
History of Medicine

MARSHALL AND WARREN: THE NOBEL PRIZE WINNERS IN MEDICINE IN 2005

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Two scientists, Barry Marshall and Robin Warren, from the Australian City of Perth won the Nobel prize in Medicine in 2005. They independently published two letters in one issue of *the Lancet* in 1983 and noticed the presence of a spiral bacterium in the epithelium of stomach.¹ In his letter, Marshall declared “if these bacteria are truly associated with antral gastritis, as described by Warren, they have a part to play in other poorly-understood gastritis-associated diseases, i.e., peptic ulcer and gastric cancer.” What was going on with this hypothesis?

The young assistant, Marshall, wanted to conduct a research in 1981 at Perth University. His boss addressed him to either collect macroscopic data by endoscopy or ask the pathologist Dr. Warren, who was looking for a clinical collaborator interested in the follow-up of patients found to have bacteria in their gastric biopsies. The first option was not suitable for him and thus, Dr. Marshall contacted Dr. Warren. After their meeting, he became enthusiastic to work on this bacterium and their collaboration on gastric diseases started from this point onward.

Marshall prescribed antibiotics like tetracycline to treat some patients who had undergone endoscopy. He observed clinical improvement and remarkable reduction in the number of bacteria in the gastric mucosa as compared to a control group. He also noticed in scientific publications that bismuth derivatives, compounds with no effect on acid secretion, are able to heal ulcer and reduce the relapse rate of peptic ulcers.^{2,3} He wanted to know how these bacteria behave under bismuth therapy.

But, he faced many problems in obtaining bismuth. He had no support from any institution or medical personality. In his book on the history of *H. pylori*, Marshall wrote that “No one was interested in revolutionizing the world of gastroenterology, partly because the concept was so outlandish and also because extensive pharmaceutical research was being carried out in Australia at the time, with nearly all drug companies acting as subsidiaries of American- or European-controlled entities.” An abstract, written based on his results, entitled “spiral bacteria in gastritis and associated disease” was submitted to the meeting of Gastroenterological Society of Australia in 1983. It was rated as the bottom 10% and not accepted among the 76 abstracts submitted by various researchers. Only 56 abstracts were accepted.⁴

Nobody believed that ulcer formation might be linked to an infectious disease. Worldwide, all gastroenterologists were prescribing the H₂-antagonists cimetidine and ranitidine, discovered by the pharmacologist James Black from the Glaxo Laboratories in England.⁵ He had won the Noble prize in 1988 for this discovery, and for studying on other receptor-blocking agents such as propranolol.⁶ These agents were able to heal all peptic ulcers within a few weeks and made the patients pain-free in less than one week. This was a great advance in medicine within the years 1965 – 1970. The theory of “no acid–no ulcer,” proposed by Schwarz, from the first decade of 19th century was well accepted.⁷

But Marshall did not give up and tried to isolate the bacterium and cultivate it in the Department of Microbiology, under the supervision of Dr. Goodwin of Perth University. He was not successful. The culture plate was either negative every time or mostly covered by bacteria and some *Candida* spp. not resembling the curved spirochetes-like bacteria seen histologically. The culture

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plates were usually removed 2 – 3 days after the failure of culture. During the Easter holidays of 1982, his technician forgot to remove the plates from the culture box. At the end of holidays, the technician observed a growth of bacteria on the plates; *H. pylori* takes more than two days to grow. Microscopic examination revealed that these bacteria resemble those observed in the gastric epithelium. The characteristics of the bacteria began to be identified. It was a Gram-negative and urease-positive bacterium. A cooperative publication in *the Lancet* was followed and the bacterium was given the name *Campylobacter pylori*.⁸

Since Marshall, himself, neither had gastritis nor carried the bacteria in his stomach (as proved by endoscopic and histologic examinations), he believed he was a good candidate to be used for proving his theory by induction of gastritis by ingestion of the bacteria. He did so, and got some mild discomfort for two weeks. On day 10 after ingestion, the bacteria could be cultured from both antral and corpus biopsies.⁹

The few publications of Marshall induced some European gastroenterologists to study the effect of bismuth derivatives on gastritis and these spiral-like bacteria.

