THEODORE E. WOODWARD AWARD

GLOBAL WARMING AND THE HUMAN STOMACH: MICROECOLOGY FOLLOWS MACROECOLOGY

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ABSTRACT

Just as there have been 20th century changes in our "macroecology," including global warming, there have been alterations in our "microecology," involving the microbial populations that colonize the human body. *Helicobacter pylori*, an ancient inhabitant of the human stomach, has been disappearing over the course of the 20th century. As such, by comparing *H. pylori*$^+$ and *H. pylori*$^-$ persons, the consequences of its colonization can be determined. The presence of *H. pylori* is associated with increased risk for development of gastric cancer and peptic ulceration, and with decreased risk for gastroesophageal reflux disease (GERD) and its sequelae, including esophageal adenocarcinoma. The disappearance of *H. pylori* (especially *cag*$^+$ strains), possibly contributing to the risk of these esophageal diseases, may be an indicator for changing human microecology.

Introduction

For the American Clinical and Climatological Association, it is fitting to discuss changing ecology. It is widely known that the "macroecology" of the Earth is changing. One indicator is the gradual "global warming," a product of the "Greenhouse effect," due to the combustion of hydrocarbons, releasing carbon dioxide. This is a change that has been occurring over the last century and probably is accelerating. In this paper, I will review evidence that an analogous process is occurring in the human body, with gradual but cumulatively important changes in our "microecology," that is, our microbial composition. My thesis is that one of our commensal organisms, *Helicobacter pylori*, is

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disappearing, which has important consequences for health and for disease. One implication of this hypothesis is that *H. pylori* is an "indicator" organism for other changes in human microecology that are less easily observed. This review is based on a selection from the research that my colleagues and I have conducted since 1985 (1–45).

HOW OLD IS *H. PYLORI*?

Helicobacter species are spiral, gram-negative bacteria that colonize the gastrointestinal tract of many mammals. A *Helicobacter* species has been identified in the stomach of essentially every mammal from which it has been sought (Table 1). In general, each animal has its own *Helicobacter* species. Stomachs are ecological niches that have been present for an estimated 400 million years, and the great radiation of mammals occurred about 100 to 150 million years ago. As these organisms differentiated, so did their stomachs. The available evidence is most consistent with the hypothesis that *Helicobacter* species are ancient inhabitants of mammalian stomachs, and that as their niches diversified so did they.

H. pylori is the predominant *Helicobacter* species in humans, and based on the above hypothesis, its ancestors have been with us since we diverged from other mammals in the distant past. Accordingly, when humans traversed the land-bridge across the Bering Straits from Asia to North America, they should have been carrying *H. pylori* and their descendants today should be carrying *H. pylori* strains with Asian genotypes. In studies of Amerindians deep in the interior of South America, examining three independent highly polymorphic *H. pylori* genetic loci, we have found exactly this (1).

These findings provide evidence that *H. pylori* has been present in humans for at least 11,000 years, the last time the land bridge was open. Further studies indicate that all modern *H. pylori* strains derive from five ancient populations, possibly arising in Africa, and carried by

TABLE 1
***Helicobacter* species isolated from the stomach in several mammals**

Helicobacter species	Animal
H. felis	cat
H. bizzozeroni	dog
H. "bovis"	cow
H. "suis"	pig
H. acinonychis	cheetah
H. mustelae	ferret
H. muridarum	mouse

humans for at least 60,000 years (2). In total, these observations are consistent with a very ancient origin of *H. pylori* in humans, perhaps since before we became humans.

Consistent with this hypothesis, *H. pylori* persists in the stomach for years (3), or decades (4), if not for the full life of its host. There is considerable and growing evidence that *H. pylori* has co-evolved with humans (5,6), and that persistence can be explained by cross-signaling between microbial populations and the host creating a dynamic equilibrium maintained by up- and down-regulatory pathways (5–8).

Consistent with its excellent adaptation to humans (6), persons living in developing countries nearly universally develop gastric *H. pylori* colonization (9). In total, these data suggest that *H. pylori* are the major constituents of the indigenous ("normal") biota of the human stomach (10). However, in developed countries such as the U.S., prevalence is much lower, with much diminished acquisition (11) compared to developing countries (9). There now is substantial evidence that as countries are modernizing, *H. pylori* is disappearing (4) (Figure 1).

WHY IS *H. PYLORI* DISAPPEARING?

Humans are the only reservoir for *H. pylori*, and all transmission must ultimately stem from humans. As socio-economic conditions have improved, *H. pylori* transmission has diminished. There is less crowding in households, family sizes have diminished, and water supplies

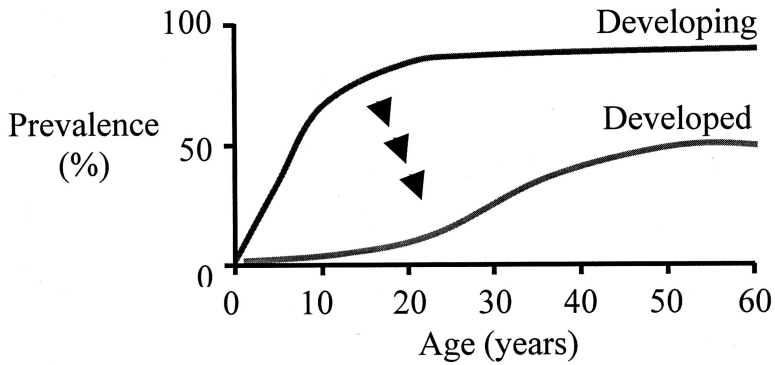

FIG. 1. Prevalence of *H. pylori* in developed and developing country populations. In developing countries, *H. pylori* is acquired early in life, and most children become colonized by age 10. By adulthood, colonization is detectable in nearly all adults. In developed countries, prevalence is much lower, reflecting a "birth-cohort" phenomenon of improved "hygiene." Since all developed countries once were developing countries, these data imply that *H. pylori* are disappearing, and there is much evidence supporting this hypothesis.

are cleaner. Importantly, we now are more than 60 years into the antibiotic era, and in developed countries, children regularly receive multiple courses of antibiotics for various ailments, especially otitis media. If each course of antibiotics eradicated *H. pylori* in 5–20% of cases, the cumulative effect of childhood antibiotic regimens would remove a substantial proportion of colonizations. Diminished transmission, together with antibiotic treatment, is likely important in the continuing disappearance of *H. pylori*. Among children in the U.S., fewer than 10% now are acquiring *H. pylori*; this is an ecologic change of large magnitude. As such, we now can consider the potential costs and benefits of *H. pylori* colonization. In all biological relationships, the effects of cohabitation on the host can be beneficial (symbiosis), deleterious (parasitism), or mixed, depending on context (amphibiosis).

H. PYLORI AND HOST RESPONSES

To assess whether the presence of *H. pylori* may lead to disease, one of the first questions is whether there is host recognition of the organism. It now is clear that there are both immunological (3,9) and tissue responses (3,12) to the presence of *H. pylori* in the stomach. The current evidence indicates that these are the host responses to an indigenous and persistently colonizing microbiota, but pathologists have called the tissue response "chronic gastritis." In my view, this is analogous to calling the cellular response to the endogenous microbiota in the colon "chronic colitis," or in the female genital tract "chronic vaginitis." There are few if any macrophages, lymphocytes, plasma cells, or polymorphonuclear leukocytes in the lamina propria of germ-free animals, but when bacteria are introduced ("conventionalization") there is infiltration and population of the lamina propria with such cells. Pathologists term this "normal," and the germ-free state "abnormal." Based on the long-term relationship of *H. pylori* with humans, and its much more recent disappearance, I believe that pathologists studying the stomach have reversed their nomenclature, calling the "normal" response chronic gastritis. This becomes a long, and perhaps philosophical discussion, but will become increasingly relevant if evidence is sustained of *H. pylori* benefit as well as cost. Regardless of what the process is called, there is universal consensus that *H. pylori* is the major cause for infiltration of the gastric lamina propria with cells of immune and pro-inflammatory phenotypes. Further, it is widely appreciated that this process per se, which is persistently present accompanying *H. pylori* usually is clinically silent beyond the first weeks of *H. pylori* acquisition (3).

H. PYLORI AND RISK OF DISEASE

However, it had long been recognized that "chronic gastritis" is a risk factor for the development of the most prevalent form of stomach cancer, the intestinal type of gastric adenocarcinoma. Working with colleagues at the Mayo Clinic, in Japan, and with the Japan-Hawaii study, we provided evidence that the presence of *H. pylori* was associated with increased risk for gastric adenocarcinoma, especially of the intestinal type (13–16). In prospective-type, nested case-control studies, the longer the interval between ascertainment of *H. pylori* status and diagnosis of the cancer, the stronger the association (14,16). Long intervals minimize the confounding effect of *H. pylori* loss during precancerous stages.

Chronic gastritis also had been recognized as a risk factor for peptic ulcer disease. As part of the Japan-Hawaii study, in nested-case-control studies, the presence of *H. pylori* was associated with the development of both gastric and duodenal ulcers (17,18).

