Perspectives Series: Host/Pathogen Interactions

Ecology of *Helicobacter pylori* in the Human Stomach

Martin J. Blaser
Division of Infectious Diseases, Department of Medicine, and Department of Microbiology and Immunology, Vanderbilt University School of Medicine; and Medical Service, VA Medical Center, Nashville, Tennessee 37232

Persistent colonization of a host by a microbe is rarely an accident. Rather than the death of the host or the elimination of the invader, persistence requires coexistence, which must be governed by equilibrium relationships that are stable during the majority of the interaction. Traditionally such relationships are divided into three exclusive categories: parasitism, commensalism, and symbiosis (1). Parasitism is a relationship in which one species benefits at the expense of the other. Most of the pathogenic organisms that medical microbiologists study fall into this category. The expense of microbial parasitism is often the consequence of the microbe's requirement for transmission to a new host. The pulmonary cavities caused by *Mycobacterium tuberculosis* are one example of this phenomenon. Commensalism may be defined as a relationship in which one species derives benefit and the other is unharmed. We consider the "normal microbial flora" of humans to mostly consist of such opportunistic organisms. Symbiosis is the biological association of two or more species to their mutual benefit. Our best-understood endosymbionts are mitochondria (2), but symbiosis in humans otherwise has not been well-explored (3).

Examples of these relationships in human biology are illustrated in Table I. However, these classifications do not seem sufficient. Even organisms that are classified as commensals or symbionts might ultimately cause disease, such as endocarditis caused by oral streptococci, or intraabdominal abscesses caused by *Bacteroides* species. The term "amphibiotic" has been used to designate organisms that may be either beneficial or disease-causing, depending on context (4). In any event, since all of these concepts are biological, they must be considered in terms of evolutionary constraints. For such analysis, efficiency of transmission, effects on reproductive ability of the host, and effects on total populations rather than on isolated individuals also must be considered. For example, an amphibiotic microbe could be a symbiont during a host's reproductive period, but a parasite thereafter.

As such, it is instructive to study the gram-negative bacteria, *Helicobacter pylori,* that persistently colonize the stomachs of humans and other primates. Understanding their intercourse with humans is important because of their medical significance (5), but also because such analyses provide paradigms of host–microbial interactions that may have applicability to other clinically significant organisms. Microbiologists in the 19th century considered these organisms as commensals, but since their rediscovery by Marshall and Warren, most current investigators believe that they are strictly parasites (6). The thesis proposed herein is that the relationships that *H. pylori* have with humans may encompass each of the three prototypes illustrated in Table I. I maintain that these relationships are fluid and depend on the population biology of both the host and the microbes, each of which are affected by environmental constraints. Microbes that are symbionts in one era may become parasites when circumstances change, and importantly, vice versa.

Evolutionary constraints on H. pylori–human interactions

To most readily understand the interaction between *H. pylori* and humans, it appears critical to assume that colonization is a phenomenon that has existed for a long time. Humans, and our ancestors, have long been colonized by a large number of different microbes, and there exists a body of evidence (for review see reference 7) that *H. pylori* should be included among such organisms. Colonization of the stomach of other mammals by organisms similar to *H. pylori* is widespread, suggesting the occupancy of an ecological niche by a large family of related microbes. Consistent with these notions are accumulating data that *H. pylori* are obligate parasites, with no free-living form in nature yet identified, and that natural infection is specific for primates, including humans. Narrow (host-specific) parasitism implies that the microbial population has a critical interest in the evolutionary fitness of the host population. Thus, selection over the millennia would have favored organisms that coevolved with, rather than eliminated, their hosts. That (*cagA*$^+$) *H. pylori* strains that induce higher levels of inflammation (8) hasten development of atrophic gastritis (9) and loss of their gastric niche illustrates that coexistence can be lost if the microbial population does not practice sufficient restraint. However, life often involves trade-offs; the higher colonization density of *cagA*$^+$ strains in the stomach that is associated with this increased inflammation (8, 10) may facilitate transmission to new hosts.

Why, then, do humans not eliminate these organisms? Evolutionary perspectives instruct that all interactions must be considered in terms of economic analyses. Thus, failure to eliminate the parasite implies that the cost to the host is greater than the benefit. This may be due to high costs (e.g., loss of vital gastric functions), or significant benefits (e.g., protection against lethal diseases), or that both cost and benefit are relatively low. Alternatively, or in addition, for *H. pylori*, the huge population size, rapid generation time, and high mutation rate may allow it to always stay a step or two ahead of

Address correspondence to Martin J. Blaser, M.D., Division of Infectious Diseases, Vanderbilt University School of Medicine, A-3310 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2605. Phone: 615-322-2035; FAX: 615-343-6160; E-mail: martin.blaser@mcmail.vanderbilt.edu

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Table I. Examples of Current Categories of Persistent Microbial Colonization of Humans