The publications of Marshall on the bacterial genesis of peptic ulcer was not credited by all protagonists of the established maxim of the pivotal role of hydrochloric acid on the development of peptic ulcer. However, the fact that bismuth derivatives heal the peptic ulcer and reduce its relapse rate, stimulated the European gastroenterologists to focus on the effect of bismuth derivatives on gastritis and the behavior of *Campylobacter pylori*. The first gathering on *C. pylori*, now named *Helicobacter pylori*, was held with only 20 – 25 participants in Ulm, Germany in 1984, organized by Prof. Peter Malfertheiner (now in Magdeburg, Germany). At this meeting, Marshall reported the effect of bismuth compounds on the electron microscopic structural changes of *H. pylori*. Other investigators confirmed the substantial inhibitory role of bismuth derivatives on the growth of this bacterium and the succeeding healing of gastritis.¹⁰

Marshall began to conduct a controlled trial in 1984 on patients with peptic ulcer, and treated them randomly in four groups; cimetidine/placebo; cimetidine plus tinidazole; bismuth plus placebo; and bismuth plus tinidazole. The rate of ulcer healing was then followed. The relapse rate during

one year after the therapy was also derived by a second endoscopic examination, testing the ureasereaction of gastric specimens (CLO-test) and microscopic observation of the presence of bacteria and their culture. Marshall found no ulcer relapse in patients in whom the bacterium was eradicated and published the results in 1988—five years after the establishment of his hypothesis.¹¹

The second large clinical study was performed with a triple-therapy regimen consisting of tetracycline, metronidazole, and bismuth compounds. This work was published by Borody et al from Australia in 1988 and 1989.^{12,13} Other clinical studies were performed first in Europe and then in other countries. An eradication trial was initiated by the author of this article in 1989 in Iran and the results were published in 1991 in an Iranian journal.¹⁴

Later on, it was found that *H. pylori* is not only the cause of peptic ulcer, but is also related to development of gastric cancer and lymphoma.

But let us see whether *H. pylori* unknown to previous investigators? Spiral bacterium was first reported as spirochetes, closely associated with the surface of gastric epithelium, at the end of 19th century by various authors; it was reported in the stomach of dogs by Bizzozero,¹⁵ and at the beginning of the 20th century in human by Krienitz,¹⁶ Kasai and Kobayashi,¹⁷ and later by Doenges.¹⁸

Among those who found the bacteria and their relationship with the content of stomach or in relation to the gastric mucosal changes, the important contribution of the German scientist Georg Ernst Konjetzny remained unknown.¹⁹

Konjetzny was born in April 1880 in Gleiwitz, a region in present Poland, which belonged to Germany before the Second World War and died in 1957 in Hamburg. He studied the morphology of stomach as a pathologist in 1907 in Chemnitz, and later on as a surgeon during his career in many surgical departments in Kiel and Hamburg. He removed all resected gastric specimens from peptic ulcer gastric cancer patients, or from patients with suspected but not verified gastric diseases. He then fixed the specimens in formalin and thoroughly studied them microscopically.

Konjetzny published in 1923 an important article entitled “chronic gastritis and duodenitis as the cause of gastric and duodenal ulcer.”²⁰ In his article, he claimed that 100% of resected gastric mucosa from patients with peptic ulcer had severe gastritis. The perception at that time was that the

chronic inflammation found in the resected specimens was a consequence of the peptic ulcer. On pages 614 and 615 of his article, he remarks: “By histological examination of gastric specimens, stained with the Nicolle method, it was remarkable to observe a close correlation between the grade of gastritis and the amount of bacteria spreading on the mucosa. In the fundus region with little or no inflammation, I could not find any bacterium. Quite the contrary, in areas with severe gastritis we observed a loss of specific glands and the occurrence of a secondary atrophy both in the area of the crypts as well as in the neck of the glands. The bacteria were found massively in the gastric pits in those areas showing severe gastritis. The bacteria were not only observed on the mucosal surface and on the adjacent mucus layers, but more often in the peripheral regions of mucosa and in the central tissue also. However, little bacteria were observed in the ulcer itself and it was completely undetectable in those areas with normal mucosa.” Konjetzny was vehemently opposed to the opinion of all contemporary scientists of his time, who defended the Schwarz theory of “no acid-no ulcer.”

He published two books, one on gastric cancer in 1938,²¹ and the other one on ulcer formation in the stomach and duodenum in 1947.²² In his book on gastric cancer, he concluded (page 262) that “ulcer and gastric cancer will be developed through silent inflammation of gastric mucosa. We are not able to distinguish between gastritis, which forms benign ulcer and that developing gastric cancer. When we were able to prevent gastritis or treat it, we would be able to prevent ulcer and gastric cancer. Prophylaxis of gastritis means prophylaxis against ulcer and gastric cancer.”

The conclusion of Konjetzny, obtained on the basis of his 30-year experience as he noted, corresponds exactly to the short communication of Warren, mentioned above. At the time of Konjetzny, nobody believed the extensive experiences of this surgeon. Sixty years later, nobody at first, believed Warren and Marshall. However, the culture of bacteria as well as the access to antibiotics, enabled Marshall to prove the infectious basis of gastritis and the associated peptic ulcer disease. He also showed complete healing after eradication of the bacteria—what was missed by the great pathologist and surgeon Konjetzny.

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