Review Article

Helicobacter pylori and its Effects on Human Health and Disease

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Abstract

H. pylori is now a known cause of gastric and duodenal ulcers, noncardia gastric cancer and gastric MALT lymphoma. In addition, the role of this microorganism in causing or preventing a large number of other diseases has been investigated, some of which include esophageal cancer, functional dyspepsia, gastroesophageal reflux disease, asthma, cardiovascular diseases, iron deficiency anemia and idiopathic thrombotic purpura. This article reviews the evidence for these associations and provides suggestions for further research.

Keywords: anemia, atherosclerosis, esophageal cancer, gastric cancer, *Helicobacter pylori*

The discovery of *Helicobacter pylori*, gram negative bacteria that colonize the stomachs of approximately half of the world's population,[1] has without doubt been one of the most remarkable achievements in medical research in the past three decades. The Australian co-discoverers Barry Marshall and Robin Warren, a clinician and a pathologist, received the Nobel Prize in Physiology or Medicine in 2005. A PubMed search of "*Helicobacter pylori*" in December of 2010 resulted in nearly 29,300 entries, and there is now a dedicated journal named "Helicobacter".

Warren and Marshall found this organism in the stomachs of about 75% of patients with gastric ulcers and the majority of those with duodenal ulcers compared to half of the normal subjects.[2] Furthermore, Warren observed that gastric inflammation was almost always present in the mucosa close to where the bacteria were seen.[2] Based on these observations, the discoverers hypothesized that these bacteria could cause gastritis and peptic ulcers.[2] This hypothesis was initially met with strong resistance from the scientific community because it was a major shift from the dogma of the time that gastritis and ulcers were mainly caused by hyperacidity due to various reasons, including stressful life events.[3] Due to its high acidity, the stomach was considered a sterile environment. Therefore, bacteria observed in the stomach were considered by many to be contamination rather than bacteria that persistently colonized the stomach, which could cause ulcers. Indeed, the abstract submitted by these two scientists to the Australian Gastroenterology Association meeting in 1983 was ranked among the lowest 10% and rejected. Persisting, however, they were able to present their observations in other meetings and finally publish some of their findings in a letter to *Lancet*.[2] In this letter, Marshall, while cognizant of the difficulties ahead with establishing a causal relationship, went one step beyond gastritis and suggested that the microorganism could also cause gastric cancer. He wrote: "*The pathogenicity of these bacteria remain unproven … if the bacteria are truly associated with antral gastritis, …, they may have a part to play in other poorly understood, gastritis associated diseases (i.e., peptic ulcer and gastric cancer)*".

Despite initial resistance, research on *H. pylori* continued, perhaps far beyond what Warren and Marshall had anticipated. A causal role for these bacteria has been explored in relation to not only gastritis, peptic ulcer and gastric cancer, but also in many other cancers, within and outside the gastrointestinal system, and in relation to hematologic, cardiovascular, dermatologic, and respiratory diseases, and other conditions such as obesity. In this review, we summarize some bacteriologic and epidemiologic features of *H. pylori*, discuss its role in causing and preventing diseases, and suggest topics for future research.

H. pylori: Discovery, microbiology and epidemiology

H. pylori are curved, gram-negative, microaerophilic bacteria that grow on chocolate agar at 37°C. The bacteria are about 0.5×3 μm in size and have up to 7 sheathed flagella that extend from one end. When initially cultured, Warren and Marshall determined that the bacteria, while not exactly similar to any previous species, perhaps belonged to the *Campylobacter* genus. Therefore, they named them "*Pyloric Campylobacter*", which later changed to *Campylobacter pyloridis* and later to *Campylobacter pylori*. However, from the beginning, it was not clear that this microorganism was in fact a *Campylobacter*, and subsequent studies made it clear that these bacteria were distinct enough from *Campylobacter* to establish a new genus named after them. Therefore, the genus *Helicobacter* was created. *H. pylori* was the first species in this genus but by now there are at least 18 validly named species including *H. felis*, *H. canis*, *H. bilis,* and *H. hepaticus*, some of which have been found in humans and, although yet unclear, may impact our health.

