

## Profile

# Nobel Prize winners Robin Warren and Barry Marshall

In the world of medical research, it would be hard to find two individuals working together whose temperaments were more diametrically opposed than Robin Warren and Barry Marshall, the joint winners of this year's Nobel Prize in Physiology or Medicine. Warren, a consultant pathologist now retired from Royal Perth Hospital in Australia, is a reserved man whose colleagues talk about his quiet persistence, thoughtfulness, and careful observation. Marshall, a gastroenterologist 14 years his junior from the University of Western Australia, has described himself as brash. Others list his creativity, determination, and entrepreneurial spirit.

Warren's quiet persistence and Marshall's energetic enthusiasm complement one another. They make what both men describe as a "good team" and have together achieved, according to the Nobel Assembly at the Karolinska Institute, a remarkable and unexpected discovery that gastritis and peptic ulcers arise from an infection of the stomach caused by the bacterium *Helicobacter pylori*. In the process, the two researchers have overturned established medical dogma and revolutionised the treatment of peptic ulcers.

The partnership began in 1981 when Marshall, a trainee doctor, asked Warren about the possibility of doing a research project with him. 2 years earlier, Warren had made a historic discovery—that gastric biopsy samples from patients with gastritis had an unexpected burden of curved bacteria. Since 1979, he had been gathering more and more samples. "As far as I was concerned the way they were arranged, they were associated with the gastritis", Warren said. "But trying to convince other people of that was impossible."

Warren recalls: "Every time I spoke to a clinician they would say, 'Robin, if these bacteria are causing it as you say, why hasn't it been described before?'" Orthodox medical teaching at the time was that bacteria did not grow in a normal stomach. However, as Warren wrote in the 2002 book *Helicobacter Pioneers*, "I preferred to believe my eyes, not the medical textbooks or the medical fraternity." Marshall also believed what he saw through Warren's microscope. "The first time I sat down with him he didn't really have any trouble convincing me there were these organisms in the stomach", he told *The Lancet*. "As far as I was concerned he was right, and I thought this was a unique observation."

Soon the two became absorbed in a study of 100 patients, and Marshall had begun trying to culture the organism—a difficult task he finally achieved in early 1982. By the end of that year, armed with preliminary results, Marshall gave a presentation at a local meeting, where he earned a patronising and negative response. "I didn't have all my ammunition ready to go", he says. "It allowed people to shoot holes in our hypothesis." It was the kind of response he and Warren were to become familiar with. "I was out there fighting battles

with the gastroenterologists", he recalls. "But Robin's very persistent; I'm also a little the same. Neither of us would really care if there were 1000 people jeering on the sidelines; it would be like water off a duck's back." Throughout this time, the two men took encouragement from talking to one another and valued the support of their wives—Win Warren and Adrienne Marshall. "In fact, there was only one doctor who did believe in what I was doing", Warren wrote, "my wife Win, who was a psychiatrist and who encouraged me".

In 1983, the two published an unusual pair of correspondence letters in this journal, including photographs of the histology and electron microscope images of the organism (*Lancet* 1983; 1: 1273–75). Later that year, at the recommendation of the campylobacter specialist Martin Skirrow from the UK's Public Health Laboratory Service, Marshall presented the findings to the 2nd International Workshop on Campylobacter Infections in Brussels, Belgium. "I think most microbiologists were convinced at the outset that this was linked to gastritis", Skirrow recalls. "He's a good salesman is Barry. He carried most microbiologists with him in his work."

Whereas microbiologists had no dogma to overcome about the causes of gastritis and peptic ulcers, the wider medical community remained hard to convince. Even the first major publication of their results, in this journal in 1984, was a difficult hurdle (*Lancet* 1984; 1: 1311–15). The editors, Marshall recalls, found it difficult to find reviewers who could agree the paper was important, general, and interesting enough to be published. It was partly with the assistance of Skirrow that the article finally appeared.

The same year, in an act born to some extent of frustration, Marshall deliberately infected himself by drinking a solution swimming with the bacterium, as part of a successful and widely reported experiment to prove Koch's postulates. But many clinicians still remained unmoved. It wasn't until the early 1990s that the evidence of Marshall and Warren became impossible to ignore, at which point pharmaceutical development and clinical practice underwent a shift towards eradication of *H pylori* to treat ulcers.

The Nobel Prize came a decade later, and was richly deserved says Adrian Lee, a leading *H pylori* researcher who was among those microbiologists at the Brussels conference. Although other researchers had reported seeing spiral bacteria in the stomach before the west Australian duo, their achievement stands alone, he notes. "There was no accumulation of evidence", he says. "What happened was that people had made observations, but had drawn no conclusions. This was a paradigm-shifting discovery."

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