Contemplating the Future without *Helicobacter pylori* and the Dire Consequences Hypothesis

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Abstract

Helicobacter pylori is a serious chronic transmissible pathogen that causes gastric structural and functional damage and is a major cause of morbidity and mortality worldwide. *H. pylori* is one of the digestive tract pathogens that has traveled with mankind since before humans moved out of Africa. Some have suggested that the long association of *H. pylori* with humans means there must be a benefit and suggest dire consequences will follow its eradication. Fortunately, there are now sufficient experiences with the outcome of treatment and with populations where the infection disappeared long ago to support the conclusion that *H. pylori* is a serious chronic transmissible pathogen that no one needs, deserves, or desires. The dire consequence hypotheses have proven to be erroneous attempts to blame some of the problems facing the modern world on a pathogen that was and is responsible for much suffering, morbidity, and mortality. It is time to join together to eradicate it and to let *H. pylori* join smallpox and polio on the hit list of undesirables.

Keywords

Helicobacter pylori is a serious chronic transmissible pathogen that causes gastric structural and functional damage and is a major cause of morbidity and mortality worldwide. At least 20% of those infected will eventually experience a clinical outcome [1]. Table 1 shows the diseases in which *H. pylori* is a major cause. None are exclusive to the infection. The lifetime risk for an *H. pylori*-infected individual to develop peptic ulcer disease has been estimated at one in six, and 10–25% of those with peptic ulcers are expected to develop complications such as gastrointestinal hemorrhage or perforation. *H. pylori* infection is a necessary but not sufficient cause of gastric cancer. Gastric cancer is the second most common cancer worldwide. The lifetime risk of developing gastric cancer is related to the prevalence of *H. pylori*-associated atrophic gastritis and in high-risk countries is as high as 19.6% in Changle, China, and as low as 1.5% in the UK [2]. These differences reflect the

variation in *H. pylori* prevalence, in strain virulence, and in host and particularly environmental factors [3].

Primitive man was home to many intestinal parasites [4–8]. Improvements in the standards of living over the last several millennia and particularly the improvements in sanitation, availability of clean water, and better understanding of the practices of household hygiene have resulted in the disappearance of these previously common intestinal pathogens. *H. pylori* is one of the last major worldwide gut pathogens that has accompanied man on his many migrations [9,10]. The 19th century witnessed the appearance of a number of "new diseases" including paralytic polio, acute infectious hepatitis, and duodenal ulcer disease. In retrospect, the first two were related to major changes in sanitation that resulted in a change in the age of acquisition of polio virus and hepatitis A virus from infancy to young adulthood and the appearance of paralytic polio and acute infectious hepatitis as recognizable diseases. It is likely that this also marked the beginning of the loss of *H. pylori* as well as a change in the pattern of gastritis and the appearance of antral predominant gastritis. This change was enhanced by changes in standards of living and diet that resulted in the appearance of duodenal ulcer disease as another significant new disease. Duodenal ulcer was initially a disease of the upper classes as they could take the advantages of improved standards of living and improved diets. The improvements in household hygiene, sanitation, diet, and general standards of living led to a break in the chain of transmission of *H. pylori* such that the infection became increasingly less common among the middle and upper classes. Loss of the infection led to loss of duodenal ulcer disease that switched from being an upper-class problem to one of the lower classes where *H. pylori* was still common and for whom there was a trickle down of improved socioeconomic conditions. Further improvements in sanitation and household hygiene led to a continuing decline in *H. pylori* prevalence to where now the infection is present in only a small proportion of the upper and middle social classes in most Western societies.

New Problems Caused by Absence of H. pylori

The fact that *H. pylori* has been part of man's burden for millennia has been considered as evidence that it "must" play some positive role and might even be a commensal [11–13]. It has been suggested that the loss of *H. pylori* from the population may be in part responsible for the epidemic of obesity, childhood asthma, gastroesophageal reflux, and esophageal adenocarcinoma. Generally, commensals are difficult or impossible to eliminate, whereas *H. pylori* is in the process of disappearing from every population where sanitation and standards of living have improved.