Given the high prevalence of *H. pylori* in the human stomach one wonders how pathologists did not discover this microorganism until the 1980s. In retrospect, there are several reasons. *H. pylori* can be visualized with silver staining but it cannot be readily seen with the usual staining methods, and therefore might have been overlooked by many pathologists. Searching the literature, Marshall realized that several papers published decades earlier had noted "spirochetes" in the stomach.[2] There are German papers from the early 1900s that suggested an association between these bacteria, ulcers, and cancer.[4] However, some of these findings were ignored thinking that these bacteria were merely oral contaminants, which multiplied in post mortem specimens or close to ulcers.[2] These earlier findings were dismissed partly, because

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the stomach has an acidic environment unfriendly to most microbes. However, *H. pylori* has developed certain capabilities that allows survival in the harsh environment of the stomach; these include the presence of flagella that allow the bacteria to swim and find more livable environments within the stomach, hiding in the mucus layer adjacent to the gastric epithelium and perhaps most important the ability to produce ammonia from urea using its urease enzyme. This latter characteristic has enabled us to detect the presence of *H. pylori* by the urea breath test. Paradoxically, however, *H. pylori* is less likely to survive in atrophic gastritis, where there is much less acid. One can mention two more reasons for the delayed discovery of *H. pylori*: the small number of international conferences and slow communications before the 1950s, which prevented investigators who saw the bacteria from communicating with others, and a strong belief that ulcers were solely the result of hyperacidity, which distracted scientists from examining apparently unrelated causes of acid secretion. "No acid, no ulcer", also known as Schwartz's maxim,[5] was first proposed in 1919.

Infection typically occurs during childhood (before the age of 10) and, if untreated, persists life-long.[6-8] Humans are the major reservoir of *H. pylori*; this organism rarely colonizes the stomachs of animals, therefore transmission is from human to human. The route of transmission is not entirely clear but it is perhaps fecal-oral and oral-oral.[9] Studies have shown that low education, parents' low education, poor dental hygiene, crowded living places in childhood and several other indicators of low socioeconomic status are risk factors for carrying *H. pylori.*[10]

H. pylori can be eradicated from the stomachs of most people by one week of therapy with the combination of a proton pump inhibitor and two antibiotics.[11-13] Once *H. pylori* is eradicated, recurrence happens at a rate of 1 – 2% per year. Although the development of vaccines has been under way for more than 20 years, there are no commercially available vaccines in the market. Vaccines are now being tested in clinical trials,[14] however, the fact that carrying *H. pylori* does not provide immunity to this organism suggests that vaccines may not be effective.

The prevalence of *H. pylori* in human populations substantially varies by country and by age group. The prevalence of colonization ranges from 30% in Sweden to 90% in Algeria and India[15,16] but these numbers are perhaps much lower than they were a hundred years ago. *H. pylori* has co-existed with humans for at least 58,000 years,[17] perhaps since their origin,[18] and once nearly all humans harbored this organism in their stomachs. However, recent advances in sanitation and antibiotic use have caused rapid disappearance of *H. pylori* from human populations,[19] especially in western countries. In the United States, for example, data from the third National Health and Nutritional Examination Survey (1988 – 1991) showed that serum samples from 57% of the population older than 70 years of age, versus 17% of the population between 20 – 29 years of age, were positive for IgG antibodies against *H. pylori.*[20] More recent data from the National Health and Nutritional Examination Survey (1999 – 2000) showed a positive IgG seroprevalence of only 5% in children younger than 10 years of age who were born in the 1990's.[21] Likewise, in Japan rates declined from 70 – 80% in those born before 1950 to 25% in those between 1960 to 1970.[22] Given that *H. pylori* colonization in most people occurs before the age of 10,[7] these numbers show a substantial decline in *H. pylori* over a period of 70 years, which reflects a cohort effect.

