CHRISTIAN FLEMMING/LINDAU NOBEL LAUREATE MEETINGS

Q&A Barry Marshall

A bold experiment

Laureate Barry Marshall, professor of clinical microbiology at the University of Western Australia in Perth, tells Meghan Azad why he risked his health to prove his theory about the link between stomach ulcers and bacteria. He shared the 2005 Nobel prize with Robin Warren for discovering the stomach-dwelling bacterium *Helicobacter pylori* and for proving that it is this microorganism, not stress, that causes most peptic ulcers.

What sparked your interest in science and medicine?

From the first day I ever saw a book I was very keen to read. My father was a tradesman, so I read about motor mechanics, electrical equipment and even thermodynamics, and my mother was a nurse, so she had anatomy and physiology books. Finding out how things worked was always a natural thing. I didn't intend to go into research but it was part of my medical training. I could have worked on lots of things besides the bacterium *Helicobacter pylori*, but that was the one that really took off.

What drew you to ulcers and *H. pylori*?

The conventional wisdom was that people developed ulcers because they were suffering from stress, which was thought to increase gastric-acid secretion to the point at which the stomach lining breaks down and a peptic ulcer forms. I was sceptical that stress caused physical diseases, and I certainly was not prepared to lie

to patients by telling them that. So I looked for a more evidence-based cause. Every medical and microbiology textbook at the time stated that the stomach was sterile, so nobody had thought of doing a culture or looking for bacteria with a simple Gram stain, a laboratory technique used to identify species of bacterium. If they had, they would have found *H. pylori* in five minutes! There were a few paradoxical things that made *H. pylori* hard to find — for example, it is often not detectable in the vicinity of an ulcer. In fact, we had cultured the bacterium months before we realized that the species was important in the formation of ulcers.

When did you realize your work might be worthy of a Nobel prize?

Robin Warren and I were jointly awarded the Nobel prize. We first identified the association between bacteria and ulcers in late 1982, and this was followed by a period of hypothesis testing and extrapolation. In April 1983, we

carried out an experiment to prove that we could kill *Helicobacter* with ulcer drugs and I knew then that we were almost certainly on the right track. Then we had our first paper published in *The Lancet* and we went out to celebrate. Robin's wife said that we might win the Nobel prize and we joked that it might happen within a couple of years, but I am glad it didn't. It would be difficult to have won a Nobel so early in your career — I think you would develop a big inferiority complex.

You swallowed a culture of *H. pylori* to prove your hypothesis. What led you to do this, and what did your family and colleagues think?

I was becoming increasingly frustrated because I was successfully treating stomach-ulcer patients with antibiotics but couldn't convince other doctors to use this approach without solid experimental evidence. I tried to infect piglets for six months, but piglets grow quickly, so it was a tough experiment to do.

Without data proving that I could reproduce an ulcer by infecting an animal with *H. pylori*, a human experiment was the only option. When I decided to drink the *Helicobacter* culture I felt a bit embarrassed, and I didn't really discuss it with my bosses in case they forbade me to do it. But I suspect they knew. I had an endoscopy beforehand to check that my stomach was normal and to establish a baseline, and my boss said: "Barry, I'm not sure why you asked me to do this endoscopy, and I don't want you to tell me." I did not expect to develop any symptoms, but I did become ill with vomiting and bad breath. A further endoscopy revealed the infection, proving that a healthy person could be infected by *Helicobacter*. Of course, there are plenty of things that can go wrong in a single self-experiment, and it is very doubtful that such a study would get published these days — even back then it was a bit of a stretch.

"When I decided to drink *Helicobacter*, I didn't tell my bosses."

Even after your self-experiment, the medical community remained sceptical that *H. pylori* was connected to stomach ulcers. How did you finally convince them?

We were keen to present our data and announce that we had discovered the cause of ulcers, so we submitted our paper to the Australian Gastroenterology meeting in 1983. It was rejected. Fortunately, my boss at the time had some experience with *Campylobacter*, which was becoming a popular explanation for infectious colitis, or inflammation of the colon. *Helicobacter* looked similar, so I spoke to a *Campylobacter* expert in Britain and we sent him some cultures. He grew them and became excited about it, too. Then, in 1984, we went to a meeting of microbiologists, who are always interested in any new microbe, and things really took off after that. It took a few more years to gain support from gastroenterologists.

There a growing body of evidence that infection with *H. pylori* during childhood may protect against immune diseases such as asthma and allergies. What is your take on this?

For the past 30 years we have had the hygiene hypothesis, which states that a lack of early childhood exposure to microorganisms disrupts the natural development of the immune system. We know that hygiene levels have increased significantly during the past century and that allergic diseases are on the rise, but linking these trends is difficult. We know that parasitic worms, which are still common in Africa but no longer in developed countries, suppress the immune system. Infection with *Helicobacter* used to be common, but since the twentieth century that has been declining in developed countries. Finnish populations show decreased immunoglobulin E, the antibody linked to allergies,

Stomach cells (stained blue) and *Helicobacter pylori* (yellow), a bacterium that causes peptic ulcers.

in people with *Helicobacter*, and in New York City, studies have found that children with *Helicobacter* have a lower risk of developing asthma, eczema or any kind of allergic disorder. These results are tantalizing, but other studies have not necessarily found the same thing.

Stomach ulcers were once firmly believed to be non-infectious diseases, but you proved that a microbe was responsible. Will other long-term diseases turn out to have an infectious cause?

As far as I am concerned, everything is environmental until you convince me that it is genetic. Take rheumatoid arthritis: we do not know the aetiology of it but we have got expensive treatments similar to the way we used to prescribe acid blockers for ulcers. Eventually we will figure out the actual mechanism that triggers this cascade of immune problems in rheumatoid arthritis — maybe it is a viral infection. Genomic and microbiological studies are extremely powerful here. For example, when my grandchildren first started mixing with other children at playgroups, they were taking home a new virus every week. We need to collect samples and ask what those viruses are so that 20 years from now, when some of those kids develop serious illness, we can look back at their microbiologic history. There are a lot of data that need to be collected and there are fantastic research opportunities that will help to solve those problems.

I understand that you are developing an edible vaccine made from *H. pylori*.

Yes, although it has been harder than we thought. The idea is that you engineer an *H. pylori* strain that is deficient in some way and cannot give you permanent colonization. Then you clone some extra DNA into it, so that

it could produce a useful peptide analogous to, for example, an influenza vaccine antigen. I expect that one day such oral vaccines will be available as food products in the supermarket, rather than requiring a needle. We are also working on probiotics related to *H. pylori* in clinical trials, and I have co-authored a paper looking at the migration of humans around the world based on variations in the *H. pylori* genome. Show me your *H. pylori* and I can tell you where you came from!

What advice do you have for young scientists?

First, do what you like to do, because turning up every day for a job you do not enjoy feels like a death sentence. Second, do not be afraid to sacrifice salary to do something that you are interested in. Third, keep some balance in your life — most of your papers are going to get rejected initially, and occasionally you're going to feel down, so it is good to have a partner with an objective perspective.

If you had to be a microbe, which one would you be and why?

Helicobacter pylori, because I would have no competition! ■

Meghan Azad is an assistant professor at the University of Manitoba and Manitoba Institute of Child Health in Winnipeg, Canada.

Her research with the Canadian Healthy Infant Longitudinal Development (CHILD) study is focused on the early-life origins of chronic diseases and the gut microbiome.