H. pylori infection may play a role in the development of symptomatic gastroesophageal reflux disease (GERD). *H. pylori* infection of the gastric corpus can impair the stomach's ability to make acid and this provides a physiologic basis for loss of the infection playing a role in development of symptomatic GERD. However, *H. pylori* can also play a role in producing GERD. For example, *H. pylori*-associated duodenal ulcer (which is associated with the presence of CagA-positive strains) has also long been known to be strongly associated with GERD [14–31]. Thus, both the presence and absence of *H. pylori* may play roles in GERD. Gastroesophageal reflux is a function of the effectiveness of the barrier mechanisms at the esophagogastric junction preventing reflux of gastric contents into the esophagus. The effectiveness of this barrier is influenced by anatomic features (presence of hiatal hernia, body mass index) as well as by drugs and foods that impair lower esophageal function. GERD is directly related to esophageal acid load [30,31]. Therefore, people living in regions of the world with a high prevalence of atrophic gastritis experience a high incidence of gastric cancer and a low incidence of GERD. Loss of *H. pylori* prevents the development of atrophic gastritis and allows those with preexisting asymptomatic or

minimally symptomatic gastroesophageal reflux to develop more significant disease. GERD has been a common disease in the United States for at least 100 years. Although there is little evidence to support the notion that it has increased in incidence recently, there is evidence that the recognition of gastroesophageal reflux has increased since the 1970s [29]. The recent increase in average body mass and the absence of *H. pylori* in the majority of stomachs in Western populations ensure that the incidence of symptomatic gastroesophageal reflux will not decline and will likely increase somewhat. It has become clear that in Western countries neither the presence of *H. pylori* infection nor *H. pylori* eradication causes GERD. At least three large studies have shown that any concern regarding the risk of *H. pylori* eradication provoking gastroesophageal reflux in the general Western population was unfounded [32–34]. *H. pylori* eradication also does not impede or change the amount or type of antisecretory drug therapy required for patients with symptomatic gastroesophageal reflux. In fact, on average, symptoms in patients with GERD are more likely to improve than worsen following *H. pylori* eradication [29,31,35].

In contrast to Western countries where atrophic gastritis is uncommon, cure of the infection in patients with preexisting asymptomatic gastroesophageal reflux and moderate to severe corpus gastritis will likely remove the inflammation-associated inhibition of parietal cell function and produce an increase in gastric acidity [35]. This increase in acid concentration will increase the toxicity of any material refluxing into the esophagus through an already impaired antireflux barrier. Whether the patient develops symptomatic GERD depends on the interplay between host factors and the resulting esophageal acid load. One can easily imagine that some patients with asymptomatic reflux will convert to symptomatic reflux by this mechanism [31,35].

Adenocarcinoma of the distal esophagus is a complication of GERD and has been increasing in incidence. Although the incidence has increased rapidly, it has actually changed from being very rare disease (e.g. around 0.3/100,000 per year in 1970 in the highest risk population of White men) to becoming a rare disease (~2.5/100,000 per year) with approximately the same incidence as brain or small bowel cancers [31,35]. This might be compared to the fact that the mortality rate from gastric ulcer in the UK in 1947 was more than 10 times higher than adenocarcinoma of the esophagus currently (i.e. approximately 30/100,000 per year in 60-year-olds) (Fig. 1). The change in the pattern of gastritis and the loss of *H. pylori* from Western populations was associated with a reduction of the incidence of atrophic pan-gastritis. This loss led to gastric cancer changing from the most common cancer in the USA in 1930 to becoming an uncommon disease (from approximately 40/100,000 in the general population to approximately 7/100,000 deaths per year).