H. pylori is genetically diverse and some are more virulent than others. Several virulence factors have been found including adhesins, which help in binding *H. pylori* to the epithelium (i.e., BabA, OipA, SabA), a vacuolating cytotoxin (VacA) that causes cell injury and inflammation, and CagA, a protein that can be delivered into the gastric epithelial cells and may increase the turnover of epithelial cells.[23] Although all *H. pylori* have *vacA*, the gene that encodes VacA, there is variation among VacA types with some considered more virulent. CagA-positive strains constitute the majority of *H. pylori* and possess the *cag* pathogenicity island in their genome, a genetic island of approximately 31 putative genes, including *cagA*—the gene that encodes the CagA protein.[23] CagA-positive strains are also more likely to have the s1 allele of *vacA*, which encodes a molecule that affects epithelial cells,[24] and are also more likely to express the *babA* product, which controls adherence of *H. pylori* organisms to Lewis^b antigens on gastric epithelial cells.[24]

With this background, we discuss some of the diseases associated with the presence or lack of *H. pylori*.

Diseases associated with *H. pylori*

Gastritis

H. pylori is now established as a cause of gastritis. The evidence for this causal relationship comes from the initial observations of Warren and Marshall, human studies by others, and animal studies.

As discussed earlier, the suggestion that *H. pylori* could cause gastritis was legitimately met with skepticism. How could scientists be sure that the association of *H. pylori* and gastritis was not due to reverse causality (i.e., gastritis provides a suitable environment for the microbe to grow) or confounding?

To test his hypothesis, Marshall did an experiment on himself. After undergoing endoscopy, which showed normal gastric mucosa, he received *H. pylori* by mouth. Histologically proven acute gastritis developed on the tenth day after the ingestion of bacteria, but it resolved in a few days afterwards.[25] Similar experiments were done by other volunteers. A fellow Australian did a similar experiment on himself but in his case the disease was much more severe and did not resolve for 5 years. Later, Morris and Nicholson ingested 10^5 *H. pylori* and developed gastritis, which was later resolved by a course of antibiotics.[26] Further adding to the evidence are several reports of epidemic hypochlorhydria during gastric secretory studies.[27-29] As shown by Graham, contamination of equipment with *H. pylori* was the likely cause. Over time, acute gastritis caused by *H. pylori* can change to chronic gastritis, a condition that is characterized by loss of glands and secretory function of glands in the stomach.

Experimental studies of *H. pylori* in animals were not initially possible because the microbe did not colonize in small animal models. However, the isolation of a closely related bacterium from the cat stomach, called *H. felis*, made it possible to investigate new small animal models. Lee and Fox at the Massachusetts Institute of Technology fed *H. felis* to germ-free mice and observed that the organism colonized the stomach in large numbers in mucus and deep in the gastric pits. Within a few weeks, they observed progression from acute inflammation to active chronic inflammation.[30] Mongolian gerbils were later developed as animal models that harbored *H. pylori* and were shown to develop chronic gastritis after receiving the bacteria.[31]

Peptic ulcer disease

H. pylori is now a fairly well-established cause of peptic ulcer. Again, there was much initial skepticism about such cause and effect relationship. A 1988 editorial in the journal *Gastroenterology* [32] stated: *"… a sizable group of skeptics claim that the cause-and-effect thesis is not verified and that the thought that antibiotics may be more effective than conventional antacid treatment for peptic ulcer disease is intuitively offensive…"* However the evidence has grown over time from animal studies, observational epidemiologic studies and *H. pylori* eradication studies.

