Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 8359–8364, July 1999
Mathematics, Microbiology

Dynamics of *Helicobacter pylori* colonization in relation to the host response

MARTIN J. BLASER*† AND DENISE KIRSCHNER‡§

*Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN 37232; †Veterans Affairs Medical Center, Nashville, TN 37212; and ‡Department of Microbiology and Immunology, University of Michigan School of Medicine, Ann Arbor, MI 48109-0620

Communicated by Avner Friedman, University of Minnesota, Minneapolis, MN, April 1, 1999 (received for review September 14, 1998)

ABSTRACT **The dynamics of *Helicobacter pylori* colonization from its acquisition through the development of steady-state are examined through a mathematical model that includes the host response. The model encompasses both host and microbiological variation. The individual capacity of the host response is shown to be a key model parameter, leading to either transient or persistent colonization, whereas the growth rate of that response has little effect. Analyses of competing strains indicate that each must occupy a specific niche, otherwise exclusion occurs. The model implies that there exists a lower bound on the host response to the indigenous microflora that is consistent with current biological views of *H. pylori*. Parallel models may be useful in understanding other persistent host–microbial interactions.**

1. Introduction

Microbial persistence in the presence of a host response by a colonized host is a seeming paradox. Yet in human biology there are prominent examples of this phenomenon, including HIV, *Plasmodium*, and *Mycobacterium tuberculosis* infections. Well-adapted microbes have evolved ways not only to circumvent these mechanisms but also to utilize host responses to their own advantage (1). Such a phenomenon has been postulated for the highly prevalent human gastric bacterium, *Helicobacter pylori* (2–4), which induces a host response in virtually all carriers but in a subset can augment the risk of peptic ulceration and distal gastric cancers (5, 6).

During the lag time between the introduction of a microbe and the development of a mature immune response after primary acquisition, the dynamics of the interaction often are markedly different from those in the presence of the fully developed immune response. In experimental *Helicobacter* infection of animals, bacterial populations are higher initially than they are during steady state (15). These data suggest that *H. pylori* follows other long-term residents of humans in the characteristic initial transient phase of infection (7–11).

We have previously presented a deterministic mathematical model describing the steady-state pattern of *H. pylori* colonization (4). In that model, the ability to induce a host response was considered adaptive, since induction of inflammation permits nutrient release, allowing maintenance of the microbial population (2, 3). The model permits the introduction of a number of variables, including bacterial competition and changes in host physiology, yet maintains steady-state characteristics. Its purpose was to describe the persistent state and was based upon the consideration that the host response was also in a highly regulated equilibrium.

To more fully elaborate the dynamics of *H. pylori* colonization, we have developed a new model that incorporates the development of the host response concurrent with *H. pylori*'s establishment of persistence. The model allows us both to examine the initial events following *H. pylori* introduction into a naive host and the development of the steady-state relationship, as hypothesized in Fig. 2*A*. The model should allow us to predict the effects of host perturbations on the *H. pylori* populations and the resulting consequences. Incorporating a dynamic host response into the model of *H. pylori* colonization is key if we are to understand the initial features of the relationship between microbe and host, as well as the phenomena that permit persistence to develop. We extend the power of our earlier model (4) to describe temporal dynamics, as well as to incorporate characteristics of the host–microbial interaction that have not been addressed previously. In the model presented here, the major role of the host response is to limit bacterial growth by limiting nutrient production. As in the previous model, we assume the major nutrient source for *H. pylori* results from inflammation and its exudate into the gastric lumen. Thus, the host response could include many possible factors, such as innate and adaptive immunity, as well as other mechanisms, such as iron-sequestration. Presently, for *H. pylori*, the mechanisms directly involved in the host response are not known.

2. The Model

In this model, we assume that microbe regulatory mechanisms by which a particular *H. pylori* strain interacts with environmental stimuli are no different during the initial and steady-state phases of the infection. Therefore, we assume that the microbial populations behave essentially identically both during the establishment of persistence and during colonization (4). We define five populations that we follow over time, t: $M(t)$ represents the mucus-living *H. pylori* population; $A(t)$, the *H. pylori* population that adheres to epithelial cells; $N(t)$, the concentration of bacterial nutrients released via inflammation; $E(t)$, the concentration of effector molecules, such as urease (16); and $I(t)$, the host response. The interactions of these five populations are shown in Fig. 1 and explained mathematically as follows.