Expectations from Current and Past Populations

One can reasonably expect to find isolated populations where *H. pylori* is absent. Such a population could easily arise via a bottle neck where the founding population by chance was *H. pylori* negative. One such population may be the Malays. In the early 20th century it was recognized that what are now known to be *H. pylori*-related diseases were very rare among Malays but were common among the Indian and Chinese immigrants living in the same region. These data suggested that the Malay population was possibly *H. pylori* negative prior to the immigration of Chinese and Indians at the turn of the 20th century and that infections in Malays are likely the result of contamination from the Indian and Chinese populations. Of course that hypothesis (i.e. *H. pylori* infection in Malays with Chinese or Indian strains) can easily be tested by genetic comparison of the strains in those populations. Recent epidemiologic studies have confirmed the hypothesis that *H. pylori* infection is uncommon in Malays and is even uncommon among the rare individuals presenting with peptic ulcer disease [36–38] (Fig. 2). A study of the prevalence of *H. pylori* among the general

population of Malays showed that the prevalence ranged from 11.9 to 29.2% [37]. Another study in northeastern peninsular Malaysia reported a prevalence of only about 4% [39]. Of interest, the prevalence of *H. pylori* infection was only about 4.5% in Javanese [40]. The presence of low prevalence among non-Western populations allows one to test the dire consequences hypotheses concerning the loss of *H. pylori*. Clearly, neither the Malays nor the Javanese are known for their propensity to be obese, to have adenocarcinoma of the esophagus as a major cause of death or for childhood asthma. Yet peptic ulcer and gastric cancer are rare, suggesting that the presence of *H. pylori* infection did convey some advantages to the population. It is also important to remember that in the West, the presence of *H. pylori* has not prevented Black and Hispanic children from becoming obese or the adults from either becoming obese or from experiencing GERD [41,42]. GERD is a reflection of the ability to make acid and in Malaysia GERD is not rare. The fact that GERD is more common in Indians than Chinese or Malays suggests that environmental and genetic factors are more important than *H. pylori* in the pathogenesis of GERD [43,44]. Adenocarcinoma of the esophagus is still very rare in Singapore (0.5 per 100,000 men), which consists of a mixed Chinese, Indian, and Malay population. However, the incidence of adenocarcinoma has been increasing along with an increase in the incidence of esophagitis, the amount of fat in the diet and probably, most importantly, obesity [45]. The incidence of adenocarcinoma of the esophagus has not been broken out for the different subpopulations; however, the precursor, Barrett's esophagus, is approximately twice as common among Indians as in Malays [44].

In summary, there are no data to support any conclusion other than *H. pylori* being a serious chronic transmissible pathogen that no one needs, deserves, or desires. Absence of *H. pylori* is to be desired and the dire consequences hypotheses have proven to be simply erroneous attempts to blame some of the problems facing the modern world on a pathogen that was and is responsible for much suffering, morbidity, and mortality. It is time to join together to eradicate it and to let *H. pylori* join small pox and polio on the hit list of undesirables.

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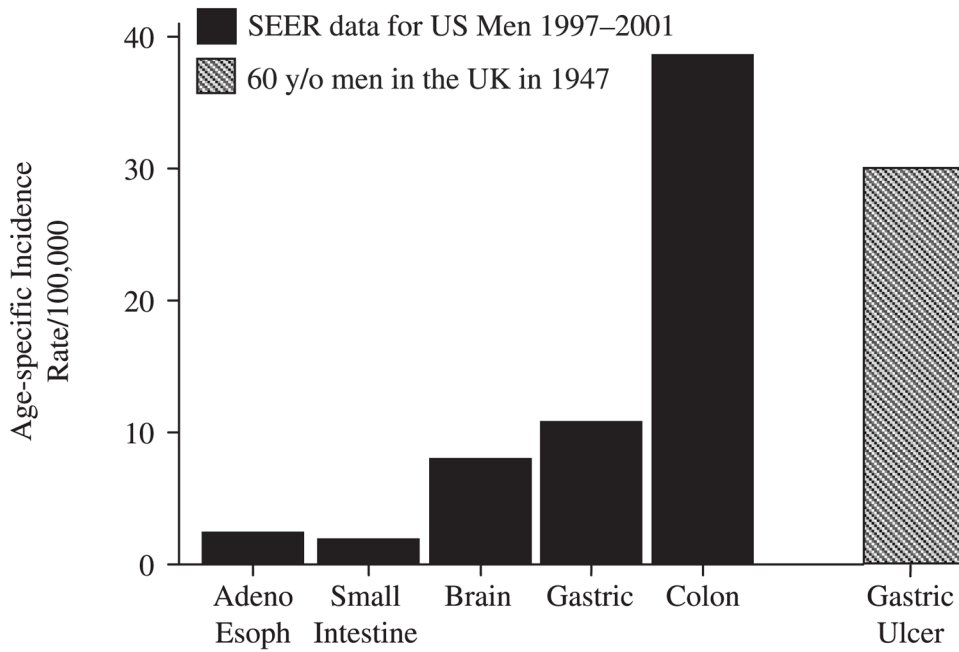47. Surveillance, Epidemiology and End Results (SEER) Program. (www.peer.cancer.gov)