DETERMINANTS OF DIFFERENTIAL RISK OF DISEASE

Although these studies showed that *H. pylori* presence conferred biological cost (= disease), most *H. pylori*-positive persons did not become ill. Thus, the next challenge was to begin to understand the factors promoting illness. The mathematical models indicated that the key factors involved the interaction between bacterium and host (5–8). Returning to the Japan-Hawaii study, we provided evidence that early life family structure was a determinant of risk, especially for gastric cancer (19). Such findings suggested that the age of acquisition reflected the early events of the interaction that then established particular patterns in the ensuing decades.

However, our major focus was on variation amongst *H. pylori* strains. While seeking to define the nature and composition of a cytotoxin produced by *H. pylori* [which we eventually purified (20), cloned (21), and showed the relation to human disease (22,23)], we found that some but not all *H. pylori* strains produced a protein of high molecular mass (128–140 kDa) (24). The gene encoding the protein was cloned and called *cagA* for cytotoxin-associated gene) (25). We found that persons carrying *cagA*$^+$ strains are at increased risk for peptic ulcer disease (24,18), as well as for atrophic gastritis and intestinal metaplasia (26), precursor lesions for gastric cancer, and for gastric cancer itself (27,16).

From the earliest observations (28), it has become clear that *cagA*$^+$ *H. pylori* strains inject the CagA protein into gastric epithelial cells via

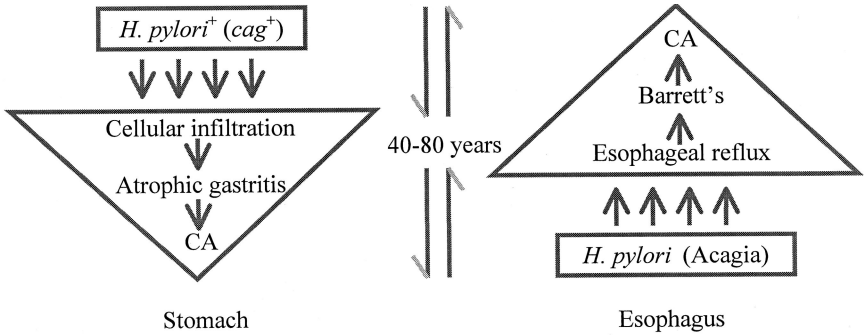

FIG. 2. Relation of *H. pylori* to gastric and esophageal adenocarcinomas. *H. pylori* colonization increases risk for atrophic gastritis and intestinal metaplasia, leading to gastric adenocarcinoma, a process requiring 40–70 years on average. Evidence now indicates that lack of *H. pylori*, especially *cagA*$^+$ strains, a process that I have termed "acagia," increases risk for GERD, then Barrett's esophagus, leading to dysplasia and esophageal adenocarcinoma, a process requiring at least 20 years.

a type IV secretion system. The stability of serum antibodies to the CagA protein over at least 21 years (4) indicates the persistence of this phenomenon. In relation to *cagA*$^-$ strains, those that are *cagA*$^+$ induce a more marked tissue response (24,26,29,30), higher levels of pro-inflammatory cytokines (31,29), and affect gastric epithelial cell cycle dynamics (32,33). It has become clear that *cag*$^+$ and *cag*$^-$ *H. pylori* strains interact with the host in different ways, with important consequences for disease (6,34).

H. PYLORI AND THE ESOPHAGUS

If *H. pylori* is truly an ancient organism of humans, and if it is disappearing, and there is strong evidence for both, then it could be predicted that there would be consequences for both health and disease (35). Consistent with this view is that gastric cancer rates are declining in all developed countries, and there also is evidence for a decline in (non-iatrogenic) peptic ulcer disease. However, in the last 30 years, there has been a marked rise in the incidence of adenocarcinomas involving the distal esophagus and proximal (cardia) stomach. The major risk factor for these cancers is gastroesophageal reflux disease (GERD), an inflammatory disorder that can lead to metaplasia (Barrett's esophagus), then dysplasia, and then cancer (34). These cancers are increasing in incidence as *H. pylori* is disappearing (36,37), suggesting that there may be a relationship.