Mongolian gerbils can be orally inoculated with *H. pylori* and used as animal models to study the pathogenesis of diseases associated with this microorganism. Six months after inoculation, chronic gastritis and ulcers were seen in the animals.[31]

A meta-analysis of observational epidemiologic studies showed that *H. pylori* increased the risk of duodenal ulcers by two-fold.[33] A large number of studies have investigated the effect of one or more weeks of *H. pylori* eradication therapy on ulcer healing and recurrence. A Cochrane review of the published trials showed that compared to placebo use, eradication therapy significantly increased duodenal ulcer healing rates, and reduced recurrence of both gastric and duodenal ulcer by three- to five-fold.[34]

H. pylori colonizes the stomach, however, most ulcers are found in the duodenum rather than the stomach. *H. pylori* possibly increases acid production in the stomach via causing chronic inflammation in the distal part of the stomach, which causes ulcer formation in the more vulnerable duodenum.

Functional dyspepsia

Functional dyspepsia, also referred to as idiopathic dyspepsia or non-ulcer dyspepsia, is diagnosed when prolonged dyspepsia (bothersome postprandial fullness, early satiety, epigastric pain, or epigastric burning) cannot be explained by structural diseases (i.e., peptic ulcer disease). Functional dyspepsia is very common, so finding and treating the causes is clinically important.

Gastric motor function abnormalities, visceral hypersensitivity and psychosocial factors have been suggested as mechanisms responsible for functional dyspepsia. *H. pylori* may have a role in the etiology of this disease by causing inflammation leading to visceral hypersensitivity or by causing dysfunctional smooth muscle motility. However, studies have not supported these hypotheses.

The results of trials have been controversial. A randomized trial, published in *New England Journal of Medicine*, showed that one year after treatment symptoms resolved in 21% of those who received treatment for *H. pylori* (antibiotics and omeprazole) compared to 7% in those who only received omeprazole.[35] However, two other trials with similar designs, also published in *New England Journal of Medicine*, found no effect.[36,37] The results of a Cochrane review and meta-analysis of the trials suggests that treatment for *H. pylori* reduces the risk of this disease by 8% (95% confidence interval of 3% to 12%) and concluded that treatment may be effective in a small number *H. pylori* positive patients.[38]

There is no consensus that *H. pylori* eradication treatment is beneficial for functional dyspepsia. Nevertheless, the American Gastroenterological Association recommends *H. pylori* eradication in patients with functional dyspepsia,[39,40] partly because it may relieve symptoms, and partly because of long-term effects in reducing risk of gastric cancer (see below, under *Gastric Cancer*).

Gastroesophageal reflux disease

Chronic *H. pylori* colonization may reduce the risk of gastroesophageal reflux disease (GERD). A meta-analysis published in 2003 showed a 40% reduction in risk of GERD in *H. pylori* positive individuals, although the results were largely different between East Asian and Western countries.[41] More recently, a population-based case-control study from the United States showed a reduced risk of GERD in individuals who harbored *H. pylori* in their stomach.[42] *H. pylori* eradication may not only increase the prevalence of GERD but also its consequences including Barrett's esophagus and esophageal adenocarcinoma (see below, under *Esophageal Cancer*).

Gastric cancer

As alluded, in their first letter to *Lancet*, Marshall and Warren suggested a possible role for *H. pylori* in the etiology of gastric cancer.[2] The idea prompted many investigators to study the effect of *H. pylori* on causing gastric cancer by laboratory, animal, and epidemiologic studies. Based on these studies, in 1994, the International Agency for Research on Cancer declared *H. pylori* as a definite risk factor for gastric cancer.[43] Since then, however, many more studies have been conducted on the relationship between *H. pylori* and gastric cancer.

Inoculating Mongolian gerbils with *H. pylori* induces adenocarcinomas in the pyloric region of the infected animals.[31] Thus far, at least 80 epidemiologic studies of the association of *H. pylori* and gastric cancer have been conducted, and the large majority have found an increased risk. Three meta-analyses[44-46] and one combined analysis[47] that have assessed the association, have found a two- to three-fold increased risk. The combined analysis, which included only prospective studies, found a three-fold increased risk but showed even higher risk (approximately six-fold) with longer follow-up. There are reasons to believe that the six-fold increase may be more accurate.[47,48] Some investigators have gone further and believe that *H. pylori* is a necessary cause for gastric cancer.[49] Assuming that the more modest relative risk of three is true, 300,000 new cases of gastric cancer are attributed to *H. pylori* each year.[50]

There is evidence from interventional studies that *H. pylori* eradication may reduce the risk of gastric cancer. A recent meta-analysis showed a statistically significant 35% reduced risk of gastric cancer in those who were treated for *H. pylori.*[51] In addition, a randomized study of 544 patients with early gastric cancer showed a 65% reduction in the incidence of metachronous gastric cancers in those who were treated for *H. pylori.*[52] Several more randomized studies are underway.