Figure 1.
Age-related incidence (per 100,000 per year) of different cancers among men in the United States is compared with the mortality related to gastric ulcer among men in the UK in 1947 [46]. The cancer data show that adenocarcinoma of the esophagus, despite its marked increase, is a very rare disease with an incidence approximately equal to small bowel cancer. Even after the marked decline in gastric cancer in the US, it remains a much more important problem than adenocarcinoma of the esophagus. Data from the SEER database for the period of 1997–2001 [47]. Clearly the trade-off of loss of gastric cancer and peptic ulcer for higher acid secretion favors eradication. Considering the low prevalence of *H. pylori* in the high-risk group of White men, all of the effects of *H. pylori* eradication have likely already occurred. However, effects from diet and obesity will continue to be felt.
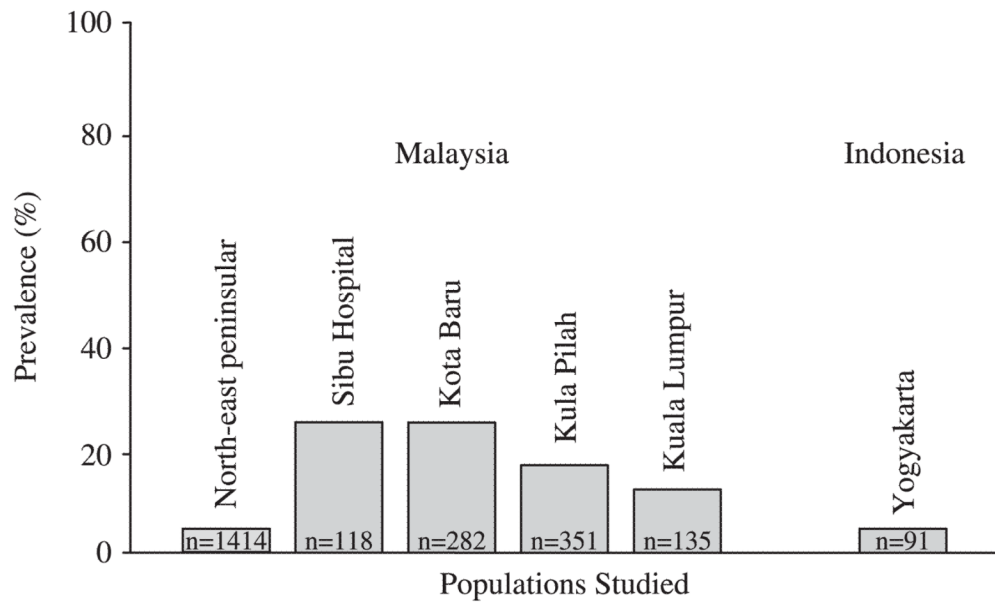
Figure 2.
Prevalence of *Helicobacter pylori* infection in low-prevalence populations (healthy and blood donor Malays [37,39] and Javanese [40]) in whom *H. pylori* infection is hypothesized to have been reintroduced following the immigration of Indians and Chinese into the region.

Table 1

Diseases in which *Helicobacter pylori* infection is a major cause

Atrophic gastritis
Increased susceptibility to gastrointestinal infections
B_{12} deficiency
Gastric carcinoma
Primary gastric B-cell lymphoma
Peptic ulcer disease
Bleeding, obstruction, perforation
Iron deficiency anemia
Thrombocytopenic purpura