Chapter 1
A Brief History of the Discovery of *Helicobacter pylori*

Barry Marshall

Abstract *Helicobacter pylori* (*H. pylori*) has infected humans in Africa since the early Stone Age. Prior to the twentieth century, the majority of the world's population was infected with the bacterium. Around the globe many researchers came close to discovering *H. pylori* and its role in gastric disease, and in Japan there were two strong areas of enquiry. The first was the study of "spirochaetes" in the stomach of mammals by Kasai and Kobayashi. The second was the work by Kimura and Takemoto on the histology of the gastric mucosa. Nearby in China, no specific pathogen was identified, but ulcer treatment with the antibiotic furazolidone was successfully trialled, and Dr. Yao Shi from Shanghai almost discovered *H. pylori* through electron microscopy studies. In Australia, in the 1980s Robin Warren and myself were able to make comparisons between healthy and unhealthy stomachs and show the striking correlation between gastritis and presence of the spiral bacterium. After drinking cultures derived from a patient, I was able to fulfil Koch's postulates for *H. pylori* and gastritis. The rationale for future treatments via antibiotic-based eradication therapy was in place.

Keywords *Helicobacter pylori* • Discovery • History • *Campylobacter* • Western Australia

1.1 Introduction

Medical scientists know that *H. pylori* was only cultured recently, in 1982 at Royal Perth Hospital in Western Australia. However, the interesting true story of that adventure and the pioneering work of many other research workers across the globe including Asia in the prior 100 years are less well known. This chapter will demonstrate the long-lived and ubiquitous association between *H. pylori* and

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mankind and how despite, or perhaps because of this, the bacterium was overlooked for so many years. It will outline some of the early microbiology and clinical research that came close to the breakthrough. It will also show how an advance in one area of technology can unexpectedly solve a major problem in another area.

1.2 Prehistory

We now know that *H. pylori* is common, infecting around 50 % of the global human population. These epidemiological facts were unravelled in the 1980s and 1990s by serological surveys. It became evident that the bacterium was present in all human races, on all continents, although it was more common in developing countries and less common in western countries or affluent communities within countries.

By examining stored serum samples from the 1960s [1] and biopsy material stored for 20 years [2], it could be shown that the infection was decreasing in the latter half of the twentieth century as standard of living increased, water quality improved and families became smaller. In poor countries like Brazil and Africa, 80–90 % of the population was still infected. Extrapolating back therefore, it could be shown that at the beginning of the twentieth century, the infection rate with *H. pylori* must have been close to 100 % in every part of the globe. Since there did not appear to be an animal vector, *H. pylori* must have been solely a human pathogen, passed on from mother to child, for generations.

In the 1990s, as genomics and proteomics allowed us to differentiate between *H. pylori* strains from different geographic locations, it was discovered that people in South America were infected with "Spanish" strains of *H. pylori*, which by sequence analysis of the vacA toxin gene were designated as "Europe 1" strains [3]. So the questions then arose: "Did the *H. pylori* from Europe infect the people in South America? Were people in South America *H. pylori*-free before this infection?" The answers came from two sources. Firstly, dehydrated Andean mummies in Peru were found to have *H. pylori* antigen in their faeces [4]. This predated Columbus by hundreds of years showing that people in Peru were also colonised by *H. pylori* more than 1000 years ago. Additionally, since the colonisation of South America by humans occurred 15,000 BP, then *H. pylori* must have been quite ancient. To reinforce this story, later genomic studies showed that *H. pylori* in South America was of Asian origin, probably arriving there with the human migrations [5]. Finally, new genomic studies of hundreds of isolates reveal that all human strains of *H. pylori* had a common ancestor more than 60,000 years ago. Thus, *H. pylori* has colonised humans ever since they walked out of Africa [6, 7]. Evidence for colonisation long before this comes from the lion strain of *H. pylori*, which had a common ancestor to the human strain 200,000 years ago [8]. Since then it has mutated to a nonpathogenic form with "shredded" toxin genes.

Since apparently all human races became infected with *H. pylori* and remained colonised until now, we can speculate on possible reasons why *H. pylori* has been so tenacious. Is there a risk-benefit equation we should study? To start the

discussion, I propose that *H. pylori*, by producing folic acid, benefits humans with borderline nutrition and poor access to fresh vegetables. This benefit might have been especially valuable during ice age migrations. Secondly, if recent observations hold true, *H. pylori* dampens immune system hyperactivity making allergic responses less troublesome [9]. As humans moved from a closeted African environment to occupy the whole planet, decreased reactivity to new environments and antigens might have been a second benefit conferred by *H. pylori*. Balancing this against the "risk" of having *H. pylori*, the risk appears rather small, especially for Stone Age humans who had short lives so they did not experience the gastric cancer risk, which takes 50 years or more to develop. Additionally, because of poor nutrition, gastric acidity was low, so peptic ulcer was rare.

