HELICOBACTER PYLORI: A GASTROINTESTINAL REVOLUTION

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Helicobacter pylori has come a long way, its controversy-ridden discovery having culminated in a rare gastrointestinal, nay medical revolution. The gastrointestinal tract itself doesn't seem capable of much excitement beyond sheer gastronomic pleasure. The advent of Helicobacter pylori radically altered the landscape. The story of its discovery is one of serendipity, doggedness and perseverance; the quintessence of scientific simplicity. It is remarkable though, that an organism that colonizes about half of the world's human guts, humanity's most ubiquitous chronic bacterial pathogen, remained undiscovered until less than 25 years ago. This is a testimony to the ingenuity of this extraordinary bacterium. Gastric epithelial bacteria had been noted in the past, but repeated attempts to culture the spiral organisms from gastric biopsies had been unsuccessful. But from a long Easter weekend in 1983, the reading of culture plates was delayed and, for the first time, a profuse growth of the organism that is now known as *Helicobacter pylori* was cultured. Barry Marshall and Robin Warren, working in Western Australia, established the link between the organism, and gastritis, peptic ulcer disease and gastric cancer in 1983, for which they were awarded the Nobel Prize for Medicine, long after, in 2005.

A view under light microscopy reveals a Gram-negative spirally shaped motile bacteria, each measuring about 0.5-0.9μm by 2-4μm with a tuft of sheathed flagella. *H. pylori* usually lives in the deep mucosa of the gastric antrum with an optimum $_{P}$H of 6-7. It doesn't do well in acid. *H. pylori* is strictly micro-aerophilic, requires carbon dioxide for growth and is non spore forming. As if those are not enough distinguishing features, it produces an exceptionally powerful urease that is about a hundred times more active than that of *Proteus vulgaris*. Following the inoculation of *H. pylori*, mostly in early childhood, there is an incubation period of a few days. There is then a mild attack of acute achlorhydric gastritis, with symptoms of abdominal pain, nausea, flatulence, and bad breath. Symptoms last for about two weeks. Benign you may say, but not in the long term. Thus, *H. pylori* sneaks in early on in life, and the event goes unremembered.

In his Nobel lecture, Barry J. Marshall, recalled the early years of Helicobacter research when he resorted to self-experimenting by ingesting a broth containing *H pylori* to prove that this bacterium, not stress or hyperacidity, caused peptic ulcers[1]:

I reflected on the achlorhydric vomiting and the halitosis. I recalled some passages from William Osler's 1910 textbook of medicine, which describe a similar illness in children... Suddenly the whole process became clear. The reason why ulcer patients could not recall an acute infection with Helicobacter was because it mostly occurred when they were tiny children, aged 2–3 years. This transient vomiting illness then settled into a lifelong asymptomatic phase, sometimes punctuated by clinical ulcer disease in adulthood.

The controversy was so much as to warrant self-experimentation. Having failed to infect animal models with *H.pylori*, Barry Marshall used himself as the guinea pig.[2] Snubbed by colleagues because conventional medical wisdom said nothing could survive in the highly acidic stomach and loathed by pharmaceutical firms, which had been selling acid blockers meant to control ulcers, Barry Marshall took this extreme step to prove his hypothesis. He said, "After a particularly frustrating time while presenting a paper [in a seminar], I decided that the way to answer the sceptics was an experiment to prove the bacterium could infect a healthy person, myself. I felt a little nauseated after I drank the broth. I then had some stomach rumblings for three days, followed by bloating and fullness after evening meals." Although his illness resolved spontaneously in two weeks, a gastric biopsy taken on the 10th day showed severe acute gastritis with many *H. pylori* organisms.[2] After that, the experiment was repeated and several publications subsequently confirmed that the hypothesis was correct.

For over a century of medical bacteriology, it was a "known fact," that bacteria did not grow in the stomach. "Known facts can be dangerous;" Robin Warren quoted Sherlock Holmes (*The Boscombe Valley Mystery)* in his Nobel lecture.[3] "There is nothing more deceptive than an obvious fact." Like Jon Franklin and Alan Doelp wrote in their book *Shocktrauma,* a novelistic documentary on pioneering American trauma surgeon, R Adam Cowley, "To a medical pioneer, yesterday's dogma is a special threat. It is

not the mysteries of nature that blind a scientist but his own unexamined prejudices, handed down to him from previous generations of scientists."[4]

The last 25 years of study have uncovered much of the complicated relationship between *H. pylori* and its host, the humans. *H. pylori* lives on gastric fluid, as it is through the production of bicarbonate, by metabolizing the urea in gastric fluid, that the organism is able to survive in the low pH environment of the stomach and produce carbon dioxide that is essential for its own growth. It colonizes the gastric epithelial cells passing into the extracellular mucous layer with its more pH-neutral conditions. Infection induces a host response, which results in mucosal damage and a chronic active gastritis. The infection occurs initially in the non-acid secreting areas of the stomach, the antrum, which is its most favoured site, though it may choose to colonize other parts of the stomach. Colonization however ceases abruptly where gastric mucosa ends. Non-gastric mucosa is restricted territory that the rules of engagement forbid that it invades. If there's an area of intestinal metaplasia in the stomach, *H. pylori* can only occupy as far as the edge, and wherever elsewhere within the gut is gastric metaplasia, especially in the duodenum; there you may find *H. pylori*. It is a highly adapted organism that lives only on gastric mucosa.

Despite the presence of chronic gastritis, most infections are asymptomatic, and the stomach looks normal on endoscopy. However, 10-15% develop PUD (3-10x increased risk), 1% will develop non-cardia gastric cancer (3-5x increased risk), and an even fewer (less than 1%) the rare mucosal associated lymphoid tissue (MALT) lymphoma.[5] There are also unresolved associations with non-ulcer dyspepsia, Gastro-Oesophageal Reflux Disease (GORD) and some non gastrointestinal diseases. The complex balance between protective and ulcerogenic phenomena, between bacterial and host responses, is impacted by environmental factors like stress, smoking, alcohol, NSAIDs, et cetera. There is now no doubt whatsoever that *H. pylori* is actively involved in the pathogenesis of duodenal ulcer, gastric ulcer and gastric cancer, and although pathogenic mechanisms are still being elucidated, several factors can be identified:

1. The ammonia produced by urease is mutagenic and also causes ionic changes in the mucus layer with consequent back-diffusion of hydrogen ions in the mucosa, thus counteracting the acidity of gastric hydrochloric acid secretion.[6]
2. Most strains of *H pylori* can be divided into two distinct phenotypes based on the presence or absence of a vacuolating toxin (vacA) and the products of the cag pathogenicity island (cagPI), a large chromosomal region that encodes virulence genes. Individuals infected with strains of *H pylori* with the cagPI have more severe mucosal damage and are more likely to have duodenal ulcers or gastric cancer.[7]
3. The production of vacuolating toxin (vacA) and cytotoxin (cagA of the cag pathogenicity island) and other substances, such as lipopolysaccharides potentiate inflammatory response from the gastric mucosa. The cagA toxin is associated with stimulation of interleukin IL-8 expression and increased inflammation which is mediated through neutrophils, followed by T and B lymphocytes, plasma cells and macrophages, with a strong infiltration of CD4+ and activation of helper cells.[8] Genetic polymorphism in the host, favoring pro-inflammatory factors like interleukin IL-1, the most potent inhibitor of gastric acid secretion, increases the risk of gastric cancer.
4. Serum gastrin is increased in *H. pylori* infected patients with duodenal ulcer, mediated through damage to antral delta cells, which normally secrete somatostatin, a potent inhibitor of gastrin release. Gastrin being the main stimulus to acid production in the parietal cells, there is high acid secretion in *H. pylori* infected duodenal ulcer patients, which results in gastric metaplasia of the duodenum with subsequent bacterial colonization and direct mucosal damage. [9]
5. Acid secretion is reduced in patients with generalised atrophic gastritis, which may be an effect of stimulation of interleukin 1-B, a potent acid inhibitor, in the body of the stomach or the consequence of antral atrophy with decreased gastrin release.[7] The generalised atrophic gastritis may proceed to intestinal metaplasia and malignancy, with possible development of gastric ulcer and/or gastric cancer.
6. There is a positive feedback loop that perpetuates the different patterns of gastritis; for example, suppression of acid with a proton pump inhibitor diminishes antral gastritis but allows *H. pylori* to colonize the corpus, which then becomes inflamed. This shows that acid secretion normally protects the corpus from *H. pylori* infection. Thus high acid secretion in people with duodenal ulcers may be self-

perpetuating because it restricts gastritis to the antrum, leaving a healthy corpus to continue secreting acid. On the other hand, low acid secretion may be self-perpetuating because it increases corpus gastritis, which further depresses acid secretion.[7]

Thus the distribution of *H. pylori* gastritis determines acid secretion and the clinical outcome of *H. pylori* infection, be that duodenal ulcer, gastric ulcer, gastric cancer, or asymptomatic infection. The pathogenic importance of *H. pylori* depends on the interaction between bacterial virulence, the host, and the environment. By affecting acid output or the severity of corpus gastritis, these factors might steer a person infected with *H. pylori* to a state of high acid secretion (predominantly antral gastritis) or to low acid secretion (predominantly corpus gastritis). This model is attractive because it allows studies of gastric physiology to be integrated with other equally important determinants of disease outcome.[7] In individuals with predominantly antral gastritis, often associated with increased acid production, duodenal ulcers are the major pathologic consequences of the infection. However in patients where *H. pylori* colonisation leads to pan-gastritis, there are inflammation of corpus and parietal cells, atrophic gastritis and reduced acid production.[7]

H. pylori cuts across all races and is distributed throughout the world. Its prevalence is strongly correlated with socio-economic conditions viz. low levels of education and income, household crowding, institutionalizations like in psychiatric units and orphanages leading to sharing of beds, secretions from upper respiratory tract of chronic carriers, poor hygiene and poor feeding practices. Familial clustering of infection occurs and family members may all be infected by the same strain of *H. pylori*. Transmission occurs via the oral route, by saliva, vomitus, fecal contamination or tainted water supplies, and unless eradicated by antibiotics, infection usually persists for life.

In developing countries, about 80% of the population shows evidence of infection, compared to only 35-40% in developed countries.[10] The prevalence of infection is even smaller in younger cohorts in developed countries. In Japanese children it is now less than 5%. In developed countries, seropositivity is low in childhood and rises slowly with age at approximately 0.5%/yr, while in the developing world the infection is acquired in early childhood with prevalence of 70% by the age of 5. [10]Overall, it is estimated that the chances of acquiring the organism increase by about 10% with each decade of life, thus a 30 year-old adult will have around 30% chance of harbouring the organism.

Helicobacter pylori shows extremely complex ethno-geographic variations in epidemiology and pathogenicity with interesting effects. In the west, as the prevalence of *H. pylori* has fallen, so too has the incidence of the *H. pylori*-related duodenal ulcers. In Africa, however infection is still endemic in the population, cagPI strains of *H. pylori* are present in almost all infected people but only a few develop clinical disease and 90% of duodenal ulcers are *H. pylori* positive. [7, 11]In spite of these, gastric ulcer is much less common in Africa and there is also a relatively low risk of gastric cancer. This phenomenon has been dubbed the "African enigma" which represents high prevalence of *H. pylori* infection with a low prevalence of gastric cancer.[12] Here is another phenomenon, which like most African problems, seems to defy scientific explanations.

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