Published in final edited form as:

Gastroenterology. 2010 December ; 139(6): 1819–1822. doi:10.1053/j.gastro.2010.10.037.

***Helicobacter pylori* and esophageal disease: wake-up call?**

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The history of science is marked by the nature of discovery (1). Sometimes discoveries bias a field, and it takes a long time for the true directions to emerge. This concept is particularly relevant to microbiology, since most of the bacteria of which physicians are aware are pathogens and were discovered due to their link with disease; *Mycobacterium tuberculosis*, *Vibrio cholerae*, and *Neisseria meningitis* serve as examples. Yet most bacteria in the human body are commensals (2).

The discovery of *Helicobacter pylori* in 1979–1982 by Marshall and Warren was a major event in the field of gastroenterology, recognized in many ways including the awarding of the 2005 Nobel Prize in Medicine (3). The initial discoveries of *H. pylori* were as pathogen: an organism in the stomach that provoked an inflammatory response, called by pathologists “chronic gastritis,” and leading, as suspected by Marshall and Warren, to peptic ulceration (4,5), and as later determined, to increased risk for intestinal metaplasia, atrophic gastritis, and gastric adenocarcinoma (reviewed in 6). After a strong body of work over the following decade, *H. pylori* became established firmly as a human pathogen (7). In consequence, major pharmaceutical companies developed methods to ensure its eradication, and governmental agencies and foundations have sought ways to promote such strategies. Why not rid the world of a pathogen that clearly may lead to a serious and sometimes lethal disease, peptic ulceration, and to a very serious and common form of malignancy-gastric cancer? Indeed, why not?

However, all mammals, even marine mammals, appear to have helicobacters residing in their stomach (8,9), and there is no evidence that any mammalian acid-producing stomach has evolved without their presence. In particular, *H. pylori* has been colonizing the human stomach for at least 58,000 years, dating from the last out-of-Africa (10), and probably much, much longer. *H. pylori* traveled with us as we have migrated to all corners of the world during pre-history (11). What are the implications of an ancestral gastric microbial colonization conserved over 100 million years of mammalian evolution? Might there not be some costs associated with changing such a longstanding relationship?

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Conflict of Interest Statement:

Martin Blaser is a co-inventor of technologies developed at Vanderbilt University and NYU related to the diagnosis, prevention, and treatment of *Helicobacter pylori* infections and complications related to their presence or absence. There are no commercial applications at the present time, nor are any licensed.

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In this issue of *Gastroenterology*, Sonnenberg and colleagues (12) report on a large study based on >78,000 US patients who had had upper gastrointestinal (UGI) endoscopy performed, and from whom histopathological analysis of gastric biopsies was done. The investigators sought to ascertain the relationships between the presence of *H. pylori*, chronic gastritis, and intestinal metaplasia with each other, and with Barrett's esophagus. The results, reflecting the straightforward design and large scale of these studies, are clear-cut. All three findings by the pathologists- the presence of *H. pylori*, chronic gastritis, and intestinal metaplasia-were strongly correlated with each another, confirming many prior studies (13,14). However, Sonnenberg et al. showed that all three findings were also inversely associated with Barrett's esophagus. The study was robust and internally consistent, so there is no doubt that the findings are correct. The important issue is how physicians, scientists, and patients should interpret these results.

Barrett's esophagus is an intermediate lesion along the pathway between reflux esophagitis [also well-known as gastro-esophageal reflux disease (GERD)] and esophageal adenocarcinoma (15). As with other pathogenetic sequences, relatively many individuals have GERD, fewer have Barrett's, and fewest develop EAC (15). Most importantly, GERD, Barrett's, EAC, (and the closely related adenocarcinomas affecting the adjacent gastric cardia), each are increasing in epidemic proportions all over the developed world (16–20), and EAC is a terrible and difficult-to-treat form of cancer. These conditions, one nested within the other, arose in the mid-to-late 20th century and are continuing to climb in incidence.

How do the findings of Sonnenberg et al. (12) relate to these events? Is there a causal relationship between the inverse association of *H. pylori* (and its related conditions), and Barrett's (and its related conditions), and if so, in which direction ($A \rightarrow B$, or $B \rightarrow A$)? Alternatively, do the findings reflect an underlying process affecting the risk of both (thus, $C \rightarrow A$ and $C \rightarrow B$), or are they just spurious? The large scale and internal consistency of the Sonnenberg study argue that the findings are not artifactual. In fact, their findings confirm and extend many other studies over the last decade showing parallel relationships in different populations, and using different techniques of ascertainment (21–25). Although, the Sonnenberg study was not designed to address the vectors and direction of causality, it should now be clear to all impartial observers that there truly is a reciprocal relationship between *H. pylori* and Barrett's.