In summary then, *H. pylori* has infected humans in Africa since the early Stone Age. Humans migrated throughout the world starting about 65,000 years ago and benefited from their cargo of *H. pylori*, which in those days, had low pathogenicity and on balance could have aided the global migration of man.

1.3 Japan

1.3.1 Spiral Bacteria in the Stomach of Mammals

In Japan, two lines of research came very close to discovering *H. pylori*. The first of these, reported by Kasai and Kobayashi in 1919, was the study of "spirochaetes" in the stomach of mammals [10]. The second close call came in the study of fibre-optic biopsies and gastritis in the Japanese population reported by Kimura, Takemoto and many others.

In brief, a strong microbiology tradition was founded in Japan by Kitasato, who had trained in microbiology under Robert Koch and, after returning to Japan, had started the Kitasato Institute. At around the same time, after also working in Germany, the Italian anatomist Giulio Bizzozero reported spirochaetes in the gastric mucosa of the dog [11]. Bizzozero's colour illustrations showed the corkscrew organisms living in the mucus layer, in gastric glands and within the canaliculi of the oxyntic cells (Fig. 1.1) [12]. This finding implied that the bacteria were acid tolerant or else might have turned off acid.

Extending this work, Kasai and Kobayashi (Fig. 1.2) observed the same spiral bacteria in the stomach of most cats. Although they could not culture these organisms in vitro, they were able to transmit them to mice and thence to other animals such as rabbits and guinea pigs. In the rabbits, they sometimes saw erosions and inflammation in the gastric mucosa [10]. At that time also, the first successes of Paul Ehrlich's arsenical treatments for syphilis had been reported, so it seemed logical to try these agents on the animal models of the gastric spirochaetes. These efforts were partially successful. Salvarsan could eliminate the bacteria from mice and protect rabbits from the pathogenic effects of the spiral organisms [10].

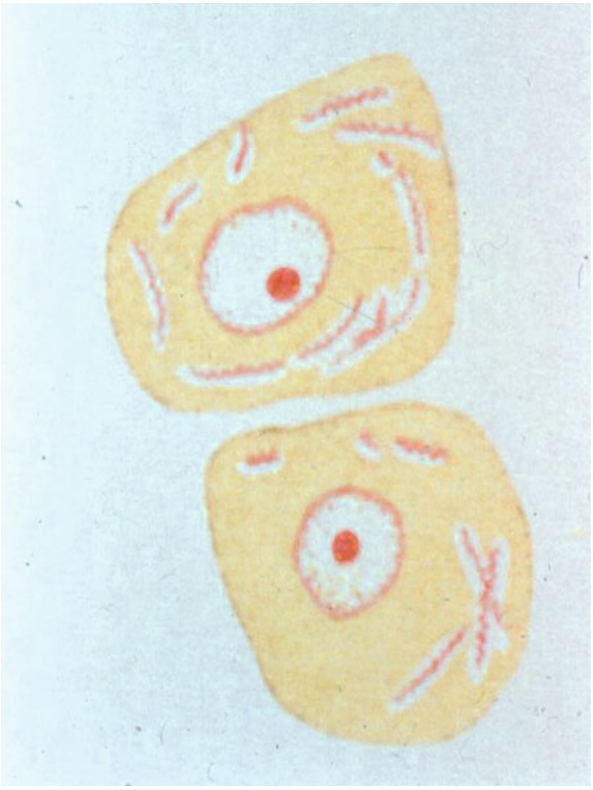

Fig. 1.1 Bizzozero's illustration showing numerous "spirilli" in the protoplasm of glandular neck cells (from [12])

With hindsight, we can see why *H. pylori* was not discovered by these investigators. Spiral bacteria appeared to be quite common in mammals, so the sighting of the bacteria in human specimens by several investigators in different countries was not surprising (Table 1.1). In fact, bacteria in the putrid gastric contents of gastric cancer patients were to be expected. Apart from gastrectomy specimens, which would have been mostly from patients with advanced gastric cancer, there was no easy way to study fresh stomach tissue from normal humans. After resection, autolysis of the gastric mucosa commences almost immediately making *H. pylori* hard to find. Additionally, by the time patients present with gastric cancer, the *H. pylori* have often disappeared from an atrophic stomach [14].

Although Kasai and Kobayashi's idea of arsenical treatment was never copied for peptic ulcer in humans, a very similar but less toxic metal, bismuth, had a long tradition as a human gastric medicine. In Europe, bismuth subnitrate had been a component of "gastritis" (dyspepsia) remedies and remains in use today. In the USA, bismuth subsalicylate (as ®Pepto-Bismol, Procter & Gamble) was used after 1900 for "infantile cholera" and "gastritis" and now remains a component of successful combination therapies for *H. pylori* [15].

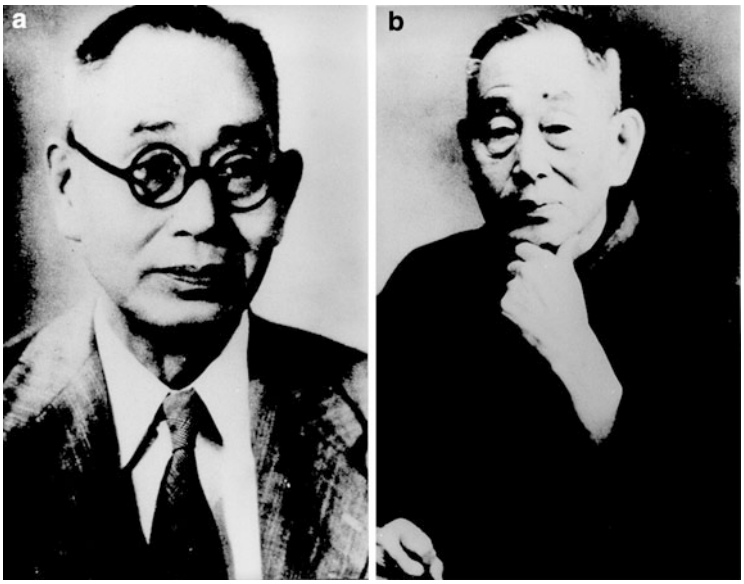

Fig. 1.2 Kasai and Kobayashi (from [13])

In retrospect, Kasai's work was largely done in very turbulent times, i.e. 1910–1918, and during World War I. Like subsequent investigators, their funding agency may have had more important infectious disease priorities. Twenty years later, in the USA when World War II was imminent, Freedberg in Boston described spirochaetes in the human stomach but could not follow it up and ultimately became a cardiologist [16].

The original work of Kasai and Kobayashi is a fine example of how curiosity-driven research, in a well-supported institute, served to fulfil the vision of earlier pioneers such as Koch, Ehrlich and Kitasato. Their studies were incomplete only because they did not have the tools available to myself and Robin Warren, i.e. microaerophilic culture techniques [17] and the fibre-optic endoscope [18].

1.3.2 Gastritis and Gastric Cancer in Japan

For at least 50 years, gastric adenocarcinoma has been recognised as the major cause of cancer deaths in Japan. To combat this, the first mass-screening X-ray examination was implemented in 1953, and in 1958 the Japan Cancer Society was established and the mass screening was promoted. The blind gastrocamera, invented in 1950, was used for gastric screening until it was replaced by the glass-fibre camera in 1975. Nevertheless, gastric cancer remains very common in Japan, with 130,000 new cases and about 50,000 deaths each year. No doubt

