These two landmark *Lancet* publications appeared almost 100 years after the first report of spiral bacteria in the human stomach and the initial speculation by several researchers that gastric ulceration was an infectious disease. Although more than 100 experimental studies suggesting a microbial cause of gastritis and peptic ulcers had been published in the first half of the 20th century, and several bacterial and viral species had been implicated as etiologic agents, the concept of an infectious pathogenesis for these common ailments was repeatedly rejected by influential authorities in both gastroenterology and pathology. The prevailing belief was that microbes could not survive in the acidic environment of the stomach and that bacteria present in resected stomachs and at autopsy were artifacts caused by contamination and post-mortem growth.

J. Robin Warren, a pathologist working at the Royal Perth Hospital in Western Australia, noticed curved rod-shaped bacilli in about half of the routine gastric biopsies he examined over a period of three years and found a direct correlation between the number of organisms in the tissue and the severity of gastritis. Convinced of the significance of his observations he enlisted the participation of Barry Marshall, a trainee in Internal Medicine, and a joint effort was launched to isolate the microorganism. Warren had noticed the resemblance of the curved bacilli to Campylobacter, a family of known intestinal pathogens. Using microaerophilic conditions that favor the laboratory growth of Campylobacter, they tried, unsuccessfully, to grow bacteria from stomach biopsies for more than a year. Serendipity delivered success when abundant bacterial growth was found in cultures that had been inadvertently left in the incubator over the Easter holidays, unintentionally extending the incubation period from two to six days.

While the isolation of *Helicobacter pylori* was a breakthrough achievement, it did not establish that the microbe caused gastritis. It was already known from autopsy studies that curved rod-shaped bacilli were present in the stomachs of many individuals who had neither gastritis nor a history of stomach disease. The successful isolation of bacteria from gastric biopsies by Marshall and Warren satisfied the first two of Koch’s four postulates, but all four had to be met to indisputably prove that the organism that had been isolated was the cause of the gastritis. In an amazingly daring feat that ultimately fulfilled Koch’s postulates, Marshall and another volunteer ingested cultures of the bacteria. Both of them developed acute gastritis proven by endoscopic biopsies from which the suspected pathogen was re-isolated. These results confirmed the link between *H. pylori* and gastritis, but since neither subject developed an ulcer, that link still remained unproven. Subsequent clinical trials showing that antimicrobial therapy could cure ulcers left no doubt that *H. pylori* caused gastric and duodenal ulcers. When Warren and Marshall used standard bacteriological tests and electron microscopy to characterize the isolated organism they found that it was not a Campylobacter species, but a newly discovered microbe that was subsequently designated *Helicobacter pylori*.

The findings of Warren and Marshall had enormous impacts. Peptic ulceration, a disease of worldwide occurrence whose definitive treatment was surgical, became a disease that could be treated and cured with antibiotics. In the United States alone, approximately 4 million people have peptic ulcers. *H. pylori* infection is present in virtually all of them when the ulcer is located in the duodenum and in the vast majority of them when the ulcer is in the stomach. Once *H. pylori* could be cultured it became possible to determine the global prevalence and distribution of the infection. Immuno-epidemiologic tests to detect the presence of anti-*H. pylori* antibodies were performed on archived blood samples and
quickly established that at least 30-50% of the world’s population was colonized with \( H. \) pylori. Great variability was observed between different countries in the incidence of the infection and the age at which infection was acquired, and in the incidence of infection amongst different socioeconomic and ethnic groups. A surprising finding was that more than 80% of infected individuals were asymptomatic and only about one in six had an ulcer.

The milestone publications of Warren and Marshall triggered numerous basic and clinical investigations aimed at understanding the biology of \( H. \) pylori, the host response to encounter with the microbe, and the cellular and molecular mechanisms underlying the pathology of \( H. \) pylori infection. In a relatively short time these investigations proved to be extraordinarily productive and answered many of the questions that had previously fueled the skepticism surrounding the concept of an infectious etiology of ulcers. Numerous virulence factors encoded by the genes of \( H. \) pylori and passenger plasmids were identified and shown to influence colonization, persistence and pathogenicity of \( H. \) pylori. A high degree of genetic polymorphism in the expression of these virulence factors was observed in different isolates. This phenotypic heterogeneity provided insight into the highly variable host consequences of infection with \( H. \) pylori. The entrenched disbelief that microbes could survive in the strongly acidic environment of the gastric mucosa was annulled by the finding that \( H. \) pylori produced urease, an enzyme that made it exquisitely suited to survive in an acidic niche. Urea present in gastric secretions is cleaved by the microbial urease to yield ammonia and bicarbonate that create a moat of pH neutrality surrounding the bacterium. Urease activity became the basis of a clinical test that was developed to screen patients for the presence of gastric \( H. \) pylori. A major boost was given to the \( H. \) pylori field in 1997 when the entire DNA sequence of the bacterial genome was published in \textit{Nature}.

Beyond its relevance to gastritis and ulcers, the discovery by Warren and Marshall ultimately led to the designation of \( H. \) pylori as a Class I carcinogen by the World Health Organization International Agency for Research in Cancer. Investigations that followed the landmark findings of Warren and Marshall established that the range of epithelial changes in chronic gastritis included hyperplasia, metaplasia, dysplasia and carcinoma. Decades before \( H. \) pylori had been isolated an association between cancer of the stomach and chronic gastritis had been recognized. The discovery that \( H. \) pylori was the major cause of chronic gastritis linked \( H. \) pylori and gastric cancer. In addition, pathologists had long observed a wide spectrum in the intensity of lymphoid cell infiltration and follicular development in stomachs with chronic gastritis. At times, distinguishing between chronic gastritis with intense lymphoid infiltration and gastric lymphoma could present a diagnostic challenge. In some \( H. \) pylori-infected patients the florid gastric lymphoid proliferation that was present met the diagnostic criteria of gastric lymphoma, but treatment of these patients with antimicrobial agents resulted in elimination of \( H. \) pylori and complete regression of the lymphoid proliferative process, an outcome that challenged the dogma that neoplasms are autonomous and neoplastic transformation is irreversible. Subsequent investigations showed that in some patients the neoplastic lymphoid cell proliferation was driven by host immune recognition of \( H. \) pylori antigens by lymphoid cells.

There are several principles contained in the \textit{H. pylori} story. One of them, a recurrent element in the history of biomedical progress, is the vital role of the independent investigator. While important large projects such as determining the entire DNA sequence of a genome typically requires the collaborative efforts of several large groups of investigators, discoveries that change paradigms often come from young independent investigators working in situations that are permissive of the high risk research that challenges established dogma. Another recurrent principle illustrated in the cascade of research that followed the milestone publications of Warren and Marshall is that diseases are sophisticated experiments of nature whose elucidation yields extraordinary societal benefits.

References

Suggested Readings