In studies with colleagues in different sites in the United States and Europe, we asked whether the presence of *H. pylori* was associated

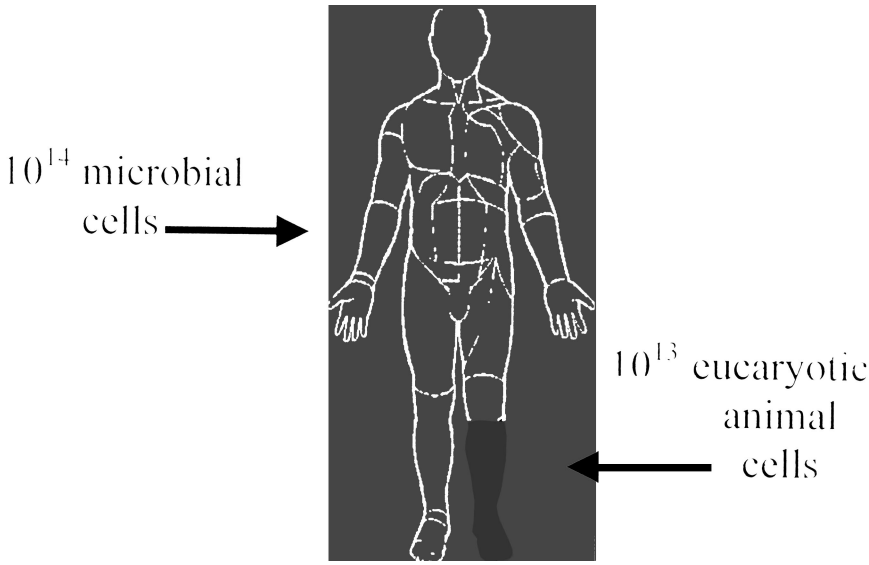

FIG. 3. Who are we? Microbial cells in the human body outnumber human cells by about 10:1. The types of organisms present in humans show great consistency from person to person, and there is increasing evidence that, as with *H. pylori*, these are ancient constituents of the human body, and have co-evolved with us. Carriage of other organisms always carries biological cost to the host, but there are circumstances in which benefits may equal or exceed cost (symbiosis). Importantly, co-evolved organisms may be a part of our physiology.

with GERD, Barrett's, or adenocarcinomas of the distal esophagus or gastric cardia. Distinguishing between cag^+ and cag^- strains was the critical element. Our studies showed that carriage of a cag^+ strain was *inversely* associated with GERD (38–40), Barrett's (38–41), and with these adenocarcinomas (42); subsequent studies by other investigators and our on-going studies in New York add support to these findings. Our model of the relationship between *H. pylori* and adenocarcinomas of the stomach and esophagus is shown as Figure 2. In retrospect, it is clear that the major risks and benefits associated with *H. pylori* are due to the cag^+ strains since these are the most interactive with the host (6,34).

CONCLUSIONS

In total, carriage of *H. pylori* (especially cag^+ strains) confers both cost and potential benefit to humans (43). There may be other benefits of gastric colonization by *H. pylori*, such as increased resistance to enteric pathogens and diarrheal diseases (44). Such a benefit could

have strongly selected for the presence of *H. pylori* when lethal diarrheal diseases were hyperendemic.

The human body contains myriad microbes (Figure 3). Many of them have not yet been described, and many others cannot be cultivated in vitro. In total, they are a metabolic compartment of the human body influencing our metabolism and physiology. If, like *H. pylori*, bacteria of the colon, mouth, vagina, or skin began to disappear, we probably could not detect it.

The position of *H. pylori* in human microecology may not only rely on its strong relationship to inflammatory, endocrine, and oncogenic properties in the stomach and esophagus (6,34). Because of its dominant position in the gastric niche, we can relatively easily track its comings and goings. As such, *H. pylori* may become the indicator organism for changes in human microecology. We now know that there exists an indigenous microbiota in the human distal esophagus (45), and are eager to study its changes in relation to GERD.

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DISCUSSION

Schiffman, Providence: Marty that was a terrific talk. How does this paradigm relate to the mucosa-associated lymphoid, tissue lymphomas, the MALT tumors, what relationship does *H. pylori* have and is there a similar genetic molecular biologic pathway?

Blaser, New York: The MALT lymphomas, the B-cell local lymphomas of the stomach are very uncommon conditions. They probably occur around 1 per million population per year. They clearly are associated with the presence of *H. pylori*, and we now know that if you treat patients who have that condition, their tumors regress. However, one of the questions about this is where is the boundary between true malignancy and a benign hyperproliferative stage. In some ways it's similar to the myoloma and the benign monoclonal gammopathy. I think, in fact, there's been overdiagnosis of what really are benign conditions which respond very well to antibiotics, which is not surprising. For the malignant conditions, it's clear that they are antigen-driven, and you can "drain the gas tank" by treating *H. pylori*, which definitely affects the natural history. So this is an advance as well, although it's on a much smaller scale.