The association between *H. pylori* and gastric cancer may vary by cancer subsite and by *H. pylori* strain. The etiology of cancers arising from the gastric cardia (the top 2 – 3 centimeters of the stomach) may be different from that of other parts of the stomach. The combined analysis[47] showed an increased risk for non-cardia tumors but did not find an association with cardia tumors. Whether or not *H. pylori* can cause tumors of gastric cardia has been debated in several publications.[48,53] Some studies have found that CagA-positive strains of *H. pylori* pose a higher risk of non-cardia gastric cancer but others have not found such association. The results of a meta-analysis suggested that among those with *H. pylori*, compared to CagA-negative strains, CagA-positive strains further increase the risk of noncardia gastric cancer by almost two-fold.[54]

MALT lymphoma

The discussion in the previous section was mostly relevant to gastric adenocarcinoma, which constitutes over 85% of all gastric malignancies. There is, however, another tumor in the stomach that can be caused by *H. pylori*, mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach, which constitutes nearly 3% of all gastric malignancies and 10% of all lymphomas.

Clinical, epidemiological observational and interventional studies have provided very strong evidence for a causal role of *H. pylori* in the etiology of this cancer. Normal gastric mucosa is devoid of lymphoid tissue but mucosal lymphoid tissue can develop in response to *H. pylori* in approximately a quarter of *H. pylori* positive subjects.[55] Nested case-control studies have shown an approximately six-fold increased risk of MALT lymphoma in *H. pylori* positive subjects.[56] Interestingly, CagA-positive strains are associated with higher risk than CagA-negative strains.[57]

Treatment data have been very convincing in proving the role of *H. pylori* in causing MALT lymphoma. In a small study by Wotherspoon and colleagues, *H. pylori* was eradicated in six patients with MALT lymphoma and subsequent biopsies showed no evidence of lymphoma in five out of the six.[58] Several other studies,[59–61] including one with 88 patients,[61] showed complete or partial regression of lymphoma with *H. pylori* eradication.

Esophageal cancer

Esophagus neighbors the stomach. Not surprisingly, therefore, after gastric cancer, *H. pylori* has been studied most in association with esophageal cancer. The two most common histological types of esophageal cancer are esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC).

A consistent inverse association has been shown between *H. pylori* and esophageal adenocarcinoma. The results of three recently published meta-analyses showed that *H. pylori* colonization of the stomach is associated with a nearly 50% reduction in risk.[62–64] One of these meta-analyses also showed an inverse association of *H. pylori* with Barrett's esophagus,[63] the precursor lesion of esophageal adenocarcinoma. One of these studies showed that only CagA-positive *H. pylori*, but not CagA-negative strains, was associated with reduced risk of esophageal adenocarcinoma.[62] It is not yet entirely clear that this association is causal, and if it is, what the responsible mechanism is. However, a few hypotheses have been offered. *H. pylori* may decrease risk of esophageal adenocarcinoma by reducing gastric acid production leading to lower acid reflux from the stomach to the esophagus.[65] It may also reduce risk by decreasing the production of ghrelin, an appetite stimulating hormone[66] and could therefore reduce body mass index, an important risk factor for esophageal adenocarcinoma.[67]

In contrast to its association with esophageal adenocarcinoma, *H. pylori* does not seem to be associated with ESCC. Three recent meta-analyses that summarized the association of *H. pylori* with ESCC found no overall association, with summary odds ratios very close to one.[62-64]