$$\frac{dM}{dt} = \bar{g}_M \alpha N(t) M(t) - \mu_M M(t) - aM(t)(K - A(t)) + \delta A(t). \quad [1]$$

The change in the mucus-associated bacterial population (M) is characterized by a mass-action growth term at rate $\bar{g}_M$ that is a function of the nutrient population (N) with growth-yield constant α; a loss term, at rate μ_M, due to mucus shedding; and a loss term, at rate $a(K - A(t))$ representing migration of $M(t)$ organisms to the adherence sites (to become adherent (A) organisms). This occurs when the A population is below the epithelial carrying capacity, K. There also is a gain term from the migration of adherent *H. pylori* into the

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§To whom reprint requests should be addressed at: Department of Microbiology and Immunology, 6730 Medical Science Building II, University of Michigan School of Medicine, Ann Arbor, MI 48109-0620. e-mail: kirschne@umich.edu.

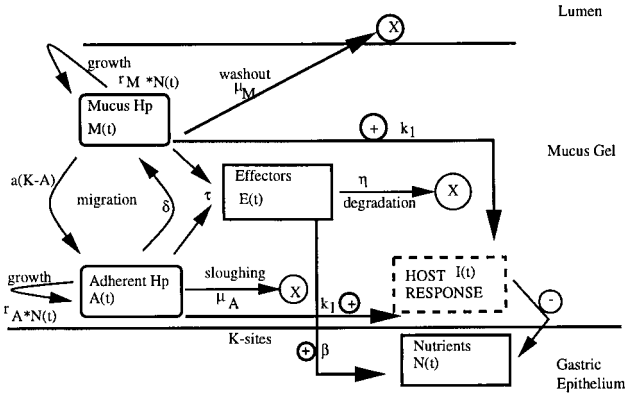

FIG. 1. Model of the *H. pylori*–human interaction, including a developing host response. The notation + indicates up-regulation, − indicates down-regulation, and **X** indicates elements that are lost to the system. The equations describing this interaction are given in the text together with the model description.

mucus population, at rate δ, due to their replication. These bacteria must move into the mucus layer when the adherent sites are at their carrying capacity.

Compared with the modeling work that has been done for the colon, it cannot be assumed that the carrying capacity of the epithelium lining the stomach is infinite (17, 18). Microbial colonization of the colon and stomach are dissimilar in the environmental pH, nutrient sources, and interspecies competition, among other factors. If adherence sites were unlimited in the stomach, then *H. pylori* populations would grow out of bounds (verified previously by the model in ref. 4). Two pieces of evidence supporting this finite capacity are as follows: the presence of adhesion pedestals induced by *H. pylori* (19) indicates irreversibility of adhesion, and recent estimates on the size of the adherent population (20), on the order of $< 1\%$ of the total mucus population size, and the fact that these sites are most advantageous indicate that a limited number of sites are available.

$$\frac{dA}{dt} = \bar{g}_A \alpha N(t) A(t) - \mu_A A(t) + aM(t)(K - A(t)) - \delta A(t). \quad \textbf{[2]}$$

The change in the adherent (A) population is marked by a growth term similar to the one in **1** above, a loss term at rate A due to epithelial cell sloughing, and gain and loss terms due to migration from and to the M population that are opposite in sign to those in Eq. **1**.

$$\frac{dN}{dt} = \frac{b}{b + I(t)} \beta E(t) - \bar{g}_M N(t) M(t) - \bar{g}_A N(t) A(t). \quad \textbf{[3]}$$

This equation represents the change in nutrient concentration (N). We consider that the size of the nutrient population reflects the extent of inflammation induced by effectors (E) that are released by the bacteria (3). Since *H. pylori* are not known to invade tissue, the host response ultimately is assumed to be limited to controlling inflammation. Thus, we assume that nutrient is inflammation limited, hence the host response ultimately limits bacterial growth, and affects population size. The change in the nutrient population is characterized by a gain term that is a function of both the effector population (E) and the host response (I). The form of the term represents the proportional relationship between effectors, E, and nutrients, N, and the limiting effects of the host response, I: if I is small, then there is little effect, but if it is large, then the rate of nutrient production is limited. Two loss terms are based on nutrient assimilation by the bacterial populations. During the initial transient, the development of the host response progressively modifies the intrinsic ability of bacterial-effector molecules to elicit nutrients from the host.

$$\frac{dE}{dt} = \frac{c\tau}{\tau + N(t)}(M(t) + A(t)) - \eta E(t). \quad \textbf{[4]}$$

