of forming ulcers and intestinal cancers.

In a research article published last year, Marshall stated: “Our study exposes a need for further information on *H. pylori* infection. Proper management of infections such as these requires monitoring with available diagnostic tools. However, this will mean that health budgets need to be extended.” He criticised the lack of government funding for long-term research of the type that led to the initial breakthrough. “Most research funding is just for a couple of years,” he said. “If there’s a problem that’s worth solving you should be able to keep going at it.”

These comments highlight the difficulties confronting Marshall and Warren from the outset. They eventually managed to overcome funding obstacles and the opposition of entrenched corporate interests to win the Nobel Prize. Their story, however, is the exception. Many other scientists are not so fortunate.

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