Iron deficiency anemia

H. pylori can cause iron deficiency anemia (IDA) in patients with bleeding ulcers or cancers. However, there is evidence that it may cause IDA in the absence of ulcers or cancer. Several case series in the 1990s, reporting 1 to 30 patients, showed reversal of refractory anemia in both children[68] and adults[69] with treatment of *H. pylori*. Furthermore, observational epidemiologic studies have shown higher risk of IDA in *H. pylori*-positive patients.[70,71] A meta-analysis of observational studies suggested a two to three-fold increased risk of IDA in *H. pylori* positive subjects.[72] However, the results of *H. pylori* eradication trials in treating IDA have been inconclusive, partly due to the small size of most of these trials, no placebo group or concurrent control group in some, and lack of power to analyze subgroup results, such as subgroups with refractory anemia.[72] The Maastricht III consensus conference recommended *H. pylori* treatment in patients with unexplained IDA.[73]

The mechanisms for a causal association between *H. pylori* and IDA are not clear but several have been suggested including blood loss secondary to gastritis, decreased iron absorption of dietary iron and increased uptake of iron by the bacteria (reviewed by Mushen et al.[72]).

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease in which antibody reaction causes destruction and lower numbers of platelets leading to easy bruising, bleeding to skin and mucous membranes, and occasionally into the brain.

An Italian group first implicated a role for *H. pylori* in the etiology of ITP.[74] The group identified 18 children with ITP of whom 11 were positive for *H. pylori* and treated for it. Of these, *H. pylori* was eradicated in eight but not in the other three. After two and four months, platelet counts rose significantly in the eight in whom *H. pylori* was eradicated but not in the three in whom the treatment was not successful or in the seven who were negative for *H. pylori*. Furthermore, antibodies disappeared in six of the eight. Since the publication of this report many other studies have evaluated the effect of *H. pylori* eradication in treating ITP.

A meta-analysis of 25 studies including 1555 patients[75] showed a response rate of approximately 50%. The response rate was highly heterogeneous among studies but it was higher among patients with milder disease and in countries with higher prevalence of *H. pylori*. The main limitation of this meta-analysis was that only one study was a randomized trial and the rest were observational studies, mainly case series. The randomized study found a significant relationship between *H. pylori* eradication and platelet recovery (46% in the eradication group versus 0% in the non-eradication group). However, it was a small study and its results need to be reproduced in other randomized trials. Therefore, the conclusion that *H. pylori* eradication leads to treatment of ITP is not fully proven but Maastricht III consensus conference recommends detection and treatment of *H. pylori* in ITP patients.[73]

Asthma

While the prevalence of *H. pylori* decreased, the prevalence of atopy and asthma increased in many Western countries during the last four decades of the 20th century.[76] This has led some scientists to speculate that lack of *H. pylori* may contribute to the higher incidence of asthma. This is part of what is called the "hygiene hypothesis" which states that lack of exposure to microorganisms during childhood may alter the balance of TH1 and TH2 lymphocytes such that more IgE-mediated allergy occurs.[77]

Several case-control studies have now shown inverse associations between *H. pylori* and atopy or asthma in Italy,[78] Denmark,[79] Iceland, Estonia, Sweden,[80] and the United States.[21,81,82] Interestingly, some studies have shown that only CagA-positive strains are inversely associated with asthma.[82] Whether future studies confirm this association remains to be seen. If the association is

consistent, there remain other questions, for example whether lack of *H. pylori* causes asthma, or *H. pylori* is merely an indicator for disappearance of other microorganisms that are responsible for the association.

Atherosclerotic diseases

H. pylori has been heavily investigated in relation to atherosclerotic diseases, including ischemic heart disease (IHD) and stroke.