In this equation, the change in the effector (E) concentration increases as a function of the size of the bacterial and nutrient populations, and decreases due to the utilization of effectors. Since we assume that *H. pylori* respond to environmental signals (in this case nutrients) independently of the host response, this equation is identical to that used in the previous steady state model (4).

$$\frac{dI}{dt} = k_1(A(t) + k_3 M(t))(k_2 - I(t)). \quad \textbf{[5]}$$

We describe the population in Eq. **5** that reflects the development and intensity of the host response (I) to *H. pylori*. The growth rate of the response is reflected by k_1. The host response initially grows proportional to the bacterial population, but this growth has a limited capacity, represented by k_2. That the immune response has a limited capacity is supported by experimental observations (21). In this model, we assume that adherent (A) *H. pylori* will have a greater impact on the host response than will the mucus-living (M) *H. pylori* due to the adherent population's proximity to host epithelial cells. This difference is reflected by the value selected for k_3, representing the proportional difference of the M to A effects on the host response; however, the model results show little change when $k_3 = 1$.

To complete the development of the mathematical model (Eqs. **1**–**5**), we must define values for the parameters and initial conditions. The initial values chosen must reflect the experimentally estimated population sizes. Since during persistence, *H. pylori* concentrations range from 10^5 to 10^8 per mm^3 (20, 22), and colonization begins with an initial inoculum, we choose a smaller value, on the order of 10^1 to 10^4 per mm^3; however, the model gives qualitatively similar results with larger initial values. We begin with no adherent population, and with fractional effector and nutrient populations. We assume that the host is naive to *H. pylori*, and thus the level of host-response activation is very low.

As terms in Eqs. **1**, **2**, and **4** are identical to those of our previous model (4), we choose values for the parameters based on the same assumptions. In Eq. **3**, we have modified the growth term to depend on the host response, and therefore we have a new rate constant, b, reflecting the effects of the host response. Since we are modeling the host response phenomenologically, we choose values for b that reflect biologically accurate results. This also is true in the case of Eq. **5** for which we have assigned an arbitrary maximal strength of the host response, k_2, and growth rate constant, k_1. For a list of parameters and their values as well as a mathematical analysis of the system, see Table 2 and the Appendix, which are published as supplemental data on the PNAS web site (www.pnas.org). A full range of values for these parameters is explored for their effects on the dynamics of the model system (c.f. Fig. 3). The results of the new parameter explorations are summarized in Table 1 and discussed in the next section.

3. Biological Analysis of the Host Response

Individuals differ in their ability to recognize and combat a newly introduced microbial pathogen; such differences can be analyzed by examining the effects that varying the parameters k_1, k_2, and k_3 has on the microbial population. Observation of natural and experimental exposures to *H. pylori* indicates that either *persistent* or *transient colonization* may occur (13, 14, 23, 24). In the first case (persistence), pathological changes develop essentially immediately (13, 14). Subsequently, there is marked inflammation of the gastric mucosa (12) during a time in which the host response has not