Table 1.1 History of the discovery of *Helicobacter*

Date	Researcher	Discovery
1875	Bottcher/ Letulle	Bacteria in ulcer margin
1881	Klebs	Bacterial colonisation and inflammation
1888	Letulle	*Staphylococcus aureus* induces acute gastritis in guinea pigs
1889	Jaworski	*Vibrio rugula* in the stomach
1893	Bizzozero	Spirochaetes in dog stomach
1896	Salomon	Gastric spirochaetes in dogs, cats and rats and showed transmission to the mouse
1906	Krienitz	Spirochaetes in the stomach with gastric cancer
1908	Turck	*Escherichia coli* induces gastric ulcer in the dog
1909	Regaud	Spirochaetes in cat and dog stomachs
1916	Suda	Spirochaetes in dog gastric glands (Japan)
1916	Rosenow	Streptococcus induces gastric ulcer
1917	Dragstedt	Bacteria do not induce gastric ulcer
1917	Kasai, Kobayashi	Spirochaetes in wild rats and guinea pigs
1919	Kasai, Kobayashi	Spirochaetes in cat, dog, rat and monkey stomachs; gastric spirochaetes transmitted between species; Salvarsan eliminates spirochaetes in mice
1921	Edkins	Experiments with *Spirilla regaudi* (*H. felis*)
1924	Luck	Urease activity in the stomach
1925	Hofmann	"Hofmann's bacillus" induces ulceration
1930	Berg	Partial vagotomy inhibits secondary infections of ulcers
1938	Doenges	Spirochaetes induce gastritis in monkeys and humans
1940	Freedberg/ Barron	Gastric spirochaetes are not pathogenic
1940	Gorham	Acidophilic bacteria induce gastric ulcer
1954	Palmer	No spirochaetes detected using H&E in 1140 suction biopsies
1966	Aoyagi	Highest urease activity in the stomach
1975	Steer	*Pseudomonas aeruginosa* induces gastric inflammation in ulcer margin
1979	Warren	Spiral bacteria in the human stomach
1983	Warren	Gastric spiral bacteria associated with gastritis in humans
1983	Marshall	*H. pylori* associated with peptic ulcer isolated and cultured
1984	Inoue	First success in culturing *H. pylori* in Japan
1985–1987	Marshall/ Morris	lnoculation with *H. pylori* proved Koch's 3rd postulate
1989	Goodwin	New spiral bacteria named *H. pylori*

Adapted from [13] and [10]

thousands of papers were published looking at the histology of gastric cancer and gastric mucosa but the *H. pylori* were overlooked. I choose just to mention studies published by Kimura and Takemoto whose landmark studies of gastritis in the Japanese population were presented in detail at a session of the American Gastroenterological Association in 1995 in San Diego.

In their earlier paper, these investigators reported the natural history of atrophic gastritis in a large series of Japanese patients. Theirs was one of the first papers using fibre-optic endoscopy to obtain precisely located biopsy material from several locations within the stomach [19]. They reported then what we know to be true: (a) gastritis commences at a young age, (b) the lower half of the stomach is involved but the disease moves proximally with age, (c) inflammation gradually leads to intestinal metaplasia and gastric atrophy and (d) eventually "nearly all" Japanese develop metaplasia and atrophic gastritis. The logical conclusion was that the gastric mucosa aged so that Japanese people ultimately developed the atrophic mucosa, with low acid secretion, which had been recognised as a risk factor for patients with Type A "pernicious anaemia" autoimmune gastritis in western countries. Various causes for the Japanese findings were postulated and some of these were probably relevant, especially salty food, pickles containing nitrate and cigarette smoking; but the presence of *H. pylori* was overlooked. Why was this so? Why did Robin and I come to a different conclusion in a far smaller series of patients in Perth in 1982?

The clue to the presence of *H. pylori* was in the changing epidemiology of gastric cancer noticed in the USA during the twentieth century. In 1930, gastric cancer was the most common cancer in the USA. Between 1930 and 1970 however, the incidence declined from a rate similar to that in Japan (60 per 100,000 per annum) to the modern rate of about seven. One hypothesis is that the consumption of fresh fruit and vegetables increased in the USA with the advent of modern refrigerators after 1930. Vitamin C prevents the formation of nitrosamines in the stomach, so there is plausible scientific data to support this. Additionally, and perhaps less importantly, *H. pylori* declined in the USA during that time such that by 1966, the seroprevalence was 60 % in California [1].

So, like many investigators before and after, Kimura and Takemoto studied a population in which *H. pylori* was almost universally present. The association between the spiral bacteria and inflammation can only be seen when "normal controls" are included in the study. For Japan, "normal" was the *H. pylori*-positive state. When Robin and I collected our first 20 or so patients in Perth, Western Australia, however, we had the advantage of a declining prevalence of *H. pylori* in a modern affluent western county. The population had smaller families, clean food and water and free access to powerful antibiotics such as amoxycillin.

Thus, in our study of only 100 gastroscopy patients conducted in 1982, only 58 had *H. pylori*. The 42 patients without *H. pylori* were the control group. In these "controls" gastritis was almost completely absent and, in most cases, the endoscopic appearance of the stomach was also normal. Age, smoking, diet, alcohol and NSAIDs were unrelated to gastritis. *Helicobacter pylori* was the only associated factor. The association was so tight that the "p value" could not be calculated using

the mainframe computers available in Western Australia. Robin Warren purchased a new Hewlett-Packard 11C calculator and found a one-tailed Fisher's test result of $p < 10^{-8}$ [20, 21].

Folding these findings back into the studies of Kimura and Takemoto, and with further studies since, we can say that the almost universal presence of *H. pylori* in the Japanese population prior to 1970 stimulated an ageing process which led to atrophic gastritis and gastric cancer. However, there is great optimism now because for the past 20 years, very few Japanese children have been infected with *H. pylori*. In addition, effective treatments have been available for decades, and the tools for *H. pylori* eradication, i.e. diagnostic tests and combination antibiotics, are freely available. By supplementing the endoscopic screening with *H. pylori* testing and treatment of the population, the gastric cancer epidemic may disappear from the Japanese population during the next generation [22, 23].

1.4 China

Numerically, China is still the country with the largest population of *H. pylori*-infected people. Even today it is estimated that 50 % of the population is infected, so half a billion people in China remain at risk of *H. pylori*-caused diseases, i.e. peptic ulcer and gastric cancer. It is not surprising therefore that pioneering researchers also came very close to discovering *H. pylori* in that country. Considering the various upheavals in China during the twentieth century, the investigators can be proud of the advances they made no doubt benefiting millions of patients.

In China, gastric cancer was always very common and remains so today, with about 35 % of all the world's cases occurring in that country. The contribution of environmental factors was always suspected in China because, in a relatively homogeneous population, cancer rates varied greatly in different provinces. Likely causes of this variation included diet and dietary carcinogens. Even today, we still think these factors modulate the effect of chronic *H. pylori* infection.

After 1970 however, several Chinese investigators became aware of the presence of gastritis in the stomach of Chinese people with peptic ulcer or gastric cancer. Similarly to the Japanese studies, intestinal metaplasia and atrophy were also quite common. In the 1970s several groups had considered that bacteria might be related in some way. A specific pathogen was not identified, but, since the healthy stomach was relatively sterile and people with gastric disease often had low acidity with a putrid gastric flora, broad-spectrum antibiotics seemed to be worth trying. There was a prior history to this. At the Mayo Clinic, oral neomycin had been used to decrease gastrointestinal ammonia production (from urease) in patients with hepatic encephalopathy [24]. Also, in Athens, Greece, Dr. John Lykoudis had used an antibiotic "brew" called "Elgaco" with great success in hundreds of duodenal ulcer patients [25, 26]. Finally, by the mid-1980s Spanish investigators had performed a study using metronidazole to treat duodenal ulcer in a

small prospective controlled pilot study which showed improved radiologic healing in the treated group [27].

In China, furazolidone was used in peptic ulcer treatment from as far back as 1972, and thousands of patients all over the country were treated [28]. Professor Zhi-Tian Zheng in Beijing conducted a clinical trial to confirm its efficacy in late 1982 to early 1983. The ulcer healing rate was 73 % for the furazolidone group (exposed to a 2-week regimen of 200 mg t.i.d.) versus 24 % in the placebo group ($p < 0.001$) [29].

After seeing our results from Western Australia in 1983, Xiao and colleagues in Shanghai revisited the use of furazolidone and carried out studies of antibiotic use in gastric disease where *H. pylori* was also correlated with histologic and clinical findings.

This work transitioned into larger studies including the 5-year "Dutchigas Project" with Professor Guido Tytgat in Amsterdam, which began in 1995. The collaborators undertook a series of projects on the eradication of *H. pylori* using bismuth/furazolidone-based and PPI furazolidone-based triple or quadruple therapies.

Some of the early studies were difficult to interpret especially where metronidazole was used, and in vitro susceptibility studies of the offending *H. pylori* strains were not available. However, there is little doubt that these Chinese investigators were very close to the *H. pylori* discovery.