Relationship	Example	Comment
Parasitism	*Mycobacterium tuberculosis*	Persistence involves latency
	Plasmodium falciparum	Strong on-going selection for human genotypes
Commensalism	*Candida albicans*	No beneficial role currently defined
Symbiosis	*Bacteroides* species	Microbes produce essential nutrients (B vitamins, vitamin K), yet can occasionally cause disease
	Oral streptococci	Antagonistic to *Streptococcus pyogenes*, but may cause disease

the host. Regardless of the exact reasons, based on the persistence of *H. pylori* for decades in the majority of the population, we can assume that selection of human genes favored coexistence rather than war. Presumably this evolutionary crossroads was reached and breached long ago, defining the now-current biological relationships. Nevertheless, it is important to remember that selection is an on-going process, and that recent environmental events (e.g., the decline in lethal diarrheal diseases, changes in family size, and changes in longevity) in many human populations all could impact selection for particular interactions.

The model

A model of this persistent interaction has been constructed, and its mathematical characteristics have been analyzed (reference 11, and Blaser, M.J., and D.E. Kirschner, unpublished observations). The central feature of the model is that in the steady state the interaction between colonizer and host is regulated. Unregulated models do not permit persistence with biologically plausible solutions (11). One feature of the model is that the organisms are interacting with the host in such ways as to optimize the gastric environment to maintain their own homeostatic niche (Fig. 1), which is the sine qua non of persistence. A regulated model is optimal as well for the host, when confronted by a parasite for which the cost of elimination is excessively high. The development of such a relationship is highly unlikely unless there is a long shared history between parasite and host, or relatives of the host, and implies coevolution. To best understand the model, four issues must be addressed.

Necessity for downregulation. Models based exclusively on upregulating events lead to unstable solutions. Downregulatory phenomena are needed to permit development of equilibria. As stated above, coexistence potentially can be favorable to both host and microbe. The human immune response includes multiple mechanisms to modulate effector functions in response to antigenic stimuli. Downregulatory events are mediated by specific biochemical signals that affect particular cells and pathways (17). Similarly, although much less complex, signal transduction in bacterial cells allows many opportunities to modulate responses to environmental stressors (12). Such interactions between the two parties can be described by models of interlocking autocatalytic processes with negative feedback.

Tolerance. Signals from lumenal microbes may be received by host cells in both the epithelium and in the lamina propria

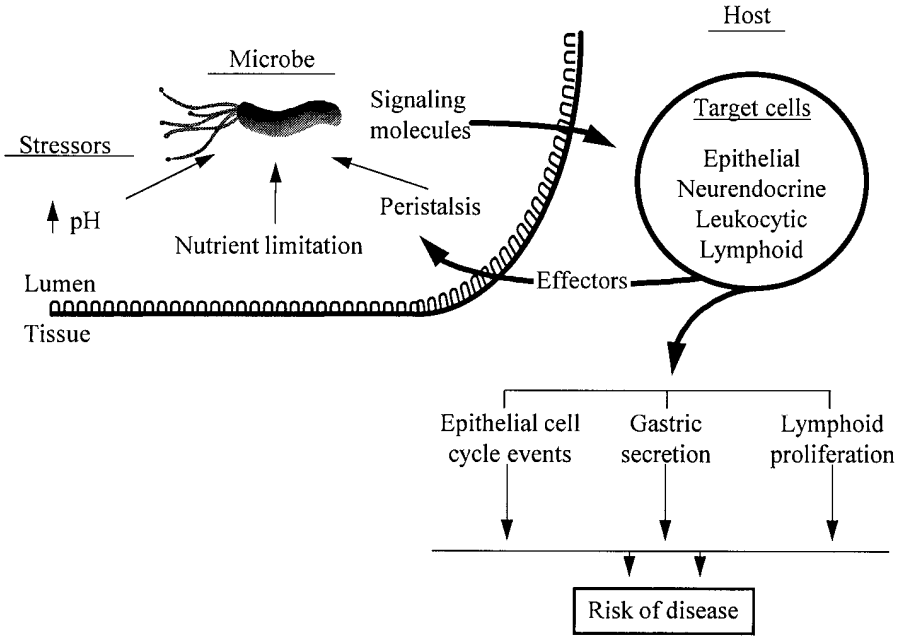

Figure 1. Model of *H. pylori* regulation of host physiology to maintain homeostasis. Environmental phenomena that affect *H. pylori* populations include gastric pH, nutrient limitation, and physical removal, via peristalsis. As with other bacteria (12), *H. pylori* regulate gene expression in response to particular environmental signals. In the proposed model, one component in this adaptation is the release of molecules that signal the host to diminish the noxious stimulus. For example, bacterial secretion of proinflammatory molecules may result in greater tissue injury, permitting nutrient release. Similarly, secretion of *N*α-methylhistamine (13) would stimulate the host to increase acid production when pH in a particular locale is too high for optimum microbial function. In this model, the equilibrium established by the colonizing population in each host is dynamic and unique. A consequence of these interactions is that the nature of the equilibrium would determine such characteristics as epithelial cell proliferation and apoptosis (14), gastric secretion (15), and antigenic stimulation of lymphoid cell populations (16). These in turn, would be determinants of the likelihood of disease under differing environmental circumstances.