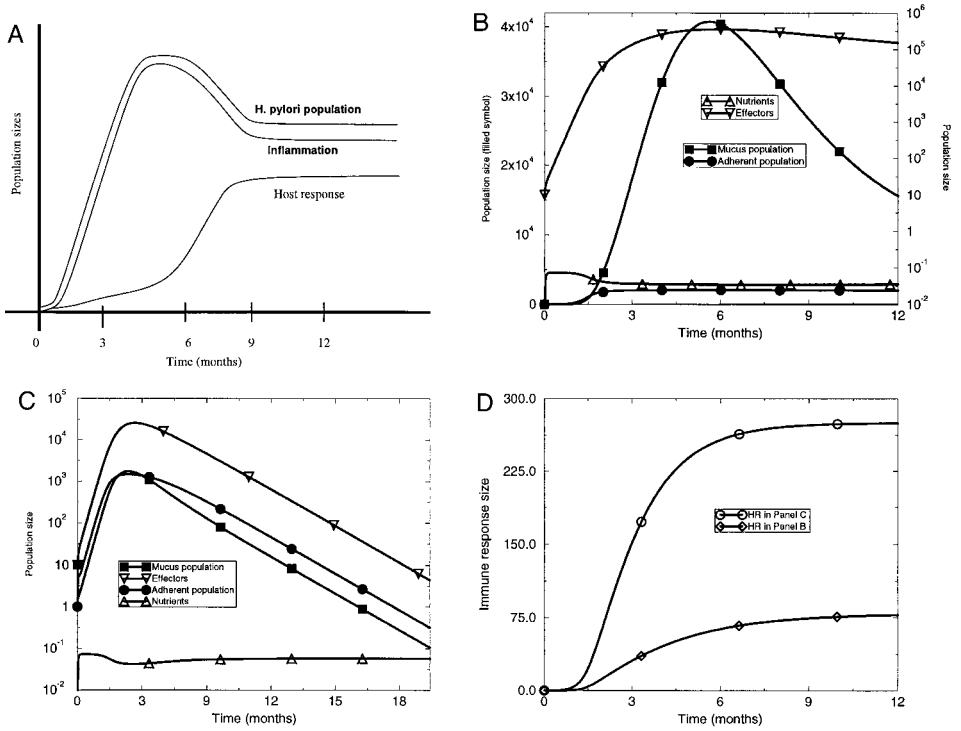

FIG. 2. Model dynamics. (*A*) A schematic representation of the dynamics of *H. pylori* populations together with the corresponding host response as observed from natural and experimental colonization data. Following the acquisition of *H. pylori*, bacterial numbers rise rapidly. Initially, the specific host response is undetectable but progressively increases, reaching its maximal level, on average, in several months. With the development of a host response, bacterial numbers and consequent inflammation reach their steady state. (*B*) The initial transient dynamics and the steady-state development of persistent colonization. (*C*) Transient colonization that results from a much larger host response (due to an increase in the host response capacity, from $k_2 = 80$ to $k_2 = 250$). For *B* and *C*, $\triangledown$ represents the effector population and $\triangle$ represents the nutrient population, whose scale is given on the right axis; ■ and • represent the mucus and adherent populations, respectively, and the scales for both populations are indicated on the left axis. (*D*) The dynamics of the different host responses for the results in *B* ($\diamond$) and *C* ($\circ$).

fully developed to the steady-state values (13). During this period, which can last up to a year (12, 13), there are marked physiologic abnormalities, including hypochlorhydria. Eventually the host response reaches the steady-state level, and the inflammation diminishes, yet persists (13). Experimental *Helicobacter* infections in test animals indicate that the bacterial load diminishes substantially compared to that prior to the development of the host response (15); human studies indicate that the gastric physiology also assumes a new homeostasis (25). The relationship between bacterial colonization and development of the host response inferred from experimental observations is represented in Fig. 2*A*. With the default parameter values, the model (**1–5**) permits an initial transient, and the subsequent development of the *colonized steady state* (persistence) with characteristics similar to those we hypothesized (Fig. 2 *A*, *B*, and *D*).

In the second case (transient colonization), *H. pylori* becomes established for a matter of days or weeks, but the host is able to eradicate the organism, presumably facilitated by the development of a strong host response (23, 24) (i.e., *the noncolonized steady state*). The model encompassed in Eqs. **1–5** permits the phenomenon of transient colonization (Fig. 2 *C* and *D*). To understand the differences between these model dynamics, we explore the host-response model, Eq. **5**. The parameter k_2 represents the capacity of the host response, and based on a mathematical analysis, it can be shown that k_2 has a greater effect than either k_1 or k_3 on the development of *H. pylori* colonization (i.e., k_2 is a bifurcation parameter; k_1 and k_3 are not). As the value of k_2 varies, the steady-state value of the microbial population (M) changes (Fig. 3). As k_2 increases from 80 toward 250, there is an exchange of stability at a transition point ($k_2^{critical}$, not shown) between the colonized and noncolonized steady states; thus, k_2 undergoes a *transcritical bifurcation*. Progressively decreasing k_2 increases the microbial population to a level beyond steady state (i.e., another bifurcation occurs), and the bacterial populations then grow without bound. Increasing the value for k_2 decreases the size of the *H. pylori* population and prolongs the interval until steady state is reached (not shown). This continues until this steady state no longer exists due to a third bifurcation—merging with the noncolonized steady state, which then becomes the attractor. A high k_2 value (i.e., the ability to mount a strong host response) may explain why in some individuals, exposure to a particular *H. pylori* strain results only in transient colonization (23, 24). However, transient colonization does not preclude the development of persistence, if at a later time, the host is exposed to an organism with different colonization characteristics. A low k_2 value is compatible with partial tolerance for *H. pylori*, which may explain high-level bacterial persistence, and the ultimate development of atrophic gastritis and gastric cancer (2, 3).

Numerical analysis also shows that increasing the growth rate of the host response (represