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A Humble Bacterium Sweeps This Year's Nobel Prize

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Earlier this month, the Nobel Prize in Physiology or Medicine was awarded to the Australians Barry Marshall and Robin Warren for their discovery of the bacterium *Helicobacter pylori* and its role in peptic ulcer disease and gastric cancer. It is the first time since 1928 that the Nobel Prize has been awarded for the discovery of a bacterium, and *H. pylori* is the first bacterium to be associated with cancer.

It was Robin Warren, a pathologist working in Perth, who, 25 years ago, first noted that spiral bacteria colonized the lower part of the stomach (antrum) in about half of the patients from which he had taken biopsies. Crucially, he noted that inflammation of the mucosal lining of the stomach (gastritis) always appeared close to the location of the spiral bacteria. Intrigued by these findings, Barry Marshall, a young clinical fellow, teamed up with Warren (see Figure 1), and together they assayed stomach biopsies from 100 patients.

Researchers working on *Helicobacter* look back on the date of Easter 1982 as the "birthday" of *H. pylori*. This is the date that Marshall was first able to culture *H. pylori* from biopsy material in the laboratory. Thinking that *H. pylori* was related to another gram-negative bacterium called *Campylobacter*, Marshall decided to try growing *H. pylori* on agar plates usually used for culturing *Campylobacter.* Although such plates are normally discarded after 2 or 3 days, there was the fortuitous intervention of the Easter holiday. Arriving back from a 4-day break, Marshall discovered colonies of *H. pylori* thanks to the extended incubation period (Warren and Marshall, 1983).

There followed a frenzy of research that began to unravel the mysteries of *H. pylori*, with data appearing on the characteristics of the bacterium, methods to diagnose it, and the host immune response (Marshall and Warren, 1984). Marshall and Warren went on to show that *H. pylori* is found in almost all individuals with gastritis, peptic ulcers, and duodenal ulcers. Indeed, more than 80% of stomach ulcers and 90% of duodenal ulcers are known to be caused by *H. pylori*. Furthermore, it became clear that stomach cancer can result in infected individuals where *H. pylori* causes widespread inflammation of the stomach lining (IARC Working Group, 1994). Inflammation is also associated with a rare stomach tumor called MALT (mucosa-associated lymphoid tissue) lymphoma. About 50% of individuals worldwide are infected with *H. pylori* (usually passed from mother to child) and develop gastritis, but many remain asymptomatic. Peptic ulcer disease arises in 10% of infected people, gastric adenocarcinoma in 1%, and gastric MALT lymphoma in less than 0.1%.

Figure 1. Barry Marshall and Robin Warren with the Author
Barry Marshall (left) and Robin Warren (center) with the author (right), who presented the award of the European *Helicobacter pylori* Study Group to Marshall and Warren at their Lisbon meeting in 1997.

Convincing the Skeptics

The implication that an infectious agent could be the cause of peptic ulcer disease was a revolutionary idea in the 1980s, and one that was greeted with skepticism by the medical community. At that time, there were numerous theories to explain the etiology of peptic and duodenal ulcers, including the linking of ulcers to lifestyle and stress. The most popular theory was that ulcers developed in response to excess acid in the stomach. This resulted in the development of drugs that blocked H_2 receptors expressed by stomach parietal cells, which when activated, induced the cells to produce acid. It is ironic that Sir James W. Black was awarded the 1988 Nobel Prize in Physiology or Medicine for discovering H_2 receptors. His work paved the way for the development of H_2 receptor-blocking drugs to treat peptic ulcer disease. Such drugs changed the management of this disease because gastric surgery became limited to cases of stomach perforation or gastric malignancy. However, the H_2 receptor-blocking drugs and their successors, the proton-pump inhibitors, only treated the symptoms of peptic ulcer disease, and the frequent relapses necessitated lifelong maintenance treatment.

The first time that Marshall and Warren presented their work at a national meeting in Australia, it was rejected outright. Whereas Warren was too shy to push their remarkable findings, Marshall had a missionary's zeal and vigorously defended their research. In

order to convince the reluctant medical community of the robustness of their discovery, Marshall did the ultimate experiment. He drank a culture of *H. pylori*, developed acute gastritis and then successfully treated the illness with antibiotics (Marshall et al., 1985). Thanks to the discovery of Marshall and Warren and Marshall's definitive experiment, a lifelong treatment was suddenly replaced by a short course of antibiotics (NIH Consensus Conference, 1994). In addition, MALT lymphoma could be successfully treated by eradicating *H. pylori* infection, making it the first human cancer to be cured by antibiotics. These developments did not please the pharmaceutical industry, although it was still necessary to prescribe antisecretory drugs in order to increase the stomach's pH, thus allowing the antibiotics to do their job.

H. pylori: Opening up New Avenues of Research

Among the more than 20,000 articles about *H. pylori* published since 1983, many have been devoted to the study of the bacterium and understanding its secrets. We now know that *Helicobacter* is very heterogeneous. Not only mammals but many other vertebrates carry their own specific *Helicobacter* species, most of which are harmless commensals. In contrast, *H. pylori* induces inflammation in its human host and cannot be considered a commensal. In 1997, *H. pylori* became the third bacterium to have its genome totally sequenced (Tomb et al. 1997), and in 1999, it became the first bacterium for which the genome sequences for two strains were obtained. The discovery of the so-called *cag* pathogenicity island in *H. pylori* reveals how commensal bacteria acquire beneficial properties that give them the upper hand in the bacteria-host relationship. Genes contained within the *cag* pathogenicity island encode proteins that enable *H. pylori* to transfer molecules to the cytosol of host gastric epithelial cells and to interfere with host cell signaling pathways. Recently, the CagA protein has been shown to disrupt the organization and assembly of apical junctions in epithelial cells and also to perturb epithelial cell differentiation (Bagnoli et al., 2005; see Cell Biology Select, page 963 of this issue). In addition, molecules comprising the *H. pylori* cell wall, especially muramyl dipeptides, are recognized by host epithelial cell NOD receptors leading to activation of the NF-κB signaling pathway and production of interleukin 8, a proinflammatory cytokine (Viala et al., 2004).

Within the last 5 years, it has become clear that host factors are involved in the pathogenesis of *H. pylori*. Gastric carcinoma has been linked to a polymorphism in the interleukin-1β (IL-1β) gene. Certain IL-1β/IL-1β receptor genotypes are associated with atrophy of the gastric mucosa due to the ability of this cytokine to block acid production. Indeed, when IL-1β is produced in large amounts, the risk of gastric carcinoma increases (El Omar et al., 2000).

Another important discovery reveals that the gastric mucosa cells that become tumorigenic are mesenchymal stem cells originating in the bone marrow. An elegant study using mice repopulated by stem cells harboring different markers showed that in animals with a long-term *Helicobacter felis* infection, stem cells homed to gastric tissue and, because of the inflammatory environment, became tumorigenic (Houghton et al., 2004). We await confirmation of this intriguing finding in other carcinomas where inflammation is present.

There are other domains beyond pathogenicity where the discovery of *H. pylori* has opened up new avenues of research. One such example is phylogeography, given that *H. pylori* has been associated with humans for thousands of years. By comparing sequences of housekeeping genes of *H. pylori* from human populations in different geographical areas, it is possible to identify strain genotypes. Models can then be developed to infer the ancient genotypes of this bacterium. Such studies reveal ancient human migrations, such as the migration of Amerindians from Asia, the Maori from Southeast Asian islands, and the Bantu from Central Africa (Falush et al., 2003). Such microbial studies complement data on ancient human migrations derived from genetics, mitochondrial DNA analyses, and language studies.

Marshall and Warren's seminal discovery that a humble bacterium, *H. pylori*, causes gastritis, peptic and duodenal ulcers, and in some cases, gastric cancer, merits the 2005 Nobel Prize in Physiology or Medicine for its remarkable impact on public health and for opening up new avenues of research. This low-tech discovery in the final decades of the 20th century—which saw the explosion of technology and the emphasis on mechanistic approaches to research—demonstrates that not all discoveries require a high-tech laboratory and the latest equipment. The tenacity of Marshall and Warren illustrates that important discoveries can still be made by doggedly pursuing unexpected results with an open mind.

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