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Helicobacter Connections**

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After preliminary studies in 1981, Marshall and Warren conducted a study in which the new bacterium Helicobacter pylori *was cultured. In that series, 100% of 13 patients with duodenal ulcer were found to be infected. The hypothesis that peptic ulcer was caused by a bacterial infection was not accepted without a fight. Most experts believed that* Helicobacter *was a harmless commensal, infecting people who had ulcers for some other reason. In response, Marshall drank a culture of* Helicobacter *to prove that the bacteria could infect a healthy person and cause gastritis. The truth behind peptic ulcers was revealed; that is, very young children acquired the* Helicobacter *organism, leading to a chronic infection which caused a lifelong susceptibility to peptic ulcers. Marshall developed new treatments for the infection and diagnostic tests which allowed the hypothesis to be evaluated and proven. After 1994* Helicobacter *was generally accepted as the cause of most gastroduodenal diseases including peptic ulcer and gastric cancer. As a result of this knowledge, treatment is a simple procedure, and stomach surgery has become a rarity.*

1. Biographical Notes

I was born in 1951 in Kalgoorlie, a prosperous mining town 370 miles east of Perth, Western Australia. Kalgoorlie was a gold rush town which sprang up in the desert after the Irishman paddy Hannan struck gold there in 1892. At the time I was born, my father was 19 years old and in the final year of his apprenticeship as a fitter and turner. My mother quit her nursing training to have me at the age of eighteen years.

We moved quite a bit through my early childhood. After my father finished his apprenticeship, my parents decided to go and work in the new uranium mine in Rum Jungle in the Northern Territory. They drove their Model A Ford up Australia's west coast about 1000 miles, but stopped at Carnarvon when the car broke down. The whaling station at Carnarvon was also offering excellent wages for good tradesmen, and my father was one of the best. We lived near the whaling station while I grew from two to four years, and my brother William was born there. My first memories are of life in Carnarvon. I recall a boat trip back to Perth on one occasion and a DC-3 aeroplane flight to Perth on another. Our house was on Babbage Island about 100 yards from the beach. We had electricity, an outhouse toilet, dirt floors in parts of the house, a telephone, a refrigerator, a car, a cat, and a dog. Nearby was a derelict steam engine on a railway siding. We had neighbours close by and other kids to play with.

By then, my grandparents had the license on the Tower Hotel in Kalgoorlie, and periodically we would return there to live. In Kalgoorlie I remember doing all kinds of things as a six- and seven-year-old including making bows and arrows, slingshots, and lighting crackers after school.

After a period back in Kalgoorlie, my mother decided to move the family to Perth where my second brother, Andrew, was born in 1958. I was seven years old at the time. I suppose my mother could see the young boys in Kalgoorlie leaving school at 16 and going down the mines to work. It was an attractive proposition for them. They earned high salaries and had a wild social life drinking and partying on their off days. She wanted more for her children and hoped we would study and enter a profession. Moving to the city was the first step. We are lucky she made that decision. My two brothers and sister all went through university and have highly successful careers and happy lives.

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 mothers medical and nursing books. I suspect I was born with a boundless curiosity and this was encouraged throughout my childhood.

Being the eldest of four children, I was expected to be the responsible one and often found myself controlling two younger brothers who shared my exuberant and inquisitive nature. I still feel guilty about the time I advised my younger brother to jump out of a tree, and he broke his arm.

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My first exposure to fame came at age twelve when I was left in charge of the younger siblings while my mother attended to the grocery shopping. I had a history of responsible baby-sitting by this time, so nothing should have gone wrong. During the morning my 18-month-old sister found a milk bottle half full of kerosene and drank some, perhaps also aspirating a little so that my brothers and I found her choking but did not know why. I called the emergency services and an ambulance arrived about fifteen minutes later. During the wait, as I had learned some basic CPR at the Royal Lifesaving Society Swimming training, I tried to perform mouth to mouth resuscitation on my little sister. I know now that it was pointless because she was actually still breathing. However, my close mouth contact enabled me to smell the kerosene and make the diagnosis of poisoning. I featured in the newspaper a few days later, with my fully recovered little sister on my lap. It was a good story about how to call the emergency number, and why you should not put poison into drink containers. Very kindly my mother did not leak to the press the fact that it was I who had left the kerosene within reach of young Marie!

In our dad's shed, my brothers and I had access to all the tools needed to build or dismantle anything. I frequently got into trouble doing both. My favourite book as a child was an old Newne's Children's Encyclopaedia, which my grandfather had bought just before World War II and donated to our family after seeing how interested we were in it. Each volume had special chapters called "Things Boys can Do". My brothers and I would pick out interesting projects. As the years went by and I grew up, I recall building a slingshot, a crystal set, a Morse-code set, various guns, a hydrogen generator for balloons, electric devices, and minor explosives. In those days fireworks had been banned, but chemicals were easily available from pharmacies and chemical suppliers so, in the tradition of Alfred Nobel, we would create various explosive mixtures and make firecrackers and bombs. This started rather benignly with simple gunpowder but graduated to more dangerous oxidising agents after a few years. Many times we were in trouble after disturbing the neighbours, but were fortunate never to cause serious injury. I often found myself in trouble with my parents when someone was hurt, but despite the minor punishments, I know my parents were quite proud of my ingenuity.

Occasionally my father, Bob, was on the receiving end of my "brilliant" work. Observing a fraying cord on his electric drill, I repaired it but accidentally swapped the neutral and earth wire. He jumped rather high when he tried to use it a few days later while standing on wet grass. On another occasion my brothers decided to fly lighter-than-air balloons for our team at the school sports carnival. Since helium was not available, we built a device which pressurised domestic house gas and filled the balloons. Our technology was rather primitive, however, and these balloons contained quite a bit of air as well, but they did float satisfactorily. My father recognised this and warned us that they might be a little dangerous if they came in contact with an open flame. As an example, he demonstrated the risk by touching a lighted cigarette to one of the balloons as it floated under the back patio. He was enveloped in a ball of flame and his eyebrows were singed off. This did not worry us very much because we had seen him in this state before, as he often seemed to be washing engine parts in gasoline and then testing the spark plugs of engines nearby.

After high school at Newman College, although interested in science and mathematics, I felt that my mathematical ability was not strong enough to do electrical engineering, so I chose medical school as an alternative that was at least as interesting, and which did not require daily exposure to calculus! In addition, the opportunity to study biological sciences was an attraction, particularly biochemistry, which was not available in high school.

I met my wife Adrienne, a psychology student, at the University of Western Australia, and we married in 1972 while I was doing my fifth year in medicine. I graduated from the university MBBS (Bachelor of Medicine, Bachelor of Surgery) in 1975 and thereafter performed internship and residencies in internal medicine at the Queen Elizabeth II Medical Centre (Sir Charles Gairdner Hospital). In those days I had no definite goals in medicine, but was interested in all aspects of clinical medicine including geriatrics, oncology, and rheumatology. I was more interested in an academic career combining research with clinical medicine in a university hospital environment. I began my training as a specialist physician in 1978. In 1979 I moved to Royal Perth Hospital in order to become more experienced with cardiology and open heart surgery, which was only performed at that hospital in Perth.

Although we didn't appreciate it at the time, my wife Adrienne and I must have been very busy during those years. We had four children, Luke, born in 1973, Bronwyn in 1975, Caroline in 1978, and Jessica in 1981. Adrienne was finishing the honours year of her psychology degree as Luke was being born. She was working in between babies as a counsellor with the Education Department. My non-medical time was spent delivering children to various child-minding facilities, renovating our house, and indulging in my hobby of computers and electronics. In the second half of 1981, my rotation took me to the gastroenterology division. It was there that I met Robin Warren. As part of my training I was encouraged to perform a clinical research project each year. I was already totally engrossed in a study of heat stroke in "fun runners" and might have progressed to sports or environmental medicine from there. However, I asked my boss, Dr. Tom Waters, if there was a gastroenterology project I could start. He told me that Robin Warren had given him a list of patients with curved bacteria present on their stomach biopsies and needed someone to follow-up the patients to see what clinical diseases they had. 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.

So I called Robin in the basement area of Royal Perth Hospital where the Pathology Department resided. It was to be the first of many afternoon visits in the next year. In those days, Robin used to drink strong black coffee and smoke small

cigars, "cigarillos" I believe they were called. I too used to indulge occasionally, and would try out one of Robin's cigars from time to time during our meetings. In our first meeting, Robin showed me slides of the curved bacteria he had seen, and explained the histopathology of the gastric mucosa to me.

I am often asked what made me listen to Robin and take up the research with him. Clearly this was an interesting thing to study, previously undescribed bacteria living in the acid-filled stomach. But I may have had other advantages compared with colleagues Robin had approached over the previous two years.

I was undifferentiated in that I wasn't coming from a background in gastroenterology, so that my knowledge and ideas were based and founded in general medical basic science rather than the dogma one was required to learn in specialist medicine. As a trainee general physician with broader training, I was comfortable with the notion of infectious disease and antibiotic therapies. I am told by others that I have a lateral thinking broad approach to problems, sometimes to my detriment. In school my grades always suffered because I was continually mucking about with irrelevant side issues which I often found to be more interesting.

Also around that time, I was aware of publications in the literature describing *Campylobacter jejuni* as a newly discovered common cause of food-borne gastroenteritis and colitis. Thus, I had seen pictures of campylobacters and could identify that Robin's organisms appeared to be quite similar. In retrospect, one advantage of doing this research in Perth was that, as a modern Western society, *H. pylori* was already in decline by 1981, so that rather than 80% of persons having the CLO, bacteria were only present in 30–50% of the population. Thus, in any biopsy collection taken that year, Robin could see both infected specimens with inflammation (gastritis) and uninfected specimens, which hardly ever had gastritis, i.e., a "control group". A further advantage I did have in 1981 was the new connection we had from the medical library to the National Library of Medicine at the NIH (Medline). Perhaps because of my interest in computer programming, this resource appealed to me and enabled me to enlist the librarians at Royal Perth Hospital to extensively search the past and current literature on gastric bacteria.

By the end of that first afternoon with Robin I was very interested. Over the next six months I followed the literature from book chapters, to their references, to deeper references, to material in library archives. I found that spiral gastric bacteria had been reported again and again but had been passed over. I could see an interesting paper being produced, perhaps in an obscure microbiological journal, but had no idea at the time of what we were really about to discover.

At the end of 1981, my gastroenterology term had almost finished, and my term allocations for 1982 had been chosen. In the midst of all this time-consuming and interesting research work I was still a physician in training. I was fitting in the research around education and patient commitments. In the first six months of 1982, I was to be a haematology registrar looking after the bone marrow transplant patients. In the second six months, I was to be the physician at Port Hedland Hospital, a rotation to a point 2000 kilometres north of Perth which attracted a "hardship bonus", i.e. $5000 extra over six months. By then, I was very excited about the spiral bacteria. I had developed a degree of confidence in our methodology, and believed that we could safely carry out a study on 100 or so patients. I was able to keep the work going, continuing the research by fitting it around my other duties.

In November 1981, Adrienne had delivered our fourth child, Jessica. I was beginning a project which would occupy every minute of my spare time for the next six months. Adrienne was on maternity leave and was full time at home. It meant I could leave much of the parenting to her. We never did find the time to complete our home renovations and at the last minute in 1986 we took out an extra home loan to pay someone to finish it for us. We had to have it in a rentable condition while we were in the USA.

I was fortunate to have a partner who was as enthusiastic about the work as I was. She also enjoys a challenge and shares my sense of adventure. Adrienne's background in psychology and experimental research was invaluable, and she was always around to discuss the design of studies and the results of various other research works I had found. Over the years we took lots of chances. I took jobs on inadequate pay for many years. As my contemporaries were making their careers and achieving success, I seemed to be falling further behind. I always had Adrienne's full support. When she urged caution or vetoed some of my excesses, I knew it was time to really listen and re-evaluate. As time went on, she became my unofficial editor. All my early papers were edited by her and she helped with much of the discussion. Her liberal arts background means she is a more fluent writer than I. Over the past 25 years she has also helped to write and edit most of my books and speeches. All of the talks and speeches given in Stockholm were written with her substantial help.

My hobby of electronics was also an important aid in my research. In the evenings during 1981, I continued with my hobby of computing and electronics, so that by the end of that year I had completed the construction of a home computer capable of word processing. I was able to type grant proposals, consent forms, and protocols. I was always on the leading edge of technology, and my communication with overseas researchers was efficient because of that. It also meant I was able to access information not readily available. By 1981 I could function better as a single unfunded scientist than many units with multiple support staff.

The family moved to Port Hedland in July 1982, and I took all my references and textbooks with me. It was an important period. I had time to do an extensive literature search by correspondence and also had time to digest the results of our study and write it up for presentation. It was a great time for the family too. Winter in Port Hedland was beautiful, every day sunny with a temperature in the 80s. We had a bit of extra money, and we spent many weekends travelling in remote communities and camping with the kids under the stars.

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. I had success-

fully completed my training as a physician and now wanted to work in gastroenterology or microbiology to continue the work. These jobs at Royal Perth were not available.

Fortune stepped in when I was approached by Drs. Norm Marinovich and Ian Hislop at Fremantle Hospital who suggested they would find me a senior registrar position and fund me to continue. Fremantle is the third and smallest of the teaching hospitals in Perth and has a tradition of openness and experimentation. In the next two years at Fremantle I had an enthusiastic group of people working with me: Ian Hislop, Norm Marinovich, Harvey Turner, David McGechie, Ross Glancy, Neil Noakes, Graeme Francis, Peter Rogers, Neil Stingemore, as well as great support from the Medical Superintendent, Peter Smith. The only downside of the appointment was that I was forced to halt my collaboration with Robin Warren. Robin did not have an appointment at Fremantle, so the pathologist there, Ross Glancy, joined the team.

They were happy and very productive years. I was able to confirm very quickly that our observations of the bacteria at Royal Perth Hospital also applied in other parts of the city; the majority of peptic ulcer patients had the organism. I was still officially unfunded. The hospital was picking up all the costs of my work. It was at Fremantle in those two years that the first effective treatments were devised. I solved the conundrum of why bismuth has been such an effective stomach treatment for the past 200 years. I did my famous self experimentation, and the early urease tests were developed.

A great piece of luck in early 1983 was finding Dr. Martin Skirrow in the UK. I got his phone number from David McGechie. Skirrow arranged for the first presentation at the European Campylobacter Meeting in September 1983. Harvey Turner arranged a travel grant to take me to Brussels and the Gist Brocades Company helped so that I could extend the trip, visit Martin in the UK and Guido Tytgat's group in Amsterdam.

In September 1983, I visited Martin Skirrow in Worcester England, and attended an endoscopy session at the Worcester Infirmary. Martin's registrar, Cliodna McNulty, was able to successfully isolate the organism three days later, showing that the spiral bug was not merely an Australian phenomenon, but was present in ulcer patients in the UK as well. Martin Skirrrow in Britain and Adrian Lee in Sydney were enormously encouraging, helping me with the microbiology in those early years.

Therefore, in 1984 there were several groups around the world obtaining results which paralleled those of our group in Perth. In Australia, Adrian Lee in Sydney with Stuart Hazel and Hazel Mitchell as well as Nick Talley, John Lambert, and Tom Borody, were early researchers who made significant advances in the *H. pylori* work. After the Brussels meeting, a core of researchers in Europe immediately picked up the research, and much of the most important work on *H. pylori* has been done by that group: my old friends, Mario Quina in Portugal, Tony Axon and Ashley Price in the UK, Francis Megraud in France, Peter Malfertheiner in Germany, Manuel Lopez Brea and Jose Pajares Garcia in Spain, Penti Sipponen in Finland, Dino Vaira and Giovanni Gasparini in Italy, Colm O'Morain in Ireland, Leif Andersen in Denmark, Alexander Hirschl in Austria, Guido Tytgat, Ernst Kuipers and Erik Rauws in The Netherlands, Michel Deltenre in Belgium, Pierre Michetti in Switzerland, and Torkel Wadstrom and Lars Engstrand in Sweden. We became a closely knit group. The European group grew out of the campylobacter group I had met in Brussels in 1983, and today I count the members of that group amongst my closest friends. We have shared a remarkable story together.

In the USA David Graham, Pete Peterson, and Martin Blazer began as critics. They set out to disprove the hypothesis, but quickly became leaders in the field of *H. pylori* research in the USA. With Tadetaka (Tachi) Yamada, although he was not directly involved in the *H. pylori* research, they played an important role in moving various bodies such as the NIH towards action and acceptance of *H. pylori* as an ulcer cause. In Asia, Takashi Shimoyama, Ken Kimura, Susumu Okabe, Yoshihiro Fukuda, Toshio Fujioka, Bow Ho, and K. L. Goh were doctors who I was in contact with through the 1980s. They were developing their own *H. pylori* research and supporting mine. In Asia, the *H. pylori* research was taken up very quickly, and I made my first visit to Japan in 1985 to present my work. There are too many others to list here. Needless to say, reports that I was alone in the promotion of *H. pylori* as a pathogen are somewhat exaggerated.

1984 was a difficult year, however. I was unsuccessfully attempting to infect an animal model. There was interest and support from a few, but most of my work was rejected for publication, and even accepted papers were significantly delayed. I was met with constant criticism that my conclusions were premature and not well supported. When the work was presented, my results were disputed and disbelieved, not on the basis of science, but because they simply could not be true. It was often said that no one was able to replicate my results. This was untrue, but became part of the folklore of the period. I was told that the bacteria were either contaminants or harmless commensals.

At the same time I was successfully experimentally treating patients who had suffered with life-threatening ulcer disease for years. Some of my patients had postponed surgery which became unnecessary after a simple two-week course of antibiotics and bismuth. I had developed my hypothesis that these bacteria were the cause of peptic ulcers and a significant risk for stomach cancer. If I was right, then treatment for ulcer disease would be revolutionized. It would be simple, cheap, and it would be a cure. It seemed to me for the sake of patients this research had to be fast-tracked. The sense of urgency and frustration with the medical community was partly due to my disposition and age. However, the primary reason was a practical one. I was driven to get this theory proven quickly to provide curative treatment for the millions of people suffering with ulcers around the world.

Becoming increasingly frustrated with the negative response to my work, I realized I had to have an animal model and decided to use myself. Much has been written about the episode, and I certainly had no idea it would become as important as it has. I didn't actually expect to become as ill as I did. I didn't discuss it with the ethics committee at the hospital. More significantly, I didn't discuss it with Adrienne. She was already convinced about the risk of these bacteria, and I knew I would

never get her approval. This was one of those occasions when it would be easier to get forgiveness than permission. I was taken by surprise by the severity of the infection. When I came home with my biopsy results showing colonization and classic histological damage to my stomach, Adrienne suggested it was time to treat myself. I had a successful infection, I had proved my point.

At the end of 1984 I was funded by the Australian Medical Research Council to conduct a prospective double-blind trial to see if antibiotics could cure duodenal ulcers. It was conditional on getting a large number of patients into the study, so I decided to move back to Royal Perth Hospital where the patient load is far higher. It meant I would be leaving my Fremantle colleagues, and it was with some reluctance that I moved. When I returned to Australia in 1996, I was asked to be Patron of the Fremantle Hospital Research Foundation, and I take great pride in having that position. At Royal Perth I was again working with Robin, John Armstrong, Len Matz, John Pearman, Stewart Goodwin, Doug Annear, and Helen Royce.

Even though I was not officially collaborating with Robin when I was working at Fremantle Hospital in 1983–84, we still met to discuss the papers we were writing for *The Lancet* and would meet for dinner with our wives. We had one of these dinners only a few weeks after my self experimentation. I was enthusiastic about the results and the severity of my illness. It was also the first confirmation of infection with documented results. I was eager to share the news with Robin, and he was equally excited about it. Early the next morning he had a call at 5:00 from a journalist in the USA who had his timing totally off. No one is ever able to figure out what time it is in Perth. When asked the usual question about "How do you know it's a pathogen and not a harmless commensal?" Robin blabbed the results of my still unreleased work with, "I know because Barry Marshall has just infected himself and damm near died"; a slight exaggeration, but it made for good copy. What he didn't know was that the journalist he was speaking to was from the *Star* newspaper, a tabloid that often features stories about alien babies being adopted by Nancy Reagan. This was right up their alley. The next day the story appeared, "Guinea-Pig Doctor Discovers New Cure for Ulcers…and the Cause".

This became one of the serendipitous, life-changing events in my life, and I have Robin's temper to thank for it. Firstly, I was contacted by a continuous line of patients in the USA who read the story and were desperate for treatment. I was able to help. I was treating patients by proxy in the USA as early as 1984. Ten years later this became important in a dispute with another doctor who claimed to be the first. I still had the records from some of these patients and was able to get in touch with them to prove my claim to be first.

The second result was that it was read by Mike Manhart, a microbiologist working for Proctor & Gamble in the USA. He tracked down my published letters and realized the economic potential for P&G, who made a bismuth drug and set up a business relationship. P&G later patented much of my work and also helped me with patents on my diagnostics. There was little money in any of this for the first 10 years, but after 1995 it became a significant income for us. P&G funded a fellowship for me in the USA to replicate and push the research there. We departed Australia, believing that it shouldn't take more than 2–3 years to convince the world that antibiotics would cure most gastric diseases.

It also brought Bruce and Claudette McCarty into my life. Bruce was head of Health and Personal Care products at P&G and became an important mentor. He arranged support funding to set up a lab at the University of Virginia. Bruce became a good friend and a keen advocate for *H. pylori* research in the USA. He taught me a lot about how business works best in a trusting and responsible way to benefit everyone. It also seemed to me that he and Claudette spent lots of time in their life just having fun with family and friends. Tragically, Bruce died in 2004. It was a great sadness for me and Adrienne that he and Claudette were not there in Sweden to see me receive the prize. He always believed in me, and his faith in the work and great enthusiasm never failed.

The 10 years spent at the University of Virginia were a chance to extend my research, particularly in the area of treatment and diagnostics. I became an advocate for treatment, though many called me a zealot. They were often hard years for the family, particularly the first few years when we were on a financial shoestring. They were rewarding as well. I had a continuous stream of letters from patients who had been treated and freed from a lifetime of pain and disruption. I worked with a great team at UVA. Richard McCallum was head of Gastroenterology and Dick Guerrant in Infectious Diseases. McCallum gave me free rein and sponsored my academic rise in the USA. I also did great collaborative work with Dick over the years. David Peura, a long-time *H. pylori* enthusiast from the US army moved to UVA in 1992. My team included nurse Susie Hoffman, nuclear technician Michael Plankey, post-doc Matthew Coombs, data manager Linda Mosen, programmer Sherry Boyd, assistant Nancy Noblette, and many others. We were regarded as being outside the mainstream, but were a great enthusiastic group and became lifelong friends.

I also met Bill and Sandy Fry in 1987. Bill owned a company called Tri-Med along with Phil Patterson and Kevin Dye. Bill Fry bankrolled a US-based study for my CLOtest diagnostic and launched it in the USA. Later he would pick up the C-14 Urea Breath Test and shepherd it through the FDA at a cost of several million dollars. I count Bill amongst my closest friends, a brilliant salesman and an example of a team leader. No matter how black things looked, Bill could always find a silver lining for us even though I am certain he was secretly concerned about our chances of success. Bill's credo which he lives by is that "Good things happen to good people". We have done a lot of good stuff together and had many great times.

Patients often wanted to make a donation to the work, so I set up a foundation to use the money for patient and doctor education about the research. On one occasion there had been a story about the cure in the Sunday papers across the USA. In the following weeks we received 30 000 letters, all with donations of a dollar or two to pay for postage and photocopying of information. We had to hire in students to handle it all.

Over the years the journalists who covered the story helped significantly in educating the public to ask for and later demand the new treatments from unwilling doctors. Suzanne Chazin at the *Readers Digest*, Terry Monmany at the *New Yorker*, Mark Ragg at the *Bulletin* and Larry Altman at the *New York Times* all wrote detailed reviews of the work that became important sources of information. The BBC show "Ulcer Wars" produced by Michael Mosley is still shown around the world.

The tide of acceptance began to turn in the early 1990s, and by 1992 I could go to meetings and receive as much praise as criticism. 1994 was a watershed year for us. In February 1994 the NIH held a consensus meeting in Washington DC which ended after two days with a statement to the effect that the key to treatment of duodenal and gastric ulcer was detection and eradication of *Helicobacter pylori*.

I had been waiting 10 years for this day, and I felt a combination of relief and satisfaction that I had achieved what I set out to do. Years before, I had developed the hypothesis, tested it, proved it, and now it had reached official acceptance.

The next year proved to be harder. I began to receive awards and recognition. At the hospital, I was still carrying a full load of patient care and research. However, I was increasingly dissatisfied. Much of my time was being spent attending meetings and travelling. I think the pressure of the previous 10 years was beginning to show. Because I had been so involved in the exponential rise of *Helicobacter*, I had been unable to update my training in new areas of molecular biology, which by then were coming to represent a large proportion of the *Helicobacter* publications.

In typical fashion, Adrienne took over the decision-making, and at the end of 1994, I took a year of leave from the university. We cashed in my superannuation and decided to live on that for a year to figure out what would be next in our lives. In that year I still travelled and lectured, but my primary work was with Tri-Med and getting the breath test through the FDA regulation process. I am proud of my diagnostics tests, the CLOtest and PYtest. They are often my forgotten children, eclipsed by my work on treatment. Although less glamorous than high-impact papers, reliable, cheap and available diagnostics are just as important in medicine as treatments. They don't always get the same recognition. After 1994 my business interests became more important. The diagnostics were starting to earn an income. In Australia, close friend Rod Blechynden took on the role of managing it for me. Rod and Adrienne now take care of the business aspects of my work. Their work frees me to focus on my research.

Once I had completed that project, Adrienne decided it was time for us all to go home. I was still unsure, but it has turned out to be the best decision for me and the family. We moved back to Perth in 1996. I was awarded the McFarlane Burnett Fellowship, which funded my lab at the University of Western Australia for a five-year period. In 1998, Tri-Med USA bought the manufacturing rights to CLOtest. I was keen to keep the manufacturing in Western Australia. It has been a long-term ambition of mine to develop industry here in Perth; I set up a new manufacturing facility here. Sadly it didn't last. Tri-Med in the USA was later sold, and the new owners moved all the manufacturing back to the USA. Tri-Med in Perth continues in a small way, doing R&D and selling medical products.

In conclusion, I want to acknowledge all those scientists who failed to recognize *H. pylori*. Without them, I would have had a very different career. Some of their stories are described in my book "Helicobacter pioneers". I also want to thank Irvin Modlin for the forward he wrote for it. He is a great guy, and was able to say things about the joy of scientific research that I never could.

One of the truly great things about winning the Nobel Prize in 2005 was that I was living and working back home. I got to share it and celebrate with those who had been involved in the initial work at Royal Perth and Fremantle Hospitals.

I continue to live in Perth, Western Australia. I have an appointment at the University of Western Australia and still see patients at the gastroenterology department at Sir Charles Gairdner Hospital. My other interests continue. I take an active role in Tri-Med, and in 2005 I began a new project with vaccine company Ondek.

There were many occasions when luck played a role in my life: meeting with Robin, the first culture of the bacteria, and chance meetings with many people who helped me and collaborated with me. I look back and am grateful to the many friends and family who helped me along the way, most importantly my wife Adrienne, my children, their partners, and my grandchildren.

2. Introduction

The title "Helicobacter Connections" refers to the two components of our discovery. Firstly, we were able to associate a new bacterium with peptic ulcer disease. Secondly, we could see that the new bacteria could explain many phenomena observed by other gastric researchers over the previous 100 years. By connecting this literature with our own observations, we were able to confirm our hypothesis rather quickly. As a result, other researchers were often dismayed at our supreme confidence that these new bacteria were serious pathogens and that antibiotics would provide a cure for peptic ulcer.

To quote historian Daniel Boorstein: "The greatest obstacle to knowledge is not ignorance; it is the illusion of knowledge". The relevance of his quotation is that in 1982 the cause of peptic ulcer was "already known". Ulcers were caused by excessive amounts of acid secondary to personality, stress, smoking, or an inherited tendency. The successful introduction of H2 receptor antagonists (H2RA) five years earlier seemed to confirm this idea because nearly all ulcers could be healed by lowering stomach acid secretion with these drugs. Thus, when *Helicobacter* was revealed, doctors were not looking for a new cause of peptic ulcer; that territory had already been taken by the illusion of knowledge.

3. Background

Figure 1 shows photographs of peptic ulcers taken at endoscopy. The upper diagram indicates the usual locations on a map of the stomach. The most common type of peptic ulcer is

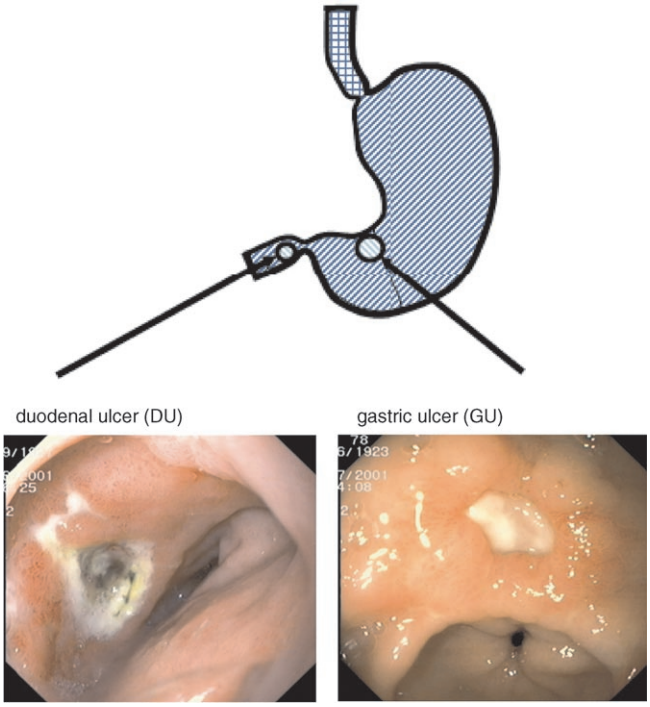

Figure 1. Typical appearance of peptic ulcers.

located in the duodenum, a few centimetres past the pyloric sphincter, which controls the outlet from the stomach. In the photograph, a dark area on the duodenal ulcer shows that this has already eroded into a blood vessel, and bleeding has occurred. Vomiting of blood is one of the major symptoms of an ulcer, sometimes with a fatal outcome if a large enough artery is eroded. Duodenal ulcers usually cause some stomach pain, typically during the night after the evening meal is digested. This is not always true however, and some people can suffer a fatal ulcer complication without any warning that an ulcer is present.

The second photograph is of a gastric or stomach ulcer. This shows the common appearance with a scarred white ulcer base, kept rather clean-looking by the digestive juices. However, it can easily be seen how this ulcer, if it was deeper, could penetrate all the way through the wall to allow gastric contents to leak into the peritoneal space, causing fatal peritonitis.

Although peptic ulceration can occur at any age, it typically develops in adulthood with a peak incidence above the age of 40. Ulcers are more common in men and cigarette smokers and tend to run in families. Once begun, ulcer disease lasts many years, with an unpredictable tendency toward healing and recurrence. From postmortem studies, peptic ulcer was known to affect 10% of the population at some time during life. According to data from the Centers for Disease Control in Atlanta, the cost of peptic ulcer in the USA in 1993 was close to six billion dollars per annum (Table 1).

It just seems impossible to imagine these days that ulcer sufferers lived their lives with the possibility of suddenly being struck down with a potentially fatal illness. This explains why it was possible to sell very expensive treatment to people with ulcers once an effective treatment was marketed. This treatment became available with the discovery of the H2RA drugs, the first two of which were cimetidine (Tagamet) and ranitidine (Zantac).

Table 1. The costs of peptic ulcer.[a]

Americans affected[b]	1 out of 10
Hospitalizations[c]	1 million
Deaths[c]	6500
Hospitalization costs[c]	US$ 3 billion
Physician office visits[c]	US$ 2 billion
Decreased work productivity[c]	US$ 1 billion
Total annual costs[c]	US$ 6 billion

[a] Centers for Disease Control, Atlanta (USA) 1993. [b] During lifetime. [c] Per year.

By 1983, Smith Kline & French was making a billion dollars per year from Tagamet. Zantac, the second drug in the H2RA class, was destined to sell more than three billion dollars per year for most of the 1980s. The only other way that ulcers could be controlled medically was with white chalky antacid, and the amount needed to heal an ulcer reliably was about a bucketful taken over four weeks. Cure of ulcer disease required removal of the lower third of the stomach by surgery. However, about 10% of patients treated with surgery became "gastric cripples", unable to enjoy food for the rest of their lives, with chronic gastrointestinal symptoms and difficulty maintaining normal body weight.

In an article from that era in Fortune Magazine, Joel Dreyfuss called Tagamet "the pale green pill that cures ulcers", but this was an overstatement because the ulcers almost always recurred once the drug was stopped. Thus cimetidine was a treatment, not a cure. By 1983 it was clear that for most ulcer patients, lifelong treatment was going to be necessary.

4. The Pilot Study, 1981

Beginning in about August 1981, I took over the clinical studies for a list of patients with the new bacteria. An initial chart review of Robin Warren's 27 best cases did not reveal any obvious associations between the bacteria and clinical disease. However, I did notice an old patient of mine, a 50-year-old woman with undiagnosed abdominal pain in whom the bacteria had been the only abnormal finding.

Then, assisted by colleagues Tom Waters, Chris Sanderson, and gastrointestinal nurse Dorothy Heys, I collected gastric biopsy specimens from patients attending for endoscopy. Since the histology of ulcer borders was often disturbed and always inflamed, Robin instructed us to sample the stomach wall (mucosa) a few centimetres away from ulcers or local gastric lesions, so that tissue would be representative of the antral mucosa in general and it could be assessed for presence of gastritis. In retrospect, these specimens were quite different from specimens of most other studies because if gastritis was present, it could not have been attributed to a nearby ulcer. One biopsy was taken for histology and one for microbiology. Robin had special stains performed on his histology specimen and John Pearman, our microbiologist, supervised attempts to

Gram-stain the tissue and culture the organism. Except for the early days of our pilot study, I did not send clinical data with the tissue specimens. Thus, in most cases, histological scoring was performed without any knowledge of the endoscopy findings. Conversely, I did not see the individual results of the laboratory analyses until much later.

5. Previous Literature on Spiral Bacteria

While these activities were in progress, I searched the literature in greater depth. Following some initial leads Robin had given me, I rediscovered several reports of spiral bacteria in animals and humans. It was apparent that the new spiral organism was not just a strange infection occurring in Western Australia, but was the same as the "spirochaete" which had been described in the literature several times in the previous 100 years. I was particularly interested in old reports from the USA. In 1940, Stone Freedberg from Harvard Medical School had seen spirochaetes in 40% of patients undergoing stomach resection for ulcers or cancer. About 10 years later, the leading US gastroenterologist, Eddie Palmer at Walter Reid Hospital, had performed blind suction biopsies on more than 1000 patients but had been unable to find the bacteria. His report concluded that bacteria did not exist except as postmortem contaminants.

Most of the old references to gastric bacteria had not connected spiral organisms to any significant disease process. The best example of such an observation was an electron micrograph taken by Susumu Ito which he included in his chapter for The Handbook of Physiology.[1] Reproduced in Figure 2, Ito's illustration shows a detailed view of *Helicobacter pylori*, with flagella present on one end. I later discovered that to obtain this specimen Ito had performed a blind suction biopsy of his own stomach. He had seen similar organisms in cats, where they were almost universally present without any associated pathology. As a result, he assumed that the human organism from his own stomach was also a commensal. Ito could not have known that in his generation almost all Japanese were infected with *Helicobacter*. According to many other studies around that time, gastritis was so common as to be a "normal" appearance in Japanese, the population that also suffered from the world's highest rate of gastric cancer. From Ito's and Freedberg's reference lists, other reports of gastric spirochaetes in animals and humans were obtained, dating as far back as that of Bizzozero in 1892.[2]

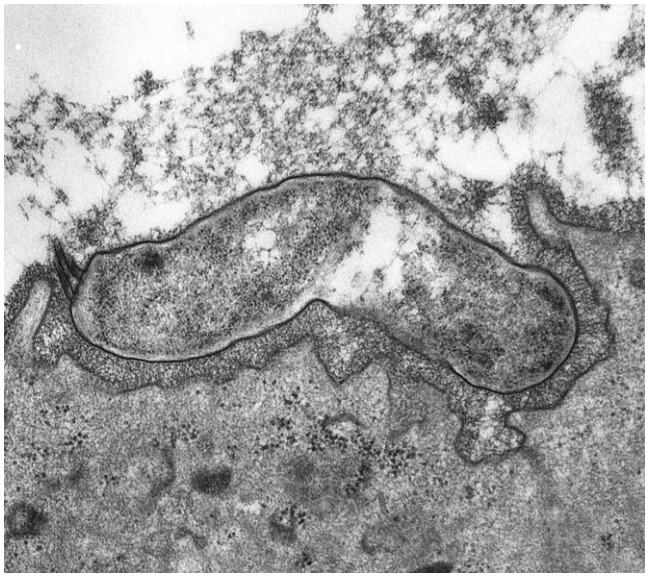

Figure 2. Susumu Ito, an anatomist in Boston, swallowed a suction biopsy instrument and sampled his own stomach to reveal the organism shown above. The smooth bacterial cell wall, sheathed flagella and proximity to the epithelial cells identifies it as *Helicobacter pylori*. Ito believed that spiral bacteria in the stomach were normal for humans, as they appeared to be in cats and dogs. He could not have known that in the 1960s almost all Japanese adults carried *H. pylori*.

In our initial series taken during the latter half of 1981, we could easily see the bacteria on Gram-stained smears of gastric tissue, but we were unable to culture them. My gastroenterology rotation was due to finish on December 31st, but my colleagues supported the idea of a prospective study, in which further attempts could be made to culture the bacteria and look for disease associations.

6. Prospective Study, 1982

Toward the end of 1981 I wrote the protocol for a prospective study of 100 consecutive elective endoscopy patients. The documents were submitted to the Royal Perth Hospital Human Ethics Committee at the end of that year so that the study could begin before March 1982.

I chose 100 patients simply because in the days before computer spreadsheets it allowed percentages to be easily calculated when we wrote the paper. The aims of the study were to determine the prevalence of the bacteria in an endoscopy population, to try to culture the organism, to see what diseases were associated with it, and to detect an infection source if there was one.

During the first half of 1982 I was actually a medical registrar in the hematology service, but I was able to fit in the study activities around my new duties. In addition, I was also conducting a study of heatstroke in marathon runners, so I was very busy.

For the new project, I would stay at the hospital each evening to interview inpatients who were due for endoscopy the next morning starting at 7:30. I would arrive early in the morning so that I could interview the new outpatients at 8:00 as they were being prepared for their endoscopies.

For each patient I was required to explain the study and then have them sign a consent form so that biopsy samples could be taken. I then asked 30 or so questions related to lifestyle, pets, travel, occupation, medications, dental hygiene, gastrointestinal symptoms, and medical conditions. Finally, I looked in their mouths to briefly assess the state of their oral hygiene and dentition.

I considered many explanations for the apparent commonness of the new bacterium. How did these bacteria get into the stomach? Could it be that people were taking cimetidine, lowering their acid level, and then being infected? Did the bacteria live in the mouth as part of the normal flora? Could

poor oral hygiene and periodontal disease be a risk factor? I asked every kind of question I could think of about dentition. I asked patients, "How many teeth do you have, and how often do you clean your teeth?", and I heard some pretty extreme answers! By my reckoning, a person who has no teeth and never cleans his teeth has good dental hygiene—but his teeth are gone. I asked questions related to diet, travel, pets, and medication.

During the ensuing endoscopy, Dorothy Heys, an important ally of mine, would remind the gastroenterologist to take two extra antral biopsies from a location away from any local lesion. The gastroenterologist would then complete the endoscopy report. During morning tea break and at lunch time I would collect the various biopsy specimens and deliver them to the pathology and microbiology labs for processing.

At the time I wrote the study protocol, I had no preconceived notion as to what diseases might be associated with the bacterium. Therefore, the main goals of the study were to understand the histology and microbiology rather than to discover the cause of peptic ulcer. However, in June, long after the endoscopies of the 100 patients had been completed, I obtained all the reports and coded these for the main endoscopic diagnoses. Diagnostic categories were simplified to include duodenal ulcer, gastric ulcer, gastritis, duodenitis bile in the stomach, cancer, oesophageal disease, and "other".

7. The First Culture: April 8–13th, 1982 (Easter)

At the time we started our studies, *Campylobacters* were very new. Harrisson's Textbook of Medicine only included *C. fetus* as a human pathogen, although *C. jejuni*, a contaminant of fresh chicken carcasses, had been recently described in the English journals as a cause of gastroenteritis. So our culture methods focused around techniques for similar organisms, generically called "*Campylobacter*-like organisms" (CLOs). We used the "Lee method", which is a microaerophilic culture technique necessary for *Campylobacter*. Professor Adrian Lee, a chicken specialist at the University of New South Wales in Sydney, had reported culturing spiral bacteria from the mouth and colon of laboratory mice.[3] In fact, with hindsight, we had chosen exactly the right technique from about one month after we started the work in 1981, but the months went by and we didn't culture the organism. This was particularly frustrating because we could see masses of bacteria on the Gram-stained mucus smears that I delivered to the microbiology laboratory within a few minutes of the biopsy having been taken.

The first successful culture was from a patient whose biopsy was on the Thursday before Easter 1982. The patient, number 37, was a 70-year-old male. He had a history of duodenal ulcer and gastric ulcer. He was anemic, with an artificial heart valve for which he required the anticoagulant coumadin in order to keep the metallic parts free of clot. So ulcer disease was a major problem for this patient's management, and his life was continuously threatened by his duodenal ulcer disease. He did have a small duodenal ulcer at endoscopy, but the research biopsies were still taken, as they did not need to be near the ulcer.

It is my recollection that at Royal Perth Hospital that month, a methicillin-resistant strain of *Staphylococcus aureus* had been detected. This "superbug", if it became widespread in Western Australia, would potentially cost the hospital about 10 million dollars per year in expensive antibiotic costs. To prevent this, some patients had been quarantined, and surveillance cultures were being performed on all staff that had been anywhere near the affected ward. The microbiology lab was very busy and so there was no time to examine my research cultures on Easter Saturday as would normally have been done. Therefore, the culture plates remained in the incubator, untouched, from Thursday morning until Tuesday morning—five whole days. On the Tuesday after Easter, small transparent colonies were present on the plates and these proved to be a rather pure culture of a Gram-negative rod. John Pearman waited until he had a second culture before he called me to the lab and, grinning like a Cheshire cat, showed me the new organism. I was pleased, but unconvinced because the cultured bacteria did not have a very convincing spiral shape. However, as I was in a good mood, it seemed an appropriate time for John to confess that the laboratory staff had been processing our research biopsies identically to the routine method used for throat-swab cultures. If nothing interesting was seen on the Petri dish at 48 h, they had been discarding the specimens! This might have been appropriate for throat cultures, because these carry many contaminating commensal organisms from the mouth which cause the plates to be completely covered with irrelevant bacillus and fungal species after 48 h. However, our research biopsies were actually rather clean.

Typically, after the endoscope was passed through the patient's mouth into the stomach, any free stomach acid was sucked out through the biopsy channel. This meant that mouth organisms contaminating the endoscope were washed away and/or killed. The biopsy forceps were introduced down the channel with their cup-like jaws closed, and they were only opened in the stomach as the biopsy was taken. Then, with the tissue sample enclosed within the forceps, it was withdrawn through the endoscope and then opened so that the specimen could be removed with a sterile needle. This meant that gastric biopsy samples were often much cleaner than other "oral" specimens. Gastric tissue samples tended to grow either nothing, or the new gastric organism. Even the nonselective blood agar plates produced almost pure cultures of *Helicobacter*, even after the 4th or 5th day.

Prior to John's confession, I had no idea that the cultures were being discarded routinely at 48 h. I had been wasting my time for six months! However, now that the bacteria had been cultured, a completely new line of research was open to me. What were these bacteria, and how did they survive in the stomach? Was there a serological response to them? What antibiotics might I use? How were they transmitted? I still had no idea that they were important for anything more than gastritis because the study was prospective and blinded.

The 100-patient study was completed at the end of May 1982. Perhaps because of my enthusiasm, I had recruited 100

patients rather quickly, with only two declining to take part. In the School of Medicine Statistics division I found Norm Stenhouse, who agreed to supervise the data analysis. This involved asking Robin and John Pearman to send their data-tables separately to his student, Rose Rendell.

I did the same with my demographic data and clinical questionnaire. I completed the process immediately before my family of six departed for Port Hedland, a mining town 1900 km from Perth in the North of Western Australia. In a frenzied weekend while my wife Adrienne was packing for the trip, I ducked out and spent all Saturday morning at the gastroenterology department photocopying the 100 endoscopy reports. Several weeks later, now the acting physician at Port Hedland, I scored patients for the presence or absence of the main visible endoscopic lesions and mailed that final data-table to Rose.

8. Data Analysis and Results

Back at Medical Statistics in Perth, Rose entered the data and then performed the analysis using SPSS. Eventually, a box of paper containing descriptive statistics and cross-tabs of bacteria vs. everything else was delivered to me in September 1982.