Toskes, Gainesville: Marty, an excellent presentation. My question relates to the disappearance of the infectivity; certainly happening in Caucasians. But there still seems to be a high rate in minority groups like Afro-americans, hispanics, and orientals. Has anyone looked at them in terms of *cag* positivity and *cag* negativity?

Blaser: It turns out that the populations where Helicobacter is most prevalent are also the populations in which *cag* positivity is also in a higher proportion of those strains. And as you correctly pointed out, *H. pylori* have not disappeared as rapidly in some of the minority populations in the United States. Interestingly those are the populations that have the highest rates of gastric cancer. They have the highest rates of *cag* positivity, and their rates of esophageal disease, interestingly, are lagging, which is also part of the dose-response biological coherence in the Bradford Hill proof of causality as well. I think I'll just stop there.

Palmer, New York: I was particularly interested in your comments about the different origins of *Helicobacter* in connection with the migration of humans, and I was reminded that the people who study mitochondrial DNA have identified seven major groups of humans (European), referred to as the seven daughters of Eve. Is there any correlation between the typing of humans by mitochondrial DNA and their *Helicobacter*?

Blaser: That's a wonderful question. One of our other studies, which I didn't have time to show you, concerned a study of Amerindians in the Venezuelan Amazon. In this isolated population, by mitochondrial DNA, everyone has Amerindian mitochondrial haplotypes, which are related to the East Asian haplotype. The markers are quite consistent. In another study that we've recently published from Ladakh, also with Marc Achtman and his colleagues, looking at Buddhists who've migrated from Tibet and Muslims who have been indigenous for the last thousand years, it's become clear that whereas mitochondrial DNA can divide humans into the seven major groups, *Helicobac-*

ter can divide them into a thousand groups. And if mitochondrial DNA is an hour hand of ancestry, *Helicobacter* is a minute or second hand. It's much more finely tuned.

Giannella, Cincinnati: Marty, from time to time one reads letters to the editors and the like of the claims of *H. pylori* involvement in non-gastrointestinal diseases. Would you just say a word about that?

Blaser: Since the discovery of *H. pylori*, finding associations has been a mini-cottage industry. Most of the associations, in my opinion, have not really panned out. The one that's quite intriguing is a recurrent association from Japan of *H. pylori* and ITP. There have been a number of studies now that have shown that patients who have ITP are usually *H. pylori* positive. If you treat them with antibiotics, platelet counts go up, and they stay up. I don't have any first-hand experience with these studies, but there's a growing literature about ITP, particularly from Asia.

Stevenson, Stanford: I'm fascinated by your last slide. I have heard some other people speak about the vastness and complexity of the microbial world. It would seem to be the case, that if we think about nature, that if something leaves the microbial scene, something else replaces it. With newer techniques we must be getting better at understanding the microbial world in which we live, and also that lives in us. Are people looking for other kinds of organisms that may, in fact, contribute to chronic diseases, and will we see a replacement like that which you described, should we decide to use antimicrobials against them?!

Blaser: Nature abhors a vacuum. So we're working with David Relman at your institution studying the gastric flora using 16S ribosomal RNA to ask what are the organisms that are present in the *H. pylori* positive stomach and in the *H. pylori* negative stomach. As you point out, there are organisms that are populating the stomach in the absence of *H. pylori*. They are generally lower in number, and appear to be predominantly mouth organisms. My prediction is that the next *H. pylori* is not going to be as benign as this one that we've had for million of years, and we may start thinking about our *Helicobacter* replacement therapy, especially those of us who have reflux symptoms. We are also studying the biota of the esophagus, and we've recently described that there is an indigenous biota in the human esophagus as well. We now are beginning to study the relationship in normal esophagus and GERD, with the hypothesis that microbial populations will change in consequence to GERD and possibly contribute to the pathogenesis there as well. I just might add one last thing, which I also didn't have time to mention, and that is that the stomach is an endocrine organ, in addition to producing gastrin gastric and somatostatin, it produces leptin and it produces ghrelin. There now is evidence that *H. pylori* positive people produce more leptin and less ghrelin than people who don't have *H. pylori*. This has implications for obesity and diabetes as well.

Stevenson: I'm going to push you to the edge. There's an old belief that there are sterile compartments in the body? Are there any sterile compartments in the body?

Blaser: Yes, it's a very good question. The work on *H. pylori* has moved me from studying pathogens to studying commensals. And I could easily spend the next ten careers examining commensals of the human body, which could include bacteria, protozoa, viral commensals like the herpes viruses and endogenous retroviruses. Commensalism is a very complex and interesting ecological relationship, appropriate to a society like ours.