**Helicobacter pylori: hiding in the modern miasma**

Justine Denomme (Meds 2015) and Jason L. Chan (MD/PhD 2017)
Faculty Reviewer: Dr. Carole Creuzenet, PhD (Department of Microbiology and Immunology)

When Ignaz Semmelweis proposed and demonstrated that hand-washing would decrease the incidence of puerperal fever in the mid-nineteenth century, he was ignored, criticized, and ridiculed. Miasma, or bad air, was believed since ancient times to cause disease, and consequently, hand-washing had no place in medical care.

Of course, this is no longer the case, but decades passed before Semmelweis’ recommendations gained widespread acceptance. His discovery was controversial and met with resistance. Eventually, the germ theory of disease replaced the miasma theory, and Koch’s postulates provided a concrete method to establish a causal relationship between a microorganism and a disease. Despite the struggles of earlier researchers and clinicians to advance medicine, resistance to new knowledge and discoveries still prevails. The story of the bacterium *Helicobacter pylori* provides a modern example of this resistance.

Today, when a person is diagnosed with peptic ulcer disease (PUD) and an *H. pylori* infection, they are promptly treated with a brief course of two antibiotics. Elimination of the bacterial infection is associated with more rapid healing of ulcers and reduces the risk of relapse. The association between bacterial infection and peptic ulcers was discussed within scientific literature as early as the late 19th century but a definitive link between peptic ulcer disease and specific bacteria was not established until 1984. Furthermore, in 1995, a study of treatment patterns of peptic ulcer disease in the United States showed that only 5% of patients were being treated with antibiotics in order to eradicate *H. pylori*. Why did this happen? Firstly, the characteristics of *H. pylori* made it difficult to study. Secondly, there was already a well-established theory regarding the etiology of peptic ulcers when the bacteria were first successfully cultured. Finally, the medical community was more resistant than the scientific community to accept infection as causative of peptic ulcers.

Unlike many other disease-causing bacteria, *H. pylori* did not easily fulfill Koch’s postulates for peptic ulcer disease. The second postulate states that a disease-causing microorganism must be isolated and grown in pure culture. With the advent of microscopy and germ theory, early bacteriologists and pathologists identified bacterial colonies associated with ulcer tissue samples on several occasions. However, *H. pylori* was not successfully cultured until 1982, by Drs. Barry Marshall and Robin Warren. The bacteria are especially difficult to culture even today because they grow 10 to 15 times more slowly than *Escherichia coli*, are microaerophilic, and require specific culture media. Interestingly, Marshall and Warren’s early experiments were only successful when a plate that was accidentally left over the Easter weekend instead of being discarded after 48 hours without growth grew colonies.

Furthermore, Koch’s third postulate states that disease should be reproduced when the cultured microorganism is introduced into a healthy, susceptible host. This postulate was memorably proven by Dr. Barry Marshall when he ingested a culture of *H. pylori* isolated from a patient with gastritis. This was the only way to fulfill Koch’s third postulate at the time because most *H. pylori* strains only infect humans. This proved to be problematic for early animal studies on gastritis. Bacteria associated with inflamed gastric mucosa of rhesus monkeys and with human gastric tissue was studied by J.L. Doenges in 1938 and later by Freedberg and Barron in 1941. Unfortunately, the bacteria from rhesus monkeys were histologically different from those in humans and bacteria were more difficult to identify in human tissue samples. Therefore, it could not be definitively concluded that bacteria caused gastric inflammation. Later, when Dr. Marshall initially attempted to implement Koch’s third postulate, he unsuccessfully attempted to transfer *H. pylori* cultures to piglets. It was only more recently that more suitable animal models were developed. Fulfilling Koch’s postulates in the case of *H. pylori* was more difficult than for many other types of bacteria. These characteristics of *H. pylori* delayed the development of efficient methods for its study can partially explain why it was not easily established as one of the causes of peptic ulcer disease.