IHD is considered a mainly non-infectious disease. However, in the past two decades a considerable number of studies have shown higher risk of IHD with markers of inflammation, particularly C-reactive protein,[83] and have implicated a number of infectious agents including *H. pylori* as possible culprits in the etiology of IHD. The link between *H. pylori* and IHD has been investigated in both epidemiologic and mechanistic studies. While a causal link is uncertain, there is some evidence for some weak to moderate association, especially with CagA-positive strains.

Part of the difficulty in proving an association between *H. pylori* and IHD is that any association may be confounded by socioeconomic status. Both *H. pylori* and IHD are more common in the more socially disadvantaged groups and imperfect measurement of social class or lack of proper adjustment for it may result in confounded associations. A meta-analysis of prospective studies in 2001 showed no overall association between *H. pylori* and IHD, especially in the more homogeneous cohorts with more stringent adjustment for socioeconomic status.[84] However, more recent meta-analyses suggest that CagA-positive strains, but not CagA-negative strain, may increase IHD risk.[85–87] The magnitude of the association, however, is small and retrospective studies have shown stronger associations than prospective ones.[85] Likewise, a meta-analysis showed a consistent association between CagA-positive *H. pylori* and stroke.[86] If an association exists it is unclear whether CagA is directly involved in atherogenesis or it exerts its effect through causing systemic inflammation but a recent study found evidence of CagA antigen inside atherosclerotic plaques.[87]

Other diseases and conditions

H. pylori has been explored as a cause of a large list of other diseases, including pancreatic cancer, [88,89] colorectal cancer, [90,91] Crohn's disease,[92] dermatologic diseases,[93] uveitis, otitis media, and Parkinson's disease as well as several others (reviewed Franceschi et al.[94] and Pellicano et al.[95]). Since *H. pylori* is a known cause of at least two gastrointestinal tract cancers (noncardia gastric adenocarcinoma and gastric MALT lymphoma), researchers have been interested in examining its association with other gastrointestinal cancers. Given that Crohn's disease, ulcerative colitis, some dermatologic and rheumatologic diseases, and many other human diseases are due to chronic inflammation, it is not surprising that *H. pylori* has been investigated as a cause. Although some of these studies have shown associations, they have not been consistent and further studies may be needed to confirm or refute any causal link. *H. pylori* has also been investigated in relation to food intake and body weight (reviewed by Weigt et al.[96]). Some hormones produced in the stomach, such as ghrelin, affect appetite. Therefore, *H. pylori* may affect weight by modulation the production and release of these molecules and their release into the circulation. Although the majority of studies have shown that *H. pylori* reduces ghrelin production[96] and that its eradication increases ghrelin levels,[97] it is yet unclear whether these bacteria affect weight.

Summary and Suggestions for Further Research

H. pylori, an organism unknown to us prior to the 1980s, is now a known cause of peptic ulcer disease, noncardia gastric cancer and MALT lymphoma. These discoveries have revolutionized many fields of medicine and medical research. Three decades ago, peptic ulcer disease could be healed by inhibiting gastric acid but the disease frequently relapsed due the presence of bacteria and chronic inflammation. It was not uncommon for patients to undergo major surgeries, such as gastrectomy and vagotomy, to reduce the relapse of the disease. The discovery of *H. pylori* and its treatment revolutionized the treatment of peptic ulcer disease from highly invasive surgeries to a course of antibiotics. As the Swedish Academy put it: "*Thanks to the pioneering discovery by Marshall and Warren, peptic ulcer disease is no longer a chronic, frequently disabling condition, but a disease that can be cured by a short regimen of antibiotics and acid secretion inhibitors.*"

H. pylori prevalence is naturally declining in many parts of the world, perhaps due to sanitary measures and use of antibiotics. Interestingly, CagA-positive strains of *H. pylori* have been disappearing faster than the CagA-negative ones.[98] With *H. pylori* declining in prevalence, incidence of diseases associated with it are declining. The incidence and recurrence of peptic ulcer disease is much less common. Rates of noncardia gastric cancer have sharply fallen in most parts of the world during the past few decades.[99] Some argue that this microorganism should be eradicated more quickly by using antibiotics or development of vaccines.