To reinforce this impression, Dr. Yao Shi, after performing electron microscopic studies of mucus structure in Shanghai, reported different appearances of the mucus, suggesting that its physical structure was somehow defective in ulcer patients. In Shi's illustrations however, the spiral shapes of *H. pylori* were definitely visible (Fig. 1.3). This work was similar to studies done contemporaneously by Steer and Colin Jones in the UK [30] and at Royal Perth Hospital by Fung and

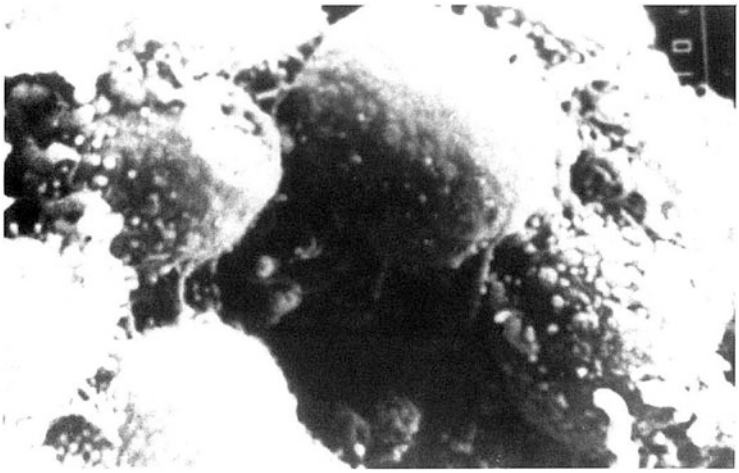

Fig. 1.3 Dr. Yao Shi's electron micrograph with visible *H. pylori*

Papadimitriou [31]. Certainly, *H. pylori* could have been discovered in China. Once again the story of the discovery reveals how curiosity-driven research, common sense clinical "pilot" studies and basic research could lead to a discovery benefiting many millions of people.

1.5 Perth, Australia, 1981–1984

The detailed history of the discovery of *H. pylori* by Robin and myself (and many others) has been well described in the book *Helicobacter Pioneers* [20, 32], so in this small chapter I can't repeat all of that. However, this is a good time to relate my personal recollection of the initial culture of the bacterium and then my later attempt to fulfil Koch's postulates for the bacterium by drinking it!

After some pilot studies where we confirmed Robin's initial impression of a strong association between the gastric *Campylobacter*-like organism (CLO) and active chronic gastritis (ACG), we carried out a prospective study of 100 patients coming to elective endoscopy. This is the study mentioned above and published in *The Lancet* in 1984. After informed consent (only one patient refused to participate), two biopsies were taken from the antrum, one for histological examination by Robin and a second one for Gram-stain and culture attempts in the microbiology department. I attended the endoscopy and prospectively coded the endoscopic findings as well as the clinical information from the patient. This information was sent to the statistician who was also blinded to all the other clinical and biopsy information. After 100 patients had taken part, the study was closed and the results were analysed by the statistician. The major outcome is shown in Table 1.2. Nevertheless, these findings failed to convince the sceptics that the association between spiral bacteria with gastritis was important. However, the study and the fact that the new organism could easily be cultured created an exponential increase in publications by microbiologists.

Table 1.2 Association of bacteria with endoscopic diagnoses

Endoscopic appearance[a]	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[b]	42	23 (55 %)	0.78
Duodenitis[b]	17	9 (53 %)	0.77
Bile in stomach	12	7 (58 %)	0.62
Normal	16	8 (50 %)	0.84
Total	100	(58 %)	

From Marshall and Warren [21]

[a]More than one description applies to several patients (e.g., four patients had both gastric and duodenal ulcers)

[b]Refers to endoscopic appearance, not histology

After failed attempts to infect piglets in 1984, I, after having a baseline endoscopy done, drank liquid broth containing the scrapings from two Petri dishes containing cultured *H. pylori*, expecting to develop, perhaps years later, an ulcer. I was surprised when, only three days later, I developed vague nausea and halitosis (due to the achlorhydria, there was no acid to kill the mouth flora in the stomach, and anaerobic waste products manifested as bad breath), noticed mainly by my wife and my mother. On days 5–8, I developed achlorhydric (no acid) vomiting. On day 8, I had a repeat endoscopy and biopsy, which showed massive inflammation (gastritis), and *H. pylori* was cultured. On the 14th day after ingestion, a third endoscopy was done, and I began to take antibiotics (tinidazole). However, by then the *H. pylori* had totally disappeared! This story was related in my Nobel acceptance lecture on 8 December 2005, available for viewing on the Nobel website [33]. Interestingly, I did not develop antibodies to *H. pylori*, suggesting that innate immunity can sometimes eradicate acute *H. pylori* infection. My illness and recovery, based on a culture of organisms extracted from a patient with gastritis, fulfilled Koch's postulates for *H. pylori* and gastritis but not for peptic ulcer. This experiment was published in 1985 in the *Medical Journal of Australia* [34] and is among the most cited articles from the journal.

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