Although identifying *H. pylori* was difficult, once Marshall and Warren presented their findings to the world, other microbiologists verified and accepted them. However, gastroenterologists were more reluctant to accept this new information. Eventually, Drs. Marshall and Warren’s work became formally recognized when they were awarded the Nobel Prize in Physiology or Medicine in 2005. In his Nobel Lecture, Dr. Marshall stated that the greatest obstacle to his work was that the cause of peptic ulcer disease was “already known”. When Warren and Marshall isolated and cultured *H. pylori*, H2 receptor antagonists were an established treatment for peptic ulcer disease. The use of these drugs, which decreased acid secretion in the stomach, helped validate a theory of the etiology of peptic ulcer disease at the time: the stomach was secreting too much acid or the mucosal lining was less resistant to stomach acid, causing damage, ulcers, and pain. It was thought that intrinsic factors such as psychological stress or habits such as smoking made the stomach lining more vulnerable to damage. In the case of ulcers caused by *H. pylori*, it is suggested that the bacteria release a bacterial infection which results in increased acid secretion due to the body’s reaction to the infection. Another predominant theory was that the stomach was too acidic for bacteria to grow. Therefore, when bacteria were historically observed on samples of gastric tissue, they were thought to be artefacts.

Based on what had been traditionally taught in medical schools at the time of the discovery of *H. pylori*, Drs. Marshall and Warren’s research would have been very extraordinary.

There are several others reasons why the medical community did not eagerly embrace Marshall and Warren’s findings. To begin, testing for *H. pylori* was originally invasive and inaccurate and physicians did not
HISTORICAL VIEWS OF MEDICINE

want to treat people with antibiotics unnecessarily for fear of antibiotic resistance.\(^\text{13,14}\) Secondly, throughout the 1980s, the pharmaceutical industry continued to pursue the development of treatments that did not account for a bacterial etiology of PUD.\(^\text{15}\) In 1988, proton pump inhibitors, such as omeprazole, were launched as an alternative to H2-antagonists.\(^\text{15}\) The pharmaceutical company producing omeprazole organized an international symposium on PUD that year, featuring 33 notable gastroenterologists, yet only one of the 67 posters and abstracts presented dealt with *H. pylori*.\(^\text{15}\) Finally, continuing medical education may not have been as effective at keeping physicians aware of changes in medical practices in the past as it is today.\(^\text{16}\) It was traditionally based on self-directed learning and self-assessment, which could lead to deficiencies in medical knowledge and a lack of accountability.\(^\text{16}\) In addition, some continuing medical education has historically been funded by the pharmaceutical industry, which could potentially introduce bias into the curriculum.\(^\text{17}\) Accepting new theories that challenge previously-established beliefs can be very difficult. In this case, the lack of resources and information likely contributed to the delay in eradication of *H. pylori* becoming the standard of patient care for gastritis and PUD.

One of the most important factors in the acceptance of the eradication of *H. pylori* from the stomachs of symptomatic patients was the discovery that *H. pylori* is carcinogenic.\(^\text{18}\) Research into the relationship of *H. pylori* and certain cancers began shortly after its discovery and by 1994 the International Agency for Research on Cancer reviewed the available literature and concluded that people infected with *H. pylori* are at increased risk for developing gastric adenocarcinoma and gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma.\(^\text{18}\) Gastric adenocarcinoma is a leading cause of cancer death worldwide and is typically associated with a poor prognosis.\(^\text{19,20}\) Interestingly, MALT lymphoma can be treated by eradication of *H. pylori* and it has been suggested that *H. pylori* eradication could help prevent future gastric cancer.\(^\text{21}\) Cancer is one of the most notorious diseases in our society, and the association of *H. pylori* infection with malignant disease was further evidence to support that an *H. pylori* infection requires medical attention.

The journey towards establishing an etiology for peptic ulcer disease was long and exceedingly difficult. *H. pylori* possesses many characteristics that make it difficult to culture and establish a cause-and-effect relationship with peptic ulcer disease. Furthermore, the idea was unappealing to many because it challenged previously established views and challenged physicians to revisit traditional medical knowledge. In order to truly provide the best possible care to patients, physicians must embrace the dynamic, surprising, and ever-changing aspects of the field of medicine. With improved continuing medical education and with improved access to medical journals online, this has never been more possible. Many fields of medical science, including *Helicobacter pylori*, are still active areas of research locally and globally and emerging knowledge will certainly continue to challenge physicians to improve medical practices in the future.

REFERENCES

4. Contagion: Historical Views of Diseases and Epidemics [Internet]. The Presi-