How can the relationship be explained? Could GERD and related conditions be causing the loss of *H. pylori*? This is highly unlikely since GERD usually develops in adults but *H. pylori* is acquired in early childhood. Could the absence of *H. pylori* be pre-disposing to GERD? As most gastroenterologists know, once acquired, *H. pylori* colonization generally persists for life (26), unless interrupted by antibiotic treatment, or by the development of chronic atrophic gastritis very late in life. Thus, since time immemorial, *H. pylori* has persistently colonized most of the world's population, essentially for their full lifetime (26), but in most cases, its presence leads to no symptoms. Indeed, when what we now know as *H. pylori* was recognized in the 19th century by German pathologists, it was essentially universal, and they concluded that it was not worth studying because it was a commensal.

During the 20th century and now into the 21st century, the prevalence of this ancestral common human bacterium has been undergoing a precipitous decline in developed countries. Now, fewer than 6% of US children are carrying the organism (27), and parallel phenomena are being observed across the developed world (28,29). *Thus, over the course of a century, the ancient, persistent, nearly universal and dominant inhabitant (30,31) of the human stomach has been essentially disappearing.* The reasons for its disappearance are manifold (32); regardless, its decline is continuing, and with effects throughout the world,

while GERD and its sequelae are increasing (20). GERD was essentially first reported in the medical literature in the 1930's (33), Dr. Norman Barrett first described metaplasia in the esophagus in the 1950s (34), and the rise in EAC began to occur in the 1970's (17). All of these trends have occurred as *H. pylori* has been disappearing, and Sonnenberg et al. (12) provide yet more evidence that this is a linked association.

Interestingly, paralleling the inverse associations of *H. pylori* and esophageal disease have come multiple reports of inverse associations with childhood-onset asthma (27,35,36), and protection from other infections (37,38), or their reactivation (39). Since the stomach produces two hormones, leptin and ghrelin, centrally involved in human energy homeostasis (40,41), and *H. pylori* status affects their regulation (26,42), could **lack of *H. pylori*** in childhood be contributing to the worldwide epidemic of childhood onset obesity and diabetes?

Isn't it time for gastroenterologists to think more broadly about the effect of an *ecological extinction* of major proportions occurring in our bodies? Since familial, and specifically maternal, carriage is important in the transmission of *H. pylori* to the next generation (43,44), it follows that this extinction affects not only us but our children and grandchildren.

Our relationships with our microbiota are not static, especially as we age; organisms that are pathogenic in old age might have been commensals or even symbionts earlier in life. Hosts respond to their commensals with both adaptive and innate effectors in the mucosa and lamina propria (45–47); why are we using the term “chronic gastritis” to describe the gastric version of the ancient conserved responses to our endogenous microbiota, which in the stomach is predominantly *H. pylori*? Many organisms that we already consider commensals are *opportunistic pathogens* (e.g. viridens streptococci, *Candida albicans*, and *Klebsiella*); we are not attempting to eradicate these organisms from everyone. The clear report of Sonnenberg et al. suggests that it is time to re-think the “why?” and “how?” about *H. pylori* and its relationship to humans.

Gastroenterologists must study the growing field of human microbial ecology to address the epidemics of today and to not be further propagating them. Ecology is complex, and *H. pylori* has a complex, deeply evolved biological relationship with humans. Simple approaches (48), like “test and treat” fail to appreciate this complexity. We clearly need to remove *H. pylori* from persons with peptic ulcer disease and from those who are at substantial risk for gastric cancer, but the latter is an important research frontier; we must understand from whom to eradicate *H. pylori* and when (6), before disease is inevitable. However, this is a relatively small segment of the overall population in most localities and is most relevant relatively late in life.

But if *H. pylori* protects our esophagus, our airways, and maybe our waistline, should we now begin thinking about giving it back in some form, especially to children, just as pediatricians give live vaccines of persistent microbes today? More than a decade ago, I speculated that doctors will be giving *H. pylori* to the children of the future (49,50). If we will someday do so, first we must have much deeper knowledge of *H. pylori*, so as to safely restore our ancient companion, maximizing benefit and minimizing risk, and to then be able to eradicate it from the right persons at the right time. Perhaps in such a way, we can curtail these growing epidemics, and before Mother Nature's introduced *H. pylori*-replacements become our new dominant gastric bacteria, without the benefit of millennia of co-evolution and likely to be much less benign.

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