

Warren and Marshall—Changemakers

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Barry Marshall and Robin Warren

Robin Warren – Change Instigator

It's not what you look at that matters, it's what you see.

— Henry David Thoreau, American essayist

The 11th of June 1979 was a day clinical pathologist Robin Warren would never forget. It wasn't just the fact this day was his forty-second birthday and he would be celebrating with his family that evening. No, something he was viewing in the microscope caught his eye which he described as “a funny-looking thin blue line stuck on the surface of the cells in some areas.”

What he did next was to examine this area with a higher powered microscope. He had no idea that by exploring this curiosity further it would change his life forever and would result in him being awarded—together with a colleague—the Nobel Prize some 26 years later. But it wasn't going to be an easy journey.

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John Robin Warren was born in Adelaide in 1937, the eldest of three sons of Roger Warren and Helen Verco. He attended a local state primary school before going on to St Peter's College where his father had gone to school. Saints, as it is known, is Adelaide's oldest, and most expensive private school. It was founded in 1847, only ten years after the first white settlers arrived in the colony.

Saints is known for its academic excellence and leadership development. Among its alumni are three Nobel Laureates as well as numerous political leaders, 42 Rhodes Scholars, sporting identities and a NASA astronaut. While Warren was a diligent student he says he was no good at sport. What he did like were his personal pursuits of photography—which became a lifelong interest—and riding his bike around the Adelaide foothills:

*I was a bit of a loner, riding on my own and doing whatever I wanted, not having to worry about how fast or slow companions were. This did somewhat hinder my social skills, but no doubt made my eventual profession in pathology much easier.<sup>1</sup>*

Warren graduated from high school in 1954 and gained a Commonwealth Scholarship to study medicine at the University of Adelaide. Founded in 1874, it is the third oldest university in Australia and one of the Group of Eight leading universities in Australia. One of the founders of the Medical School in 1885 was Sir Joseph Cooke Verco and Robin's mother was a great-niece of Sir Joseph. Numerous members of the Verco clan have graduated from the University of Adelaide over the decades, many from the Medical School, Dental School or Nursing School. His favourite uncle, Dr Luke Verco, was a well-loved country doctor. Studying medicine was obviously in his

blood line but he had no pressure from his family to do so. Becoming a doctor was something he himself had decided on from an early age.

After graduating in 1961 from medical school he spent a further year as a resident at the Queen Elizabeth Hospital in Adelaide before he could qualify to practise as a doctor. This is where he met another trainee doctor, Winifred Williams. They married in 1962.

His first job as a qualified doctor was that of Registrar in Clinical Pathology at the Institute of Medical and Veterinary Science Institute, which was the main pathology laboratory in Adelaide. This sparked his interest in pursuing a career as a pathologist and so he took on a training position as Clinical Pathology Registrar at the Royal Melbourne Hospital. In 1967 he was admitted to the Royal College of Pathologists of Australasia as a fully qualified pathologist. His next move in 1968 was to Perth to take up the position of consultant pathologist at the Royal Perth Hospital.

The practice of pathology, with the detailed examination of the body, including dissection and inquiry into specific maladies, dates back to ancient times. However, pathology as a formal area of speciality was not fully developed until the late 19th and early 20th centuries. Today there is a range of sub-specialties, and although Robin trained as a general pathologist his ongoing work was mostly in histopathology which involved the microscopic examination of biopsy specimens.

Warren describes his work in the laboratory:

*I was working in the pathology laboratory, and you've got to understand that, as far as the clinicians are concerned, the pathologist is there as a service man: he does what they ask and that's the end of it. They just send down biopsies from what they want looked at. Usually, I suppose, the most common biopsies from the stomach were from peptic ulcers, gastric ulcers—because gastric ulcers are fairly often malignant.<sup>2</sup>*

The main function of the stomach is to store food and to start the digestion process. The wall of the stomach secretes hydrochloric acid and an enzyme called pepsin achieve this breakdown of food. After the stomach, food passes into the duodenum, the upper part of the small intestine.

Peptic ulcers are sores that occur in the lining of the stomach or duodenum. If left untreated they can have serious consequences from internal bleeding, infection or blockage of the digestive tract.

The traditional thinking was that stress and spicy foods were the cause of peptic ulcers. The treatment was antacid tablets and powders to combat excess production of acid blamed for damaging the delicate stomach lining. For the pharmaceutical companies, antacids were largest-selling prescription drugs in the world – a \$3 billion market. Surgery was used to treat bleeding ulcers and was a procedure not immune to complications arising post-surgery.