On the first assessment I noted that most of the patients with ulcers were positive for the bacteria, as were about half of the patients without ulcers. This was interesting, but I tried not to get excited about what could have been sheer chance. I then went back to the endoscopy reports and double-checked the data. Rather than finding that I had over-read the number of duodenal ulcers, the opposite was true. I found that the one duodenal ulcer patient without bacteria had undergone surgery soon after her endoscopy, and the bacteria were present when the far larger surgical specimen had been examined. I added her to the infected group. Later, Robin must have rechecked the samples and agreed that bacteria were present. I then double-checked various other fine details and submitted the revised data with more specific analysis requests back to Rose. While I awaited the final set of tables, I searched the literature for further reports of gastritis and gastric bacteria, especially as they might relate to an association with peptic ulcer.

The results of our study of 100 patients are shown in Table 2. The association of bacteria with endoscopic diagnoses was dramatic. Just over half of all the patients had bacteria, but all patients with duodenal ulcer had bacteria; 13 out of 13. Imagine that you're tossing a coin, how often do you get 13 heads in a row? The chance of 13 consecutive "heads" would be less than 1 in 1000. The actual *p* value for this association, using a two-tailed test, was 0.00044. So our finding was very, very unlikely to be by chance.

This finding appeared at a time when academic physicians were used to seeing hundreds of patients in clinical trials of peptic ulcer treatments. Typically, those studies were designed to demonstrate the differences between two acid-lowering drugs. Large numbers of patients were necessary to differentiate an 85% cure rate from a 90% cure rate. So would gastroenterologists accept a revolutionary discovery, the main cause of peptic ulcer, on the basis of 13 patients from Perth, Western Australia? It was just not going to happen.

Table 2. Endoscopic findings and bacteria.[a]

Endoscopic Appearance	Total	With Bacteria	*p*
Gastric ulcer	22	18 (77%)	0.0086
Duodenal ulcer	13	13 (100%)	0.00044
All ulcers	31	27 (87%)	0.00005
Oesophagus abnormal	34	14 (41%)	0.996
Gastritis	42	23 (55%)	0.78
Duodenitis	17	9 (53%)	0.77
Bile in stomach	12	7 (58%)	0.62
Normal	16	8 (50%)	0.84
Total	100	58 (58%)	–

[a] Total number of patients in this table exceeds 100 because some patients had more than one diagnosis. Four patients had both gastric and duodenal ulcer; all were positive for bacteria.

A second and extremely interesting aspect of the data was that 18 out of 22 patients with gastric ulcer had the bacteria. Four patients had both types of ulcer and all were *Helicobacter*-positive. So with only a gastric ulcer, 77% had the bacteria. But with duodenal ulcer, 100% had the bacteria. This difference was not statistically significant, but was very interesting if it held up. If our hypothesis was correct, why would duodenal ulcer be more tightly connected to the gastric bacteria than gastric ulcer? Why would ulcers occur down in the duodenum, where the type of mucosa is different (intestinal type, in fact) and to which the bacteria did not attach? The varying connection between ulcer type and the bacteria seemed an unusual finding at first, but it rang a bell.

I remembered that I had read a paper about gastritis written by Magnus in 1952.[4] He studied accident victims in Minnesota, and found that quite a few had peptic ulcer disease. Interestingly, he noticed that where he found gastric ulcer, gastritis was present in 80% of the cases, but if he found duodenal ulcer, gastritis was present in 100%. He could not explain why gastritis would be linked so strongly to the ulcer of the duodenum, rather than the stomach. Magnus discovered almost the exact same percentages that we had found for the link between bacteria and peptic ulcer. It was certainly a paradox, and so everybody had ignored Magnus's findings because they did not fit with what people thought would be the norm. When I presented our data in October 1982 at a meeting in Perth, a local gastroenterologist said to me: "Barry, you've got that wrong; people with duodenal ulcers don't have gastritis. The stomach is usually normal.". From what I had seen of Warren's biopsies, I could say, "How do you know, since nobody ever biopsies the stomach of duodenal ulcer patients?". In case I was wrong, I went back and checked my facts. By the end of 1982 I was certain that our data was actually quite consistent with other poorly understood studies. The other interesting fact I knew from the literature was that when gastric ulcers developed in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), the gastric mucosal histology was usually quite normal, that is, gastritis was absent. This seemed to fit with the four patients in our study who had gastric ulcer, but

normal histology. The questionnaire recorded that they were taking NSAIDs.

This all seemed rather logical to me. In the stomach, anything you eat is directly applied to the mucosa. So you could have *Helicobacter* causing ulcers associated with gastritis, and this would be the most common variety. Alternatively, even if *Helicobacter* were not present, the stomach wall could be corroded by anything else you might swallow. Yet whereas NSAIDs could sit around in the stomach for many hours, it would be quite difficult for them to actually reach the duodenum in high enough concentrations to cause an ulcer. So you might expect that a purer form of peptic ulcer would exist down in the duodenum, where the influence of ingested drugs was much less. My hypothesis would be strengthened if *Helicobacter* were present in the duodenum. But how could they cause trouble down there, on intestinal-type mucosa to which they could not stick?

Microbiological studies

During the second half of 1982, John Armstrong received some culture specimens and had them negatively stained to examine the morphology of the organism more exactly. He showed that it was 3.5 μm long, with 1.5 wavelengths of a spiral form. Usually, five or so flagella could be seen at one end of the bacterium. The flagella were sheathed, which meant they were more related to *Vibrio* and *Spirillum* species (i.e. cholera) than *Campylobacter* species, which have an unsheathed flagellum. An image of a dividing organism was chosen for our letters to *The Lancet* which were published in June 1983.[5]

Besides the morphology, we attempted to characterise the new bacterium according to the presence or absence of various biochemical markers, as shown in tables in Bergey's Manual of Determinative Microbiology. In 1982 there was not much else one could do to characterise newly discovered bacteria. In the days before polymerase chain reaction, techniques for analysis of DNA were rudimentary. The biochemical tests revealed a rather chemically inert organism, unable to produce acid from the metabolism of simple sugars. The new bacterium was catalase- and oxidase-positive and, at least in the hands of the technician at Royal Perth Hospital, it was urease-negative. One can only speculate as to how the urease enzyme of *Helicobacter pylori* could have been missed.

So by the end of 1982 I was starting to get pretty excited about this. I finished my training at Royal Perth Hospital and was offered an endoscopy training post at Fremantle Hospital with Ian Hislop, who had a background in gastritis from his days as a fellow at the Mayo Clinic. He said to me: "Barry, this is intriguing data. I think you're wrong, but it is a curious finding, and we need to look into it.".

Robin and I took two months to decide on a way to publish our first letters to *The Lancet*. Robin, quite rightly, could claim the initial observation and association with gastritis as his own work. However, I claimed that we now recognised the importance of his observation because of the clinical study and the linkage with peptic ulcer. If we were correct, then the discovery was worthy of the world's most widely read clinical medical journal, rather than a specialist pathology journal interested in gastritis. We called the editor of *The Lancet*, David Sharpe, who suggested we write two separate letters detailing Robin's initial findings in the first and our joint work in the second.

In my June 1983 letter to *The Lancet*, I described a new species of bacteria, a cross between a *Vibrio* and a *Campylobacter*. I mentioned some of the microbiological data, but did not reveal any of the linkages with peptic ulcer disease. According to the extensive literature on gastritis, there were two major diseases which could be caused by the mucosal inflammation. These were peptic ulcer and gastric cancer. Although there were masses of papers on gastric cancer, the histology was described rather poorly in most of these, and illustrations were never detailed enough to reveal bacteria. From our studies, however, it appeared that nearly all gastritis was associated with the new bacteria. All the "other" types of gastritis seemed rather rare. Perhaps the many different types of gastritis were just different names for the same thing, described at different stages of its natural history.

Since the new bacteria were associated with gastritis, my reading convinced me that this process was a launching pad for other important diseases. I expressed this hypothesis with the sentence: "then they may play a role in other poorly understood gastric diseases such as peptic ulcer and gastric cancer". Somehow David Sharpe allowed it to reach the printers; I suppose he was tired of arguing.

More hypotheses:

After sending our letters to *The Lancet*, Robin and I continued collaborating as we wrote a full paper to the same journal. There was quite a lot of data on those 100 patients, so it was a complicated process to present it all in a concise and logical form. After several months of study, we both knew every detail of every case by heart. I did have other activities, but by 1983 had decided to focus my career on the new bacterium and see where it led me.

As we planned the full paper and I studied more patients in my daily practice, several new conclusions dawned on me. From the 1982 data I could create the Venn diagram in Figure 3 which details a population similar to what we saw in our endoscopy patients. The patients in the large green circle did not have *Helicobacter*, so they might be regarded as "normal". About half the patients we saw did have *Helicobacter* and they are shown as the large red inner circle. I knew that the patients with duodenal ulcer were almost all within this red group. In fact, there were almost no duodenal ulcer patients in the green group. It seemed almost impossible to get a duodenal ulcer if you didn't have *Helicobacter*.

In addition, I was certain that some people with duodenal ulcer would have experienced *Helicobacter* eradication just by accident, as part of high-dose antibiotic treatment for other infectious diseases. So assuming these people existed, I would have expected to see patients with *Helicobacter*-negative duodenal ulcer disease. Yet such persons were exceedingly rare, if they existed at all.

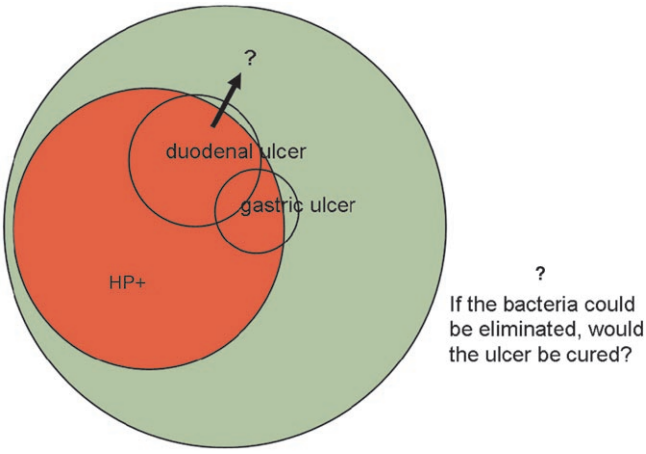

Figure 3. Disease associations for *Helicobacter pylori*.

In a mental experiment I could extrapolate backward from the above observations. Referring again to Figure 3, if I could eradicate *Helicobacter*, I would move a patient from the red group, where a duodenal ulcer was possible, into the green group, where an ulcer was nigh impossible. Therefore, just on the basis of logical reasoning I could conclude that antibiotic treatment, if it permanently eliminated the bacteria, would also cure ulcers.

As I started work in 1983, I realised that a lot more data would be needed before the new bacterium could be accepted as an important pathogen. I set about to answer the following questions:

Q1: Do patients with bacteria have antibodies?

A: Yes. Laboratory technician Greg Wynn stained some *Helicobacter* smears with sera from my infected and uninfected patients. He could easily demonstrate the presence of IgG with anti-human fluorescent antibodies. This proved that the human immune system considered the bacteria to be pathogens.

Q2: Do antibacterial agents heal gastritis?

A: Yes. Robin and I had suggestive data from the patient we treated with tetracycline in 1982. Then, in 1983, I observed that bismuth, a time-honored ulcer treatment mentioned by Kussmaul over 100 years earlier, killed *Helicobacter* in vitro. In a single-blind prospective study of about 30 patients, I documented suppression of the bacteria and temporary healing of gastritis when patients took De-Nol, an ulcer treatment containing bismuth. Regrettably, the bacterial infection usually relapsed, as did the gastritis and the ulcer. This experiment, although only partially successful, did encourage me to try other treatments in the ensuing 12 months. However, for the next 12 months, it did seem to many people that *Helicobacter* was just commensal flora associated with, but not causative for, peptic ulcers.

Q3: Had Koch's postulates been fulfilled for the new bacteria?

A: No. Koch's postulates are the time-honored way in which new bacteria are proven to be pathogens. There are four postulates, as follows:

1. The bacteria must be present in every case of the disease.
2. The bacteria must be isolated from the host with the disease and grown in pure culture.
3. The specific disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy susceptible host.
4. The bacteria must be recoverable from the experimentally infected host.

My attempt to fulfill Koch's postulates started in January 1984 with experiments on four piglets. I collaborated with Stewart Goodwin, Chief of Microbiology at Royal Perth Hospital, who had developed an interest in *Helicobacter*. He and Robin found many spiral bacteria (mostly *Campylobacter*) on my piglets, but the *Helicobacter* I instilled did not take. Their stomach biopsies remained normal. Eventually the piglets grew so large that I was obliged to terminate the experiment and, like most failed experiments, it was never published. This was a rather frustrating time because without an animal model, it was difficult to see if the new bacterium could cause disease.

Q4: What is the natural history of the disease process?

A: This was a major puzzle. Try as I might, I could not elicit a history of an acute illness from my ulcer patients. Clearly they could not have been born with gastric bacteria. I had many adults with the bacteria, but I had no clue as to where and when the bacteria had been acquired.

Q5: Was this disease confined to people with ulcers?

A: No. Interestingly, I saw many patients who had ulcer symptoms, but in whom no ulcer could be found. Many doctors believed that such patients had a psychosomatic illness. However, I soon collected many such "crazy people" in whom symptoms greatly improved during antibiotic treatment. I started to believe that it was not always necessary to have a visible ulcer in order to suffer from ulcer symptoms. Perhaps duodenal inflammation, a pre-ulcer condition, could cause pain. This concept had already been discussed by authorities in the field including Howard Spiro, author of a major gastroenterology textbook. According to Spiro, our bacteria might be the cause of duodenitis, an inflammation of the duodenum which was also called "Moynihan's disease".

Q6: How does *Helicobacter* survive in the stomach?

A: By hiding under the mucus layer where the pH is neutral. Initially, Robin and I could see that the bacteria were beneath

and within the mucus layer, so they might not be exposed to acid in the chronic stage of the infection.

Q7: Do ulcer treatments that heal ulcers affect the bacteria?

A: Maybe. I had continued my search of the literature from 1890 to the current date, but with many new interpretations. Bismuth salts had been used to treat gastric diseases for about 200 years. It was well known that heavy metals were antibacterial to spirochaetes, as bismuth, arsenic, and mercury had all been used to treat syphilis. In Germany, bismuth had been a component in stomach therapy for 200 years, and many antacid mixtures still contained bismuth salts. In Australia and Europe, bismuth subcitrate was a proven ulcer treatment sold under the brand name "De-Nol". This drug healed ulcers just as well as cimetidine, but without decreasing stomach acid. In fact, its mechanism of action was rather mysterious, perhaps related to some kind of coating action which protected the mucosa from acid. Of special interest to me was the fact that ulcer recurrence was less after bismuth treatment than after treatment with cimetidine.A typical example of such a clinical trial is shown in Figure 4. Martin, Hollanders, and co-workers[6]

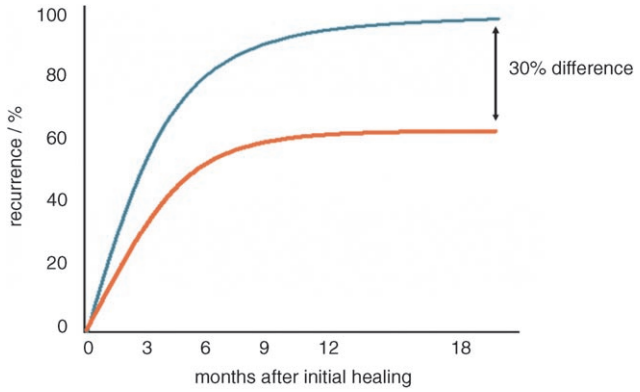

Figure 4. Relapse curves for ulcers treated with the H2 blocker cimetidine (green) or bismuth subcitrate (red).

treated duodenal ulcer patients with either cimetidine or bismuth. After the ulcers had healed, patients remained off all treatment until their ulcers recurred. At two years, about 90% of patients had suffered an ulcer recurrence in the cimetidine group, but significantly fewer patients, only 60%, had ulcer recurrence in the De-Nol group. The authors commented that "drug treatment given for a short period in duodenal-ulcer disease influences the progress of the disease". De-Nol seemed to heal the ulcer far better than cimetidine, but they could not understand why. Some commentators believed that the relapse was merely delayed, and the follow-up period merely needed to be extended. However, in my interpretation, a remarkable thing had happened. Since relapse curves in both groups were more or less horizontal after two years, I concluded that no further relapses would be expected in either group. This meant that 30% of patients in the bismuth group had been completely cured. This could be explained if bismuth had eradicated the bacteria. Was ulcer treatment with bismuth acting as an "antibiotic"? At last, I had a new hypothesis that I could test very simply.

Q8: Was bismuth an antibacterial?

A: Yes. My laboratory colleagues at Fremantle Hospital helped me carry out the simple experiment described below. 10-mm filter papers were dipped into De-Nol liquid and allowed to dry. *Helicobacter pylori* were then heavily inoculated onto individual blood agar culture plates. The discs were placed in the center of the plates which were cultured from Friday until Tuesday. When examined on the fourth day, a clear zone of bacterial inhibition was present around each of the discs (Figure 5a). I had discovered that *Helicobacter* was exquisitely sen-

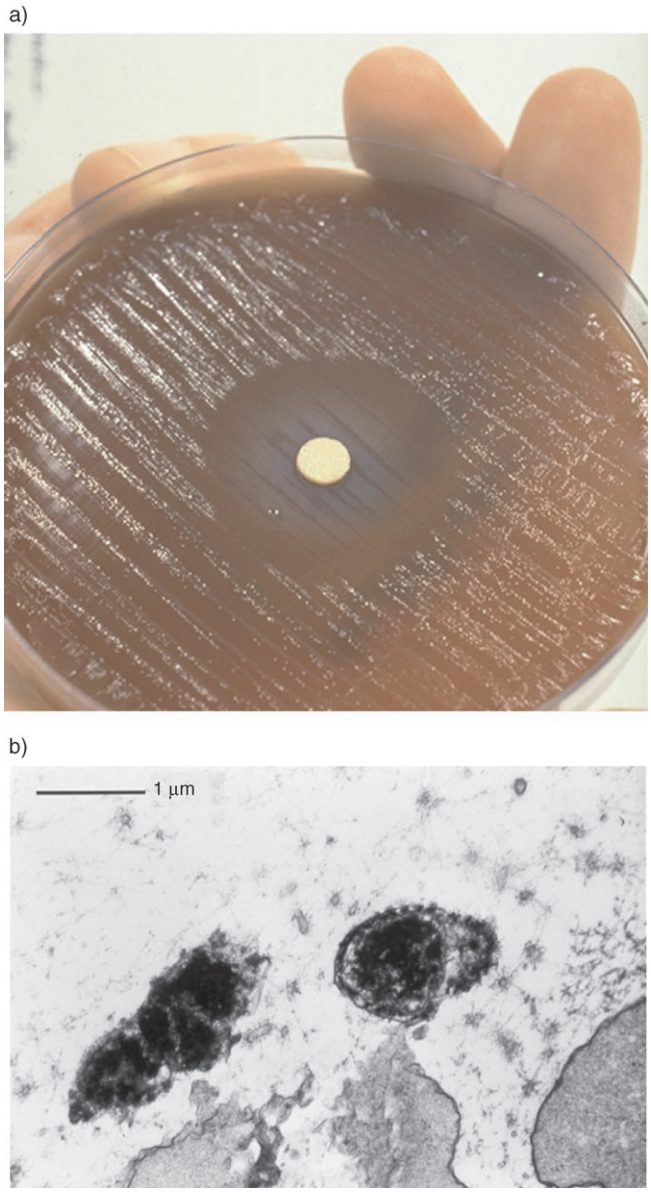

Figure 5. Bismuth effect on *Helicobacter pylori* in vitro and in vivo: a) inhibition of *Helicobacter pylori* growth by disc containing bismuth citrate (De-Nol); b) electron micrograph of *Helicobacter pylori* in the gastric mucosa 30 min after treatment with bismuth.

sitive to bismuth. It was probably the most exciting day of my life when I saw that bismuth had killed the *Helicobacter*. It all fitted too perfectly to be a coincidence. Everyone had forgotten that in the days before penicillin, bismuth was an important antibacterial therapeutic agent. I think that was the first time it crossed my mind that we might win the Nobel Prize. My keen intern, Vinod Ganju, of Indian descent, then agreed to take some bismuth and undergo a gastroscopy, as shown in Figure 5b, the numerous *Helicobacter* organisms could be seen practically exploding with dense bismuth precipitates all around them. The experiments described above enabled me to solve a major clinical dilemma. To test my theory, I wanted to perform a double-blind clinical study in which antibiotics were compared with a standard acid-lowering ulcer treatment such as cimetidine. However, antibiotics were so experimental that it would be unethical to ask people with potentially fatal ulcer disease to try out something which might not work. Ulcer patients always had to have an active therapy to heal their ulcers. However, bismuth was already proven as an ulcer-healing agent, and it did not lower stomach acid. Therefore, in order to suit our placebo-controlled study design, I could boost it with antibiotics and have a control group with placebo in various ways. After telephone advice from Walter (Pete) Peterson in Dallas, and various primitive power calculations, I designed a four-arm study using H2 blocker alone vs. H2 blocker with antibiotic vs. bismuth alone vs. bismuth with antibiotic. My grant application to the National Health and Medical Research Council (NHMRC) reached the interview stage, but it was clear that the panel members were rather skeptical. They opened the interview by stating that they refused to separately fund my plan to develop a serological test for ulcers. It just seemed too far-fetched. Somewhat annoyed, I replied that I had already developed a serological test which worked very well. Grudgingly perhaps, the NHMRC did agree to fund my clinical trial for one year. The title was: "The effect of antibiotics on duodenal ulcer relapse". It seemed very unlikely to them that I could recruit 100 patients from a single center. Therefore, I was instructed to provide a satisfactory progress report 12 months hence, in order to obtain the remaining two years of funding. The budget of about 50000 Australian dollars included my salary but no computer upon which I could save my data. During 1984, before the NHMRC funding came through, I received some extra support from Smith Kline & French, Pfizer, and Abbott, each for about 12000 Australian dollars.

9. Drinking *Helicobacter*: The Attempt to Fulfill Koch's Postulates

Disbelievers

In the months after my failed pig experiments, things went badly. I could see that bismuth was healing gastritis, albeit temporarily, but I had no convincing data to prove the bacteria were indeed pathogens. I could also see that several years might go by before we could discover a cure for the infection. The extreme skepticism of my colleagues led me to believe that I might never be funded to perform the crucial trial of antibiotics.