Others, however, have cautioned against a possibly hasty decision about *H. pylori* eradication. Not everyone is adversely affected by *H. pylori*. Only 10 – 15% of carriers experience peptic ulcer disease and perhaps less than 3% will ever be diagnosed with gastric cancer.[1] An indiscriminate use of antibiotics may lead to widespread bacterial resistance. Therefore, the current guidelines suggest that treatment should not be universal, rather it should be limited to those who may benefit from treatment, such as those with gastric or duodenal ulcer, functional dyspepsia, MALT lymphoma, ITP, and those who wish to be treated for *H. pylori* only after full consultation with a physician.[73] More importantly, there is growing evidence that *H. pylori* may prevent against some childhood diseases, such as asthma, and adult diseases such as esophageal adenocarcinoma. Incidence rates of esophageal adenocarcinoma have sharply increased in Western countries in the past few decades[100,101] and it is possible that these increased rates are partly due to a decline in *H. pylori* prevalence. In parallel, the incidence rates of gastric cardia adenocarcinoma, another cancer that *H. pylori* may protect us against,[48] are increasing in some Western countries.[100] Another piece of evidence consistent with a protective role of *H. pylori* is that esophageal adenocarcinoma rates are still low in most developing countries,[102,103] where *H. pylori* is still common.

Dr. Martin Blaser, an eminent researcher in the field of *H. pylori*, argues that since *H. pylori* has been with humans for tens of thousands of years despite its potential for causing disease may imply that there are beneficial effects for humans, too. He cites some of the more recent studies pointing to a preventive effect of *H. pylori* on asthma and esophageal adenocarcinoma as evidence for such potential benefit.[21,81,104,105] Therefore, he warns that any decision on complete eradication of *H. pylori* may be premature.[19,106,107]

There remain many lines of important research in assessing the effects of *H. pylori* on health and disease. Studying the associa-

tion between *H. pylori* and asthma has just begun. It is important to know whether there is an association, whether *H. pylori* delays the age of onset of asthma and whether these potential associations are limited to CagA-positive strains. Studies are pointing to a protective association between *H. pylori* and esophageal adenocarcinoma but only in CagA-positive strains. However, given that few studies have assessed CagA positivity in relation to esophageal adenocarcinoma,[62] more studies are needed on this topic. A number of studies have found an association between disappearance of *H. pylori* and obesity (reviewed by Weigt et al.[96]). More studies are needed to confirm or refute such association and, if confirmed, mechanisms need to be further investigated. Some have suggested that *H. pylori* may stop weight gain through its effect on hormones such as leptin and ghrelin but lack or presence of *H. pylori* can solely be a marker for the lack or presence of other gut microbiota. New technologic advances in microbiomics may enable us investigate this latter hypothesis. *H. pylori* is highly diverse. In addition to CagA, several other virulence factors have been identified.[108,109] Some, but not others, can be tested for in serum samples collected in epidemiologic studies. Developing markers for the other virulence factors that can be tested in epidemiologic studies can be potentially very important in our understanding of pathophysiology of diseases caused or prevented by *H. pylori* and in distinguishing between harmful, innocuous, and potentially beneficial strains of *H. pylori*. Investigating the associations between *H. pylori* and other helicobacter species such as *H. hepaticus* and *H. bilis* with cancers of other organs, such as cancers of the colon and bile duct [110,111] is another blossoming field of research. Developing vaccines and testing them in humans is also another line of important research.

Francis Crick, the co-discoverer of the DNA structure, recounts a story of his early life, when he read Arthur Mee's Children's Encyclopedia. He enjoyed reading about science but was worried that by the time he grew up—"*and how far away that seemed*" - everything would be discovered. His mother reassured him that "*Don't worry …There will be plenty for you to find out*".[112] We have come a long way in our investigation of the effects of *H. pylori* on health and disease but to paraphrase Elizabeth Crick "*there is plenty for us to find out*."

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