During the 1970s fiberoptic gastroscopes were introduced to make it much easier for a gastroenterologist (a bowel specialist) to examine and take match-head size pieces of tissue from the stomach lining for diagnosis by a pathologist.

On a typical day Warren would have 20 or 30 biopsies to examine in an afternoon usually looking out for cancer. One biopsy could require many slides to be prepared. Most biopsies would be straight forward and didn't take long. Around a quarter would be more difficult in trying to work out what was there. He would work through the slides, do the analysis, write a report and send it to the typing pool. He would then need to be review the typed reports and sign them off at the end of the day.

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So what happened on 11th of June 1979 that was so special?

Usually Warren would be looking at tissues using a low power microscope as most things of interest can be seen. The biopsy was from a patient suffering severe gastritis—an inflammation of the stomach lining. On this occasion he observed a “a funny-looking thin blue line stuck on the surface of the cells in some areas.” Being curious as to what it might be, he then used the highest power light microscope he had available to clearly see little organisms—bacteria—growing there.

Warren was well aware that that bacteria could not grow in the stomach since stomachs are acidic. But every so often he might come across something unusual as a once off. Was this one of these

occasions? His colleagues finally agreed these bacteria were there but didn't believe their presence was of any significance.

That day he concluded in his report with the following statement:

*These bacteria . . . appear to be actively growing and not a contaminant. I am not sure of the significance of these unusual findings, but further investigation of the patient's eating habits, gastro-intestinal function and microbiology may be worthwhile.*³

No one else in his department was interested, so he set out to find out in his own time if this was a common occurrence and what these bacteria doing there in the stomach. And as soon as he started looking he found instances of bacteria being present in around half the biopsies he examined.

Why hadn't he noticed them before? This was a question he asked himself and was later to find out that the presence of bacteria had been noted over the last 100 years but no one took it further.

Over the next two years he collected more evidence to be able to come up with the conclusion that signs of inflammation were always present in the stomach lining close to where the bacteria were seen. He didn't believe he had all the proof he needed but since he couldn't get cooperation from the clinicians to provide the particular biopsies he needed, he couldn't go any further. He was at the stage of reporting his preliminary findings and was in the process of writing his paper. It seemed that his ability to change the traditional view of how ulcers were formed was doomed to failure.

But then a dramatic change took place. It was the middle of 1981 when Barry Marshall walked into his office. He had just been appointed as the new gastroenterology registrar and as part of his specialist training he was required to write a research paper before he moved on to his next assignment. Warren explained what he had come up with so far, but said later that Dr Marshall "did not seem particularly interested". But Marshall did agree to take a series of biopsies during the rest of that year showing apparently normal stomachs for Warren to see if the bacteria was present.

This was the breakthrough that Warren needed—he had found a clinician who would provide him with the samples he required to prove his case. Marshall did provide the biopsies during the remainder

of the year and became very interested in following through on the study whenever he was able. So much so that two years later Marshall was leading the charge to have their now combined research accepted by the medical community.

Robin Warren had made his major contribution as a change initiator and now it was time for Barry Marshall to become the change master. Eventually both would be recognised as joint winners of the Nobel Prize in Physiology or Medicine in 2005.

Barry Marshall – Change Master

*The greatest obstacle to discovery is not ignorance
—it is the illusion of knowledge.*
—Daniel J. Boorstin, American historian

When trainee specialist Dr Barry Marshall first met with Dr J. Robin Warren, a staff pathologist at the Royal Perth Hospital, he had no idea that their collaboration and dogged persistence would eventually change a core belief of the medical profession and save half-a-million lives a year—each year, for ever—and for him to become a Nobel laureate.

The year was 1981 and Marshall was undertaking internal medicine training to become a specialist physician. Originally he had just intended to be a general practitioner after he completed his medical degree. He then started to be interested in the more complicated and demanding parts of medicine. As he explained:

I felt that the average stuff didn't challenge me enough, and I felt that subjects like diabetes were pretty challenging, high blood pressure, rheumatoid arthritis, cancer, those things in internal medicine, where the tough cases always existed also geriatrics, because patients have many conditions.⁴

In 1979 he had been appointed as Registrar in Medicine at the Royal Perth Hospital and he was in the process of exploring a number of specialties and now it was his turn to study gastroenterology in

depth. He had no real desire to specialise in this field but Warren's discovery of bacteria in sterile stomachs did interest him. He always liked a challenge and, as he was encouraged to take on a research project in each year of his specialist training, this could be a neat project he could complete and then move on to another field.

