



THE **STORIES**

07

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Barry Marshall

Treating Stomach Ulcers

Every day, in clinics and laboratories across the globe, thousands of doctors, researchers and scientists venture quietly on voyages of discovery as they seek to answer the mysteries of our time. Most build on previous knowledge, making small but useful contributions to their field and attracting little in terms of public recognition, but for a fortunate few, the secrets they unlock are of such global significance, they are honoured as thought-leaders of their generation.

One such individual of recent times is Barry Marshall, who in 1981 found evidence to support his theory that peptic ulcers and most stomach cancers were caused by bacteria.

But rather than being welcomed, the discovery was initially ridiculed and rejected by many in the medical community, who had long held that such conditions were the result of lifestyle factors such as excessive stress and a rich or spicy diet.

At only 31, with the future of his medical career, and a wife and four young children to consider, Marshall could easily have buckled under the weight of the ‘expert’ criticism being levelled against him. However, certain that hundreds of thousands of ulcer sufferers were being given unnecessary medications and surgeries each year, he chose instead to use conference presentations, meetings and associated research papers to fight to make his findings known.

Now a Nobel Laureate, Marshall enjoyed a relatively humble upbringing, born to teenaged working class parents in the gold mining town of Kalgoorlie, 800 kilometres east of Perth. Living above his Grandfather’s pub/TAB, he quickly learned good money could be made scouring the floors and grounds of the pub for dropped cash, and if he was bored he’d tag along behind Bertie, the pub’s heavy-drinking yardman, as he went about the business of beheading chooks and chopping wood.

When he was old enough to venture out into the neighbourhood, he and his mates tested out homemade catapults and bows and arrows, as they rode around on their bikes, or made fireworks in each other’s backyards. His mother’s nursing and medical books entertained him on rainy days, and when he was able to, he watched on as his highly skilled fitter-and-turner

father showed him all there was to know about making engines, machines and other things ‘work’.

Worried her sons would end up in the mines if they stayed in Kalgoorlie, Marshall’s mother insisted the family move to Perth in 1958, and when he found himself in the seaside suburb of Scarborough, young Marshall discovered new ways to sustain his adventurous spirit, fossicking through the nearby second-hand metal yard, and snorkelling or surfing around the rocks at the local beach.

“Being the oldest I suppose I was pretty much left to myself a lot of the time as a child and I guess I liked to live dangerously,” he told broadcaster Norman Swan in an interview in 2008.

“I learned that things could always be risky and things could always go wrong, but I learned to be a risk taker.”

It seems he also learned where there was a will, there was a way, and he learned to never give up when faced with a challenge.

“I felt there was nothing out there that I couldn’t do if I had a go at it and learned enough about it,” he told Swan.

And it was most likely that adventurous, risk-taking, but determined, spirit that drove Marshall to stand with confidence against the bulk of the medical community and the power of the global pharmaceutical giants when he discovered the real cause of ulcers.

Remarkably, exactly a century before Marshall’s discovery, pathologist Edwin Klebs had noticed the appearance of bacteria-like organisms inside the gastric glands of those with ulcers. Over the next 60 years, a number of studies and research papers identified links between this particular bacterium – *Helicobacter pylori* (HP) – and ulcers, but because of the strongly held belief within gastric medicine that bacteria couldn’t survive the stomach’s acid environment, such findings were largely ignored.

In 1940 another young doctor examining pieces of stomach removed during a range of different operations identified a significantly increased prevalence of this bacterium in ulcer patients and wondered whether there

was a link. Like Marshall, Dr Al Freedberg had only been out of medical school a few years at the time, and although he went on to become a leading cardiologist, developing one of the earlier treatments for angina, his pioneering work and research publications on stomach ulcers was largely ignored.

In a *New York Times* interview a few years before his death in 2009, the 101-year-old admitted he'd always been "very upset" that colleagues, including his own boss at the time, thought he was wrong and discouraged him from continuing the research.

Marshall himself said in 2005 that he believed Freedberg "would have won the Nobel Prize in about 1951, just as I was getting born," had he been able to pursue his line of investigation into ulcers.

Fortunately, 40 years later, when Marshall and his research partner, pathologist Robin Warren, found fragments of evidence suggesting that, for some reason, *Helicobacter pylori* could live happily within the stomach, and perhaps could be the cause of ulcers, Marshall's inquisitive and tenacious spirit induced them to keep probing. With his knowledge of electronics and computing, Marshall built his own computer, giving himself access to the latest international research, information about grants and funding opportunities, as well as the ability to print and submit consent forms and protocols for his research.

The pair developed their hypothesis, and in 1982 set about proving it. One of the first steps was to try to produce a culture of the bacteria, which proved unexpectedly difficult until fate lent a hand. Their usual procedure was for the lab technician to check the petri dishes in the incubator every two or three days; if no culture had grown in that time, they would be discarded. On the Friday before Easter, a locum technician forgot this routine procedure, and the long weekend holiday meant the dishes weren't removed from the incubator until the following Tuesday. This five-day incubation period proved crucial: when next checked, the culture had grown.

This fortunate piece of luck meant the bacteria could now be isolated, named, studied and replicated for their research.

“We figured out how Helicobacter pylori could live in the stomach by hiding in the thick, acid-resistant layer of mucus that coats the stomach wall, and we could play around with it in the test tube, doing all kinds of useful experiments. We also quickly learned which antibiotics could kill it.”

But these developments fell far short of impressing the wider medical community. In his Nobel Prize biography, Marshall wrote:

“In October 1982 I presented the preliminary findings from our study to the local College of Physicians meeting, where it received a mixed response. I found that my contract at Royal Perth would not be renewed the following year.”

Fortunately, however, there were also some who were very interested in what Marshall had to say. Norm Marinovich and Ian Hislop, both doctors at Fremantle Hospital, the smallest of Perth’s three teaching hospitals, approached Marshall with an offer of a Senior Registrar’s position and urged him to join their research team to continue his work. Over the next few years they began using certain antibiotics to treat patients with peptic ulcers, achieving excellent results.

They continued to unravel the secrets of this mysterious bacterium and carefully documented their successes from their trials. But Marshall says even with this mounting body of evidence, speaking out and changing the opinions of the establishment or the status quo wasn’t easy.

He and Warren had proven the existence of *H. pylori*, they could explain how it survived in the stomach, and they even had evidence that antibiotics could eradicate it and relieve the symptoms of sufferers, but still critics argued there was no proof it could actually cause an ulcer, and insisted it had most likely invaded the stomach only after the ulcer had weakened the patient’s immune system.

This was one of the main lines of argument put forward by the drug companies. At that time, about 10 per cent of the global adult population were suffering from ulcers, and the ulcer-drug (acid blocker) business was worth three to five billion dollars each year. According to Marshall, these large corporations were understandably acting in the interests of their shareholders.

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“As far as they were concerned, people had ulcers all their life,” he told Swan, “and so their projection was, ‘If we start you on drugs for your ulcer you will need to spend \$1 to \$3 a day for the next 10 or 20 years to keep your ulcer under control.’

“If suddenly ulcers could be cured and it became unnecessary to take these drugs all the time, the share value would go down by three-quarters, so they didn’t want to support us, and they did all kinds of other research trying to prove that bacteria did not cause ulcers.

“Basically they said ‘No ... You get ulcers, so your immune system is weakened, and then you get the bacteria.’

“They were very sceptical.”

The established international gastroenterological community also found it difficult to accept that a young general physician and a pathologist from Perth could have proven their entire branch of medicine had been on the wrong track in the treatment and management of ulcers for so long. The lack of support from colleagues in Australia stung Marshall the most:

“The worst day in the whole lot of it was the rejection letter from the Australian gastroenterologists back in 1983,” he later said in a 2008 interview.

When it had become clear to Marshall and Warren that they’d made an incredibly important discovery, the duo wrote a two-page letter to *The Lancet* (one of the world’s oldest and best known general medical journals) to stake their claim to the discovery. Once that was in press, they took the same information and created an abstract for a presentation they wanted to make at the Australian Gastroenterological Society’s meeting to be held in Perth later that year.

“Back in 1983 five hundred dollars was a lot to spend on an airfare to Melbourne or the east coast of Australia, but with the meeting being in Perth we could afford it, and we had a vision of presenting our amazing discovery about the cause of ulcers to the world.”

But instead of being welcomed to speak at the conference, they were dismayed to be told their abstract had been rejected.

“We were sent the standard letter: ‘Dear Dr Marshall ... So many submissions ... yours was ranked 67th and we could only accept 57 ...’ the letter read. I still have that letter, and I always tell researchers to keep your rejections in a bottom drawer and years later you may be able to show them to your students, as I do.”

Disappointed, Marshall went to his supervisor at Fremantle Hospital, microbiologist David McGeachie, who decided to contact Dr Martin Skirrow, a renowned microbiologist from England, who he knew was interested in bacteria similar to the ones Marshall had cultured. The pair quickly created strong professional links, and Skirrow worked quickly to bring Marshall to Brussels, to make his first presentation at the European Campylobacter meeting in September 1983.

That presentation was well received, and set the scene for a major article to be printed in *The Lancet*, seven months later.

As the weight of evidence grew, so too did Marshall’s confidence that they were right, but detractors’ claims that *H. pylori* was simply an ‘opportunistic’ invader of a weakened host still dogged him. His attempts to infect healthy animals were failures. Finally, he realised that if he was going to prove his hypothesis that *H. pylori* colonisation could occur without the presence of an ulcer in a healthy human host, he was going to have to use himself as a guinea pig.

In 1984, after undergoing tests to ensure he was ulcer and *H. pylori* free, he drank a cocktail of infected fluid which, as anticipated, left him with an extensive gastric infection. Whilst not conclusively proving that such an infection would always lead to ulcers, it did prove that there was no need for there to be a prior weakness or an ulcer for this bug to be able to colonise the stomach.

Marshall says they were now rubbing shoulders with some of the scientific and medical leaders of the world, and the rejections from those in Australia became less of an issue, but he still had no idea how hard the road ahead towards universal acceptance would be.

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Those who personally knew Marshall and had been privy to his and Warren's research were supportive, but without formal recognition or international interest, their findings were at real risk of being ignored. Marshall decided the best way to gather support was to present his findings at conferences and face up to the questions and dissent of the audience.

“At one conference, I can remember almost leaping off the stage and wanting to throttle people who were making inane comments about the whole thing.”

But by the early 1990s the tide of acceptance began to turn, and by 1992 Marshall could go to meetings and have 50/50 support for his work. He was regularly being invited to be a keynote speaker at conferences, which reflected well on Australia.

Finally, in 1994, the US National Health Institute declared the correct treatment for duodenal ulcers was the eradication of *H. pylori* using antibiotics.

Marshall says they always knew they would win the battle, but even so, 'victories' can be sorely delayed. With few other options, he said it was conferences that gave him exposure to a global audience, as well as exposure to certain pharmaceutical companies, which then provided funding for his future research. Over time, Marshall's attention has spread to diagnostics and the associated business side of his work. Conferences were important here, too, as they can play a huge part in industry by raising awareness of other technologies that are available, and providing opportunities to promote your work. Marshall believes conferences and exhibitions also provide a mechanism for the technology companies to expand, not just by meeting potential buyers' needs but also by developing potential global distribution channels.

For example, he said that when his own company was showcasing his diagnostic products at conferences, it wasn't the actual sales at the conference that were of greatest value, but the enormous mailing list they gained access to.

Another vitally important element of a good conference, according to Marshall, is good media management.

“If the conference gets its media ducks in a row it can gain huge exposure. Conferences need to have a media budget and local media should be encouraged to access these world leaders for stories whilst they’re here visiting. Organisers should get the news crews out the day before the conference and have the coverage continue throughout.”

He cites the practice in Japan, where conference organisers get a public speaker to talk to parliament about the proceedings, generating priceless publicity.

Marshall believes that, if conference media is planned correctly, organisers can utilise the publicity to provide multiple benefits for their cause or for the research and products being showcased. Again, he draws on his own experience:

“[In the 1980s] the Australian health care system was so good that people already had access to low cost care, and had little incentive to look for alternatives.”

They believed what their doctors had told them; that their ulcer was a result of their genetics or their lifestyle, that they would just have to live with it, and that antacids were the best way to manage it. Of course, Marshall believed many of them had been misdiagnosed, and knew they were simply not aware of the alternative treatments being tested, but he had no legitimate or ethical way to formally access these people or get information to them about what he was doing because it was seen as somewhat unethical for scientists or medical researchers to directly use the media to attract publicity or attention. But by speaking at conferences about his discoveries and the trials he was conducting, reports often appeared in local media and before long his office would be inundated with people wanting to be involved.

He said similar levels of public or commercial interest could be generated when the media reports on new technologies being showcased at conferences. He recalled a news segment about tiny cameras that had

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been developed to travel down patients' throats, allowing specialists to see inside their gut. When patients then came to be treated, they would often demand what they had seen on TV. Essentially, he sees that, by using media effectively, conference organisers can reach much larger audiences than just those in attendance. In terms of medical and scientific conferences, this has the power to shape patients' understanding and desires, and it can actually fuel a medical market.

He added that sponsors and investors also feel they've received better value for their investment when there is significant media exposure associated with a conference.

In fact, in terms of the overall importance of conferences to the field of science and medicine, Marshall ranks them 8 out of 10.

“Scientific development would happen anyway, but new knowledge is terribly important and it's also important for your own career to be exposed to that new knowledge. Conferences give you access to material that's not going to be published for a year or two, so if you don't go to a conference at least once every two years you become out of touch and your ideas could be superseded.”

Marshall believes it is vital that Australian researchers go to international conferences to become known, and that international conferences are hosted here so local issues can be discussed one-on-one. He believes there is much potential for conferences in Australia to attract those from Asia and Indonesia, particularly conferences held in Perth, although Perth is a more difficult destination for those travelling from Europe and the United States. Marshall also believes it is important that conference organisers attract good sponsors to subsidise costs, but the most important thing organisers need to do is generate interest, so that people are calling you, wanting to attend.

He says that if Australia wants to keep its home-grown scientists and make them world class, local conferences are vitally important, and young researchers in particular should be encouraged to attend.

“They provide a means to keep you connected to the world and give you access to new knowledge. Young researchers should try to do at least a poster presentation as well when they attend a conference, because anything, even if it’s small, can go on a CV. It shows they are trying, and that they’re a self-starter, and this can increase opportunities for jobs overseas.”

“All of this provides exponential benefits as it links Australian research with world leaders, keeping them up to date and garnering international recognition, which will lead to a growth in those wanting to pursue research careers here in Australia.”

Another very important benefit of conferences for Marshall is the personal connections and friendships that are made.

“Those friendships are invaluable, and provide an ongoing means of support. I remember people who came to my early conferences and now I forever owe them a favour because they supported me when my field was tiny and controversial.”

Now Professor of Clinical Microbiology at The University of Western Australia and Director of the Marshall Centre for Infectious Diseases (Research and Training), Marshall has a string of awards including the Florey Medal, the Benjamin Franklin Medal for Life Science, the Order of Australia, the Keio Medical Science Prize, the Buchanan Medal and more. What started out in 1981 as little more than a possibility for a “nice little research paper” about a new strain of bacteria would one day earn Warren and Marshall the most coveted of scientific awards.

“Robin and I thought we had a chance at a Nobel, but years had gone by since our discoveries, and we hadn’t won. Robin had retired, but we still always went down to the pub for fish and chips on the night of the big announcement.”

“When we finally heard in 2005 that we’d won, there were mixed emotions. It was a bit like dying and going to heaven; once you get there what do you do?”

Clearly there is no single factor to be credited for this achievement, which has undoubtedly saved lives and diminished the suffering of millions of

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people throughout the world. Marshall's colourful, adventurous childhood with capable, loving parents stimulated a thirst for answers, gave him the practical knowledge he needed to find them, and nurtured in him the courage and risk-taking spirit he needed in order to stick to his convictions.

Timing and luck played their parts too, as did the encouragement and friendship of Warren, Skirrow and other important supporters along the way. But it is also clear that conferences played an extremely important part in the process. Conferences and seminars provided Marshall with the opportunity to publicly showcase his and Warren's work in front of receptive – and not so receptive – local and international audiences. For, it is highly likely that without that level of controversy, interest and support generated as a result of conferences, the weight of the opposition against them would have at best significantly delayed the development of the simple and cost-effective diagnostic tests and treatments for these infections or, at worst, like Freedberg, may have discouraged these Nobel Prize winning adventurers from continuing with their work at all.