I found the response to my presentations very illogical and rather irritating. One day, after I presented my histology data showing the healing of gastritis with bismuth, the senior hospital pathologist stated, "Dr. Marshall, these changes seem very subtle.". Actually the changes were quite dramatic, and this was the first time anyone in the world had been able to heal gastritis! I bit my tongue to stop myself from saying, "are you crazy?". Others suggested again that these commensal bacteria merely infected people who already had ulcers. Quite clearly, however, I had presented data from patients with gastritis who did not have ulcers.

I realised then that the medical understanding of ulcer disease was akin to a religion. No amount of logical reasoning could budge what people knew in their hearts to be true. Ulcers were caused by stress, bad diet, smoking, alcohol, and susceptible genes. A bacterial cause was preposterous. Also at about that time, I began to realise that there was some urgency to this work. I had admitted a young man with diffuse gastric bleeding. Basically, there was oozing of blood from his whole stomach, and he was receiving daily blood transfusions. He had not taken any aspirin, had not consumed alcohol, and had no coagulation disorder. I wondered if *Helicobacter* could be involved. At endoscopy I encouraged Ian Hislop to obtain a few gastric biopsies to search for the bacteria. The specimens were full of pus cells, but unfortunately I could not find any *Helicobacter*. A colleague commented, "Well, Barry, you can't expect *Helicobacter* to cause everything.". The patient continued to bleed, the transfusions continued, and therapy continued with higher doses of acid blockers, antacids, and anticholinergics. Maybe they even tried iced water gastric lavage. A few days later I tested his serum with my prototype antibody test. He gave a strong reaction, positive at a dilution of 1:5012. The patient had been transferred to the surgical ward and was still bleeding. The political situation at Fremantle was becoming rather delicate. Clearly, I was obsessed with the gastric bacteria. I detected a certain coolness amongst my more senior colleagues. The patient was being managed by the surgeons now, so perhaps they would like to try a course of amoxicillin; it seemed such a simpler thing to do. I discussed my findings with the registrars in charge of the patient. Two days later, as the bleeding continued, the patient underwent total gastrectomy. I was too upset to go back to see him, and to this day have never followed up his case further.

10. *Helicobacter* Is Present in Healthy People

By mid-1984, using a somewhat crude serological test (by today's standards) I had discovered that 43% of "healthy blood-donors" in the port of Fremantle had *Helicobacter*. These people were apparently quite well, which meant that it was not necessarily fatal to have *Helicobacter*. Also by then, I had treated several patients with bismuth and metronidazole with a 100% cure rate for my first four cases. It seemed that I had a cure. Patients were having a fantastic clinical response. Maybe

it was safe for me to try swallowing the bacteria to see what really happened.

11. Ethics?

Although I am not one to stew over such things, the implications of my experiment did pass through my mind, albeit fleetingly. The only person in the world at that time who could make an informed consent about the risk of swallowing the *Helicobacter* was me. Therefore, I had to be my own guinea pig. If I submitted an ethics committee application and had it rejected I probably would have performed the experiment anyway, and then I would not have been able to publish it. Perhaps I would have been sacked, and my medical career would have been over. So I decided to do it anyhow using the "don't ask, don't tell" strategy. I had some unofficial support from my senior colleagues because the experiment required endoscopies by Ian Hislop and assistance from the chief of microbiology.

I remember proposing a hypothetical experiment with my microbiology boss, David McGechie, who laughingly declined to "take the bug". While thinking about the project I asked my gastroenterology chief, Ian Hislop, to carry out an endoscopy on me in order to obtain some healthy control tissue. I did not explain that this was to be the baseline sample, but I suspect he knew.

That same day, I performed a biopsy on yet another patient who was positive for *Helicobacter pylori*, but who did not have an ulcer. In vitro experiments revealed that his organism was sensitive to all our antibiotics, so I treated him for 14 days with my new therapy and arranged a follow-up endoscopy two weeks after that. His biopsy came out negative. It was now or never.

12. Drinking *Helicobacter*

On the morning of the experiment, I omitted my breakfast, but took 400 mg of cimetidine, believing that the infection might be easier if my stomach acid level was lowered. Two hours later, Neil Noakes scraped a heavily inoculated four-day culture plate of *Helicobacter* and dispersed the bacteria in alkaline peptone water (a kind of meat broth used to keep bacteria alive). I fasted until 10:00 in the morning when Neil handed me a 200-mL beaker about one quarter full of the cloudy brown liquid. I drank it down in one gulp, then fasted for the rest of the day. A few stomach gurgles occurred: was it the bacteria or was I just hungry?

For the next three days I had no symptoms and continued to work normally. On the third day I felt over-full after a modest evening meal of Chinese noodles; I sipped water during the evening to help my digestion. During the time between the fifth and eighth days I awoke very nauseated just as dawn was breaking, and ran into the bathroom to vomit in the toilet. Each day I vomited mostly clear slimy liquid, without any acid present. I recall thinking that it was rather strange, but in my sleepy state, I never thought to catch any of the material and merely flushed it away. During those days I spent many hours performing serological tests on hundreds of serum samples, so I had been working extra hours each day and also over the weekend. I felt very tired and lethargic, but assumed it was merely the many hours of sitting at the bench. I was also sleeping poorly, feeling clammy at night. My wife told me I had "a putrid breath". Unbeknownst to me, my colleagues at Fremantle Hospital had also noticed my halitosis that week, but were more polite. If I felt depressed it may have been the illness or just loneliness, as my laboratory staff found other duties far away from my bench!

After 10 days I asked Ian Hislop to perform another endoscopy on me which he did at the end of a rather busy afternoon of endoscopies. I was very uncomfortable during the procedure and rather weak afterward, as I had been fasting all day. I recall that it was someone's birthday and I was able to finish off the chocolate cake after my test. The endoscopy had been a preliminary study, done just to confirm or refute the presence of a bacterial infection. To my joy, spiral bacteria were present on the Gram stain of the first biopsy. The next day Ross Glancy showed me a pathology specimen teeming with *Helicobacter* and pus cells. The experiment had succeeded; *Helicobacter* was a proven pathogen.

13. My Wife's Reaction

I had not discussed the experiment with Adrienne until the evening of the day I swallowed the culture, and she had been observing my deteriorating condition without saying too much. While I was sure she would not have approved of the experiment ahead of time, once I began she accepted it as an important milestone. Like me, she felt the need to fast-track the research. However, she had been in a car accident two weeks before and had two cracked ribs and a moderate whiplash. Now she was caring for four children and a husband who was becoming worse by the day. I don't recall wondering if I might transmit the bacteria to her or the children—rather selfish of me, I suppose. I think the reality was that we were both quite young, barely past 30 years old, and like most young people had a strong belief in our own invincibility.

Although I had discussed the proposed self experiment in general terms a few months earlier, and Adrienne had not been radically opposed to it, there was probably another reason for not telling my wife that the time had come. I could see that the outcome might make a very large difference to our lives. I had submitted a grant application for funding in 1985, but it was quite likely that my application would fail. In addition, if nothing happened in my experiment, if the bacteria did not take, if gastritis did not develop, then my whole hypothesis could be wrong. At the very least, the disease was far more complicated than I had supposed, and it would be extremely hard to convince the skeptics that we had found something important. If that occurred, my future jobs might be in clinical medicine, and I would be off interviewing for placement in a private practice, perhaps in a remote area where my eccentric ulcer theories were less well known.

On the other hand, a successful infection with *Helicobacter* would point toward a career in clinical research, which is more

exciting but likely to be financially insecure. I chose not to raise the issue until the family settled down a little. (Nevertheless, a few months later I did perform an endoscopy and biopsy Adrienne just in case she had picked up the *Helicobacter* infection.)

14. Spontaneous Cure

The two biopsies taken on day 10 were not enough to really define the pathology, so I scheduled another endoscopy four days later. By then my vomiting had stopped, so I assumed I had entered the asymptomatic phase. At the next endoscopy, the stomach seemed normal and, surprisingly, we could not find *Helicobacter* in any of the eight samples which were taken. Cultures, histology, and electron micrographs were all bacteria-free, with the appearance of healing gastritis being the only abnormality. I had apparently eradicated the *Helicobacter* myself, without antibiotics. Serum samples taken at the time and a few months later were negative for *Helicobacter* antibody.

Whatever happened to cause the *Helicobacter* to disappear continues to be a mystery to this day. Many reports say that I took antibiotics to eradicate the infection on the instructions of my wife. This was not really the case. I decided to terminate the experiment and treat myself with the antibiotic tinidazole, but I did not take the tablets until after my endoscopy on the 14th day. In retrospect, tinidazole as a single agent would not have worked in any case. In a subsequent trial, 23 out of 24 patients merely developed antibiotic-resistant bacteria, which were then rather difficult to eradicate.

15. Synthesis

As I wrote the paper in the subsequent months, I reflected on the achlorhydric vomiting and the halitosis. I recalled some passages from William Osler's 1910 textbook of medicine which describe a similar illness in children. I then re-read papers I had discovered which described epidemics of gastritis in laboratory volunteers. Achlorhydria had been observed in those cases too. Suddenly the whole process became clear. The reason why ulcer patients could not recall an acute infection with *Helicobacter* was because it mostly occurred when they were tiny children, aged 2–3 years. This transient vomiting illness then settled into a lifelong asymptomatic phase, sometimes punctuated by clinical ulcer disease in adulthood. Because the bacteria were not affected by any of the usual ulcer therapies, ulcer disease became a lifelong problem, with a relapsing type of pattern. You could be infected by family members, even your mother, so it seemed to be hereditary. It was spread by the faecal–oral route, so individuals in lower socioeconomic groups were more likely to catch it. Varying epidemiologic patterns could explain many of the differences in ulcer incidence around the world. I could see there was plenty of interesting research ahead. As Robin and I had just had our main paper published in *The Lancet*,[7] the editor of the *Medical Journal of Australia* wrote to me requesting a paper about the bacteria, so I sent him two papers. After detailed review by the late Professor Doug Piper of UNSW in Sydney and substantial revision, the papers were accepted and published in April 1985.[8,9] There is no doubt that the editor was sticking his neck out very far to publish the self experiment with its enclosed hypothesis. However, it was very timely because yet another epidemic of achlorhydric gastritis had been published in the preceding month in the *British Medical Journal*, again without the authors being able to detect a pathogen.[10] The editors of *The Lancet*, seeking to claim the *Helicobacter* high ground for ever more, then editorialised my paper in their journal, giving it far more notoriety than it might otherwise have had. I kept my head down for a few months, held my breath, and waited for the sparks to fly. But nothing happened. The gastroenterology community might have been too stunned. Pete Peterson, in a telephone conversation with me in 1984, said, "Wow. You're a real cowboy, Barry.". Coming from a Texan I thought that was a supreme complement.

Many years later the experiment was immortalised in a comic created by the Abbott company, makers of the most important antibiotic for *Helicobacter*, clarithromycin. By combining that drug with amoxicillin and an acid blocker called omeprazole, it became rather easy to treat *Helicobacter* with an 85% cure rate. A panel of the Abbott comic is shown in Figure 6. In it, my colleague Neil Noakes says, "You're crazy!", whereas, while drinking the brew, I say, "There's no other way!". In 1984, both statements were true enough.