(18). Metabolic products and physiological alterations from the host can signal the microbe in multiple ways, including changes in pH, nutrient supply, and physical removal (Fig. 1). Persistence is most easily achieved in a framework in which there is a high degree of tolerance by each party for the other, and in which signaling is tightly regulated. From the standpoint of the organism, the ability to maintain a very low profile maximizes the efficiency with which its signals to the host elicit responses. With low background noise, a small signal can be audible, and multiple signals can synergize. From the standpoint of the host, tolerance of organisms that are not life-threatening minimizes the energy-requiring and/or destructive aspects of responding to all of their signals. The ultra-low biological activity (19) of the *H. pylori* LPS and the expression of host epithelial cell Lewis antigens on the bacterial cell surface (20, 21) are examples of the organism limiting its constitutive signaling to the host. The ability of the organism to modulate Lewis expression in vivo (22) permits optimal adaptation to particular host microenvironments. However, variations in tolerance, due to particular host–strain combinations, may be substantial. For the host, the immunologic status at the time of introduction of foreign antigens is an important determinant of the nature of the immune response achieved (23, 24). The ability of the host to transduce the signals received, using cytokines such as IL-8 or immunocytes, affects the nature of the tolerizing environment. Host variability in responsiveness represents an important arena for future research.

Microbial diversity. *H. pylori* are highly diverse at the genetic level (25, 26), and phenotypic differences are increasingly being recognized. Such diversity implies that the requirements of the organisms vary, as do the means by which they achieve their goals. One important difference identified among strains is the presence of the *cag* pathogenicity island (27, 28). Evidence is emerging that *cagA*$^+$ and *cagA*$^-$ organisms have differing life-styles in the hosts they colonize and in associations with disease (8). Increasing the complexity of mechanistic analysis are the observations that individuals may be simultaneously colonized by multiple *H. pylori* strains (29), that strains may change (clonal variation or "quasispecies" formation) over the course of colonization, and that horizontal gene transfer occurs among strains (30). Thus, no single isolate represents the gene pool of the total population with which a host has been colonized. The continuing diversification of *H. pylori* is consistent with ongoing selection in the human stomach.

Disease. It must be presumed that the *H. pylori* population reaches a dynamic equilibrium in each host. In the model presented, clinical disease (as opposed to pathologic findings in tissue) is not a regular outcome, but an accidental result involving an imbalance between parasite and host. From the microbe's perspective, disease is part of the price of maintaining its niche. There is no evidence yet that *H. pylori*–induced chronic diseases facilitate transmission. Since disease (peptic ulcer, cancer) occurs in only a minority of subjects and usually after reproductive age, its cost to the microbe, and to the evolutionary fitness of the host population, is low. Importantly, *H. pylori* population diversity per se, or combinations of particular hosts with particular bacterial populations may be determinants of clinical outcome. The characteristics of the equilibria established between host and microbe may help determine risk of disease, according to the model proposed in Fig. 1.

For well-adapted organisms like *H. pylori*, interactions that protect the host from disease, as well as cause disease, are both possible. The existence of aspects of *H. pylori* colonization that are beneficial to the host would have significant impact on the frequency of colonization in affected populations. The natural extinction of *H. pylori* over the course of industrialization in developed countries suggests that in the current environment, any symbiotic role during the reproductive years is minor. This observation does not necessarily imply lack of symbiosis in the past, nor in the future.

Could malignancies induced by resident gastrointestinal flora, including *H. pylori*, ever have had benefit to humans? Gastrointestinal cancers (like most cancers) increase exponentially in frequency in the elderly, after the reproductive period is generally over. In times of abundant food resources, old age is valued by humans. During scarcity, longevity limits the nutrients available to reproductively active populations. "Programmed death" (analogous to apoptosis?) of the elderly by mechanisms not injurious to younger individuals may benefit the species by maximizing nutrient availability to reproductively active populations. Overpopulation is as much a danger to humans as it is to trees. Cancer as a means for culling the herd is less dangerous to the species than is the spread of highly virulent infectious agents from undernourished (susceptible) elderly populations to those who have not completed their reproductive years. These concepts may help explain the worldwide ubiquity of neoplasia in elderly populations.

Conclusions

The terms parasite, commensal, and symbiont may not be applicable to microbes such as *H. pylori* (or *Bacteroides* species) which have apparently coevolved with humans. All parasites are selfish, but for many successful ones there has been selection for restraint. Understanding the mechanisms involved in the restraint may allow us to intervene medically, when necessary, or better still to harness individuals in these microbial populations that can be used to accomplish specific purposes. Thus, future research may be profitably aimed at finding ways to use the probiotic properties of persisting organisms, such as *H. pylori*. Based on the well-orchestrated interactions with their hosts, such microbial characteristics may be subtle, and their exploitation may require much human imagination. Understanding the biology behind host–microbial interactions (31) will provide the substrate for the next wave of clinical advances.

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