In fact, this project would be the makings of his career.

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Barry James Marshall was born in the (in)famous mining town of Kalgoorlie, Western Australia on September 30, 1951. At the time of his birth his father, Robert, was a 20-year old apprenticed tradesman—a fitter and turner—and his mother, Dianne, an 18-year old trainee nurse.

Located 595 kilometres (370 miles) east of Perth, in the 1950s Kalgoorlie had a population around 15,000 people and was recognised as Australia's richest goldfield. It was also renowned as a hard drinking town and for the “ladies of the night”.

His parents didn't stay long. During the next four years the family moved around several locations in Western Australia before returning to Kalgoorlie briefly before finally settling in Perth in 1958. His mother had recognised that Perth had more to offer in education and the drinking culture of Kalgoorlie was not the ideal lifestyle for her family.

Marshall's first schooling in Perth was at St John's Catholic School in Scarborough, run by the Dominican nuns. He was interested in all his school's subjects and was generally a dedicated student. He didn't particularly excel at sport and was never the first to be picked for team sports. What he did have was practical, worldly intelligence from being exposed to the work of his father in all things mechanical and electrical and in his mother's involvement in nursing. He was curious about everything and a sponge for learning. In his 2005 biography he wrote:

*In school I sporadically hit the top of the class but mostly did not work hard enough to stay up there. At home I had plenty of interesting reading material. Dad always explained the car engine when he repaired it and he had many technical books so I was*

*making electromagnets by age eight as well as reading my mother's medical and nursing books. I suspect I was born with a boundless curiosity and this was encouraged through my childhood.*<sup>5</sup>

For secondary schooling he attended Marist Senior College (now Newman College) firstly at the Subiaco campus and later moving to a new campus in Churchlands. He enjoyed his experience and was especially interested in science subjects. However it was only the students in the top math class that learned biology and he missed out. 1968 was his last year at high school and by this time he had an interest in going to university to study engineering or possibly study medicine, so he applied for both.

Early in 1969 he received notification that he had been awarded a scholarship to study Electrical Engineering at Curtin University and then he was somewhat surprised and delighted to learn he had been admitted to the Medical School at the University of Western Australia.

He found the first year curriculum in the medical school to be very intense. He struggled with aspects of mathematics, physics and chemistry and had to work hard to get through the exams. Some of his friends succumbed to the distractions of university life and were among many to fail the year and ended up elsewhere. He knew this was his one chance; he was now the eldest of four children and he couldn't let his parents down when they were the ones paying for each child's education.

His major activity away from study was to enlist in the Western Australian University Regiment—the Citizen Military Forces part of the Australian Army. This earned him some pocket money from attending weekend sessions and periodic camps. During his two years in the CMF he trained to become an officer and learned some valuable lessons in how to train others and how to present to others. This experience was to give him great confidence for public speaking in later years.

After the tough first year he now found the pressure was off and he started to enjoy the comradery and antics of university life:

*My performance . . . was patchy, because you have other things on your mind once you're in university mainly the opposite sex*



*and having a few beers with your mates just to make sure that you don't get too geeky by all the study and everything you do. I think I had a pretty good balance at university and I was always interested in the subjects, but I did find it quite difficult to actually put in hours and hours intensively studying everything. So I always looked for short cuts. So if I could figure out how I could get through a subject by doing a minimal amount of study and cramming in the last couple of weeks that was usually my strategy.<sup>6</sup>*

While still undertaking his undergraduate degree, he met Adrienne, a psychology student, and the two married in 1972. As he got further into his course he began to think about his future career after graduating. He decided he wanted the challenge of helping people overcome disease.

Upon finishing his undergraduate degree in 1974, he performed internship and residencies at the Queen Elizabeth II Medical Centre in Perth. From 1977 through 1982 he held a range of registrar positions and in 1983 was awarded the Fellowship of Royal Australian College of Physicians (FRACP). It was during this period that he met Robin Warren.

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When Robin Warren said he had a list of patients with bacteria present on their stomach biopsies and needed someone to follow-up the patients to see what clinical diseases they had, Marshall's interest was aroused:

I was especially interested because one of the people on Robin's list was a woman I had seen in my ward, who had severe stomach pain but no diagnosis. In desperation we had referred her to a psychiatrist and commenced antidepressant medication for want of a better treatment. The only abnormal finding had some redness in the stomach and Robin's bacteria on the stomach biopsy.⁷

Marshall was intrigued why the presence of bacteria hadn't previously been seen by others. So he searched the past and current

literature on gastric bacteria and found that spiral gastric bacteria had been reported many times over the last century but passed over. And yet, the prevailing wisdom was that bacteria could not exist in the stomach.

At the end of 1981 Marshall designed a study to select 100 people who were coming to hospital to have stomach biopsies. Approval was granted by the ethics committee to have additional biopsies taken and the six-week program was launched early in 1982. Marshall had no trouble gaining the permission of patients to carry out these tests as he says he has a knack of communicating clearly and succinctly in a way that people can understand. It was also a double-blind study whereby the researchers would only learn about the patients after the results were processed, thus removing any chance of bias.

In order to understand more about the bacteria, Marshall needed to grow a culture. It would then be possible to conduct tests to see, for example, which antibiotics could be effective against it and to determine if ingesting the culture into an animal would cause the disease. Warren and Marshall could see that their spiral bacteria had some similarities to a known organism called *Campylobacter jejuni* but the culturing technique successfully used with this organism did not work with their new organism. It was April 1982 before they finally understood the conditions required to grow a culture. Marshall was then able to proceed to identify an antibiotic which would kill the bacteria. But there was no success forthcoming in the animal research using rats and pigs.

In the second half of 1982 he was the physician at Port Hedland Hospital, a rotation to a point 2,000 kilometres (1,200 miles) north of Perth. This gave him the chance to fully analyse the results of the study and write it up for presentation.

The results were surprising. First, the presence of bacteria was not related to any significant symptoms, only bad breath and burping. This meant that the bacteria could be present in a person's stomach and they not be aware of it. Secondly, the gastroscopy reports of patients with ulcers showed most gastric ulcers were associated with the infection, but every patient with a duodenal ulcer was infected with the bacteria.

Warren and Marshall were now in a position to tell the world. Their concern was there was nothing to stop others from making the same findings and they should make their claims first.

Marshall presented the preliminary findings to the local College of Physicians meeting in October 1982. The response was mostly negative with the objection being that the findings of a correlation between stomach inflammation and duodenal ulcers was simply wrong. This was Marshall's first real experience of evidence being ignored by the "experts" under the illusion of their knowledge—their worldview.

The next opportunity was a presentation at a meeting of the Gastroenterological Society of Australia to be held in Perth in May 1983. Their abstract was rejected, apparently on the basis it wasn't viewed as being important enough.

By this time Marshall was back in Perth working as Senior Registrar, General Medicine and Gastroenterology at the Fremantle Hospital. The medical staff were mostly supportive of the work Warren and Marshall had done, especially the staff microbiologists. While pathology is a medical specialty looking at disease processes and their cause, microbiology deals with the isolation and identification of infectious agents such as bacteria, viruses, fungi and parasites that cause disease. One of the services of clinical microbiologists is to culture bacteria.⁸ If the gastroenterologists weren't interested, maybe microbiologists could help, and indeed they did.

The Lancet is a peer-reviewed medical journal of high standing so was a good place to be published and gain credibility. The problem was their initial letters sent in January 1983—one from Warren and one from Marshall—were not accepted at first due to the lack of peer reviewers.

The bright light was being accepted for presenting at a meeting in Brussels in September, 1983. This was helped after Marshall was put in touch with Dr Martin Skirrow, a renowned clinical microbiologist in the UK. He was able to replicate Warren and Marshall's observations and was instrumental in recommending for *The Lancet* editor to go ahead and publish their letters. Their letters appeared in *The Lancet* on 4 June 1983.⁹

Marshall explained the response to writer Claudia Cornwall, author of a book on medical discoveries:

*The letters got virtually no reception. There were a few microbiologists who read them. But gastroenterologists could not assimilate it or use it. They would hardly ever treat anybody with antibiotics. Infectious disease was not what they did.*¹⁰

There were now small pockets of people who replicated and supported their work but there was still rejection by most gastroenterologists. The issue now facing Warren and Marshall was the common view that these bacteria were not the cause of stomach disease but came along after the event. If Marshall could show that the ingestion of the bacteria into a previously healthy animal resulted in gastritis and/or ulcers, then this would be proof. They tried this on rats and pigs for months but for various reasons it didn't work out.