16. Treatment For *Helicobacter*

Toward the end of 1984 things begun to accelerate at Fremantle Hospital. By prescreening potential endoscopy patients with a serological test, I dramatically increased the concentration of *Helicobacter*-positive patients in my clinic. By combining bismuth with metronidazole, I was able to eradicate *Helicobacter* in most patients within just two weeks. When that failed I could use bismuth with amoxicillin to cure half the remainder. For people facing stomach surgery for ulcers, all these antibiotics seemed rather trivial.

The local GPs noticed the remarkable results and kept sending more patients. Very soon it seemed that this was a miracle cure for people with stomach problems. I had a treatment which cured most of them in two weeks. Not only that; patients who had carried a diagnosis of "functional" or psychosomatic gastric symptoms were so pleased to have a real diagnosis—*Helicobacter* gastritis.

In July 1984, I was called by Dr. Larry Altman, medical writer for the New York Times. I did not know at the time that he was almost finished writing a book on self experimentation. After the interview he published a major article about *Helicobacter* which he later said was rather difficult to get past his editor, as the medical community in the USA was extremely skeptical at the time. However, his article triggered a further interview between a journalist from the tabloid newspaper *The Star* and Dr. Warren. The outcome was that people from all walks of life, in many countries, suddenly became aware of gastric bacteria and the possibility that ulcers could be cured

Figure 6. Ulcer Tales: A comic describing the self ingestion of *Helicobacter.* This page shows Neil Noakes saying, "Dr. Marshall, you're crazy!", to which I reply, "There is no other way!".

with antibiotics. For years after that, I spent many hours per week sending out treatment advice by mail.

17. Diagnostic Tests

In 1984 Dutch investigators reported that *Helicobacter* produced massive quantities of the enzyme urease. I realised that this allowed the organism to produce ammonia and thereby survive in the acidic stomach. In search of a rapid diagnostic method for gastroenterologists, I discovered that that urease was also detectable in gastric biopsies. With a little trial and error, I built a rapid urease test, which enabled me to make the diagnosis of *Helicobacter* in a few minutes without laborious laboratory testing. This test, which I called the CLOtest (*Campylobacter*-like organism test), became the world's first commercial diagnostic test for *Helicobacter pylori*. It is still marketed by the Kimberly Clark corporation.

My other studies with Simon Langton in the biochemistry department at Fremantle Hospital revealed that urea was absent from the gastric juice of patients with *Helicobacter*. The bacteria had presumably destroyed all the urea for conversion into ammonia and CO_2. CO_2 would be expired in the breath. This understanding eventually matured into an idea for a breath test in which a carbon radioisotope tracer (^{14}C) was used to detect *Helicobacter*. In the simplified final version of this test, a patient swallows a capsule containing ^{14}C-labeled urea, and merely blows up a two-litre balloon 10 min later. The presence of ^{14}C-labeled CO_2 in the breath indicates that *Helicobacter* is present. The test has an important role in confirming that *Helicobacter* has been eradicated after treatment. Once it became available, noninvasive testing allowed many investigators to develop very effective treatments for *Helicobacter*. The urea breath test is still a major diagnostic test, commonly used in many countries, and is based on either the ^{13}C stable isotope method described initially by Graham and co-workers from Baylor Hospital in Houston,[11] or on the ^{14}C method described by myself and Ivor Surveyor at Royal Perth Hospital.[12]

Proof: a placebo-controlled double-blind trial

In 1985 I moved back to Royal Perth Hospital because I believed that it would be easier there to recruit the 100 patients necessary for a clinical trial. I was under pressure, as I had only been funded for one year. The study was designed to determine if the new treatment (antibiotics) was the same as the standard of care (cimetidine); cimetidine plus placebo was therefore the control group. The most active group was bismuth plus tinidazole, a combination which we knew eradicated nearly all *Helicobacter* infections within two weeks. I knew that most people continued to believe that ulcers were psychosomatic, so it was important to ensure that patients were completely unaware of which treatment they received. Clearly, however, smart patients could figure out that they were taking bismuth, because it caused black faeces. Therefore, it was necessary to add a group who took only bismuth with placebo tinidazole. I knew that the *Helicobacter* cure rate with this therapy was not more than 30%, so in the final analysis most of the patients so treated would be expected to have an ulcer recurrence. Finally, to be fair to the makers of cimetidine, it seemed appropriate to include a cimetidine plus tinidazole group. If it worked, this would be a convincing test of the hypothesis, as it avoided many of the blinding issues present with bismuth treatment. The four treatment groups were thus:

1. cimetidine plus placebo,
2. cimetidine plus tinidazole,
3. bismuth plus placebo,
4. bismuth plus tinidazole.

The study design meant that all groups contained a well-known ulcer-healing treatment, either cimetidine or bismuth for eight weeks. In addition, for each of these therapies, antibiotic or placebo would be given during the first 14 days. The treatment groups therefore contained increasingly strong anti-*Helicobacter* action.

After eight weeks of treatment, patients would stop all medication for two weeks and then undergo endoscopy to see if the ulcer was healed. After that, patients with healed ulcers would be re-examined at three, six, and 12 months to see if the ulcer had recurred. If the ulcer was seen to have returned, then the patient was removed from the study and was called a "relapse". In addition, patients were removed from the study if they became unwell and needed to restart ulcer treatment. In this case they were asked to have a final unscheduled endoscopy to document the presence or absence of a visible ulcer, but were removed from the study in any case, regardless of the findings.

Whenever an endoscopy was performed, biopsy tests were taken to see if *Helicobacter* was still present, or if it had been eradicated. The results of these biopsies were only made available if patients had already been removed from the study according to the other rules. In addition, in order to maintain stringent blinding, I was never allowed to speak with patients in the study, in case they mentioned side effects and thereby indicated what medication they were taking.

As part of the study I included a psychometric test called the Jung Scale, which approximately measures things such as sleep patterns, optimism, well-being, etc. I wanted to see if the so-called ulcer personality had anything to do with the ulcer disease. Since I could not talk to patients, I hired my brother and sister-in-law, Andrew and Kim, to interview patients before they came to each endoscopy.

18. Study Progress

With the aid of the local television news, hundreds of patients applied to take part in the study. I could then include only the most severe cases with already proven ulcers. Patients who were cigarette smokers were known to have rapid ulcer recurrence so I included these as preference. This meant that the results of my study would be known rather soon. If patients were not cured they would only last a few weeks without treatment.

Within four months I had screened about 300 patients and selected 100 of these who had both a duodenal ulcer and the bacteria. Seven patients were found to have the ulcer but no bacteria. One of these turned out to be a lymphoma case, so our special testing for *Helicobacter* resulted in an early diagnosis and a lucky cure for the patient (with chemotherapy and radiotherapy).

By the time of my NHMRC grant review interview in 1985, I had recruited the necessary 100 patients, and quite of few of the early recruits had already experienced healing and then recurrence of their ulcer. By deduction I could tell that we already had a significant result. I knew this because all the patients who had relapsed were still infected with *Helicobacter*. Since the active treatment would have eradicated the bacteria in at least half the patients, I could assume that patients without bacteria were not relapsing. I knew that I had chosen the worst ulcer patients I could find for the study, so for them to last more than two months without symptoms was unusual.

In the final result, the study showed that ulcer healing was more common and recurrence less common if *Helicobacter* was eradicated. Since the aim of our study was to cure patients, success only occurred if a patient healed his ulcer and remained healed with no further treatment for twelve months. Using these criteria, a dramatic difference was seen between patients who still had bacteria and those in whom the bacteria had been eradicated, as shown in Figure 7. Simply stated, in order to cure 10 patients with the old treatment, one would have to treat 104 patients. But to cure 10 patients with the new treatment one would only need to treat 14 patients. Variations of our study have since been published hundreds of times with the same or better results.

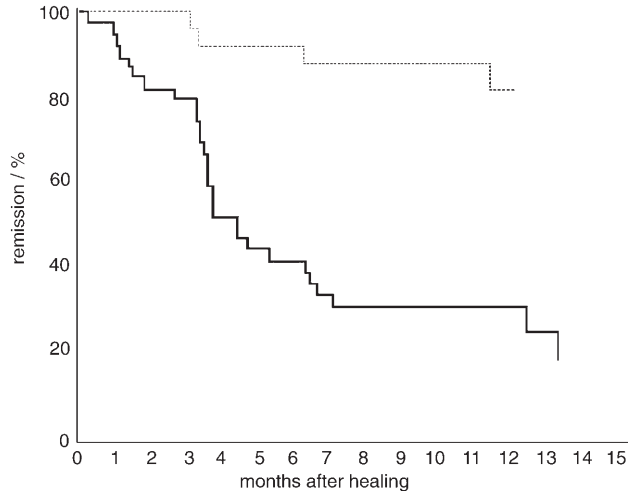

Figure 7. Duodenal ulcer relapse following *Helicobacter* eradication. Status: *H. pylori* + (——); *H. pylori* − (- - - -).

Two other results are worthy of note. Firstly, in our study, cigarette smoking made no difference to the result, provided that the *Helicobacter* had been eradicated. Of all the ulcer risk factors, smoking was known to be the most adverse, causing almost all doctors to insist that ulcer patients discard their cigarettes. Other studies have confirmed that so-called risk factors for peptic ulcer are all rather inconsequential relative to the risk of persistent *Helicobacter*. When ulcers occur without *Helicobacter*, NSAID-type drugs are usually implicated.

Secondly, the Jung Scale results showed that the patients' mental status improved when I eradicated their *Helicobacter*. When patients were in remission from their ulcer, *Helicobacter* eradication correlated with significantly lower Jung scores. Thus it seemed likely that the "ulcer personality" merely reflected a diminished state of health related to chronic infection of the stomach. Perhaps low-grade gastrointestinal symptoms persisted even when the ulcer was not present. The psychosomatic aspects of peptic ulcer have since been largely ignored, but have been studied as part of treatment for non-ulcer dyspepsia. In general, they have been found to be irrelevant. The idea that high acid levels are caused by "stress" was based on erroneous models of peptic ulcer in rats and in monkeys, in which the most important factor, *Helicobacter*, remained uncontrolled. It has subsequently been shown that *Helicobacter* gastritis, by interfering with local endocrine negative feedback in the stomach, can lead to excessive acid secretion.

19. Acceptance

Even more convincing studies of antibiotic use were published by Rauws and Tytgat (Amsterdam) in 1990,[13] Graham et al. (Houston) in 1991[14] and Hentschel et al. (Vienna) in 1993.[15] For the extreme skeptics, Hentschel's was the most convincing study because he did not use bismuth. Therefore, the blindedness of the study could not be questioned. In 1994 the National Institutes of Health convened a consensus conference in Washington, DC which was attended by an experienced international faculty of gastroenterologists, physicians, and infectious disease experts. It was concluded that in all cases of peptic ulcer, the essential first step was the identification and eradication of *Helicobacter pylori*.

20. Postscript

The history of the discovery of *Helicobacter pylori* has been described in more detail in the book *Helicobacter* Pioneers, by Blackwell.[16] The genome of *Helicobacter* was sequenced by Tomb et al. in 1997.[17] Presently, more than half the people in the world are still infected by *Helicobacter*, and it is believed that about 800 000 persons die from related stomach cancer each year. Much clinical and basic research continues, and is primarily focused on the aetiology and prevention of gastric cancer. In developed countries, gastric surgery is now a rarity, and ulcer disease is cured by general practitioners at its first presentation. In Australia, the cure of peptic ulcer has reduced the number of upper endoscopies by about 75 %, freeing up clinical resources for colonoscopic diagnosis and treatment. This should have a flow-on effect, causing a reduction in colon cancer as well.

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Keywords: gastritis · helicobacter · nobel lecture · ulcers

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