So it was in June 1983, the same month *The Lancet* published their letters that Marshall decided to take the bacteria himself and see what happened. He felt it was possible the hospital's ethics committee would not sanction this experiment and so he proceeded with only a couple of people knowing. Even his wife wasn't aware of what he was planning to do. After undergoing a stomach biopsy to confirm he didn't already have the bacteria, he drank a broth containing the bacteria cultured from a patient with gastritis. The result was startling. Within a few days he was feeling unwell and vomiting up clear liquid. That's when he had to tell his wife what was wrong with him. Another biopsy confirmed he had inflammation of his stomach lining which was cured after a short treatment with antibiotics, much to his wife's relief. He now believed this was all the proof they needed to convince the medical establishment of that the bacteria was the cause of these stomach ailments but there would in fact be years before this happened. But to many observers, one experiment is not enough, especially when the subject of an experiment is the researcher himself.

The next major step was the publication of their joint paper in the 16 June 1984 issue of *The Lancet*.¹¹ Again there was little result other than more researchers studying the bacteria and repeating their results. The bacteria was initially called *Campylobacter pyloric* but eventually given the name *Helicobacter pylori*.

Then something interesting happened when *The New York Times* published an extensive article about the discovery on 31 July 1984.¹² This article and derivatives from it also appeared in newspapers

around the world and sparked such interest from patients suffering from gastritis and ulcers that doctors were contacting Marshall for information on how they could treat their patients. Also news of Marshall's act of infecting himself with the bacteria leaked out to the mainstream press even though a paper describing the experiment was not published until 1985.

But much more work needed to be done before acceptance would be widespread. One issue was that of finding the most effective treatment régime. Bismuth had been used to treat gastric diseases for 200 years and was also used as an ulcer treatment. The problem was that these diseases could reappear after a year or two. It turned out that the best treatment was a combination of bismuth with selected antibiotics. This took time to sort out to make sure there was no reoccurrence one or two years later. Also many in the medical profession were sceptical of previous miracle claims which failed to deliver the promised outcomes and preferred to wait. Some critics would claim that Marshall's expectation of a quick acceptance of the new approach was unreasonable and that it's to be expected that a development of this type would take many years to find full acceptance. From Marshall's point of view he was impatient and frustrated that the simple treatment of antibiotics was not being used enough and that lives were being unnecessarily lost.

Over the next few years Marshall continued to work on further aspects of the *Helicobacter pylori* organism, working both in the USA and in Australia. While Marshall had become the main driver in the ongoing research, Robin Warren still contributed to it while staying on at the Royal Perth Hospital doing the job he loved, pathology. He retired in 1997.

Their ideas were recognized officially in February 1994 when the National Institutes of Health in the US issued a "consensus statement" declaring that *Helicobacter pylori* was a gastrointestinal pathogen and that ulcer patients infected with the microbes needed antibiotics as well as anti-acids.¹³

Both Warren and Marshall received numerous awards from 1989 onwards culminating in the 2005 Nobel Prize for Physiology or Medicine.

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Warren and Marshall made the ideal combination as change initiator and change master. Robin Warren had the ability to see the anomaly of unexpected bacteria in biopsies and proceed to explore their significance in the face of disinterested colleagues. But he also knew he needed someone better equipped to follow through with further research and bring about the needed change in the treatment for gastritis and stomach ulcers.

Luckily he found the right person in Barry Marshall who could see the big picture, was a good salesman—even good salespeople face rejection from time to time—who was good at making the right connections with the wider world, and was creative and determined to bring about change to the institution that mattered—the medical profession. The story also demonstrates the problem of highly-trained medical specialists living in their “silos” and not working enough with those in other disciplines.

## Endnotes

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- [2.](#) "Dr Robin Warren, pathologist". *Australian Academy of Science*. Web. 17 Jan 2016.
- [3.](#) Warren, J.R. "The discovery of *Helicobacter pylori* in Perth, Western Australia." In: B. Marshall (ed.) *Helicobacter pioneers: first-hand accounts from the scientists who discovered helicobacters, 1892-1982*. Oxford: Blackwell, 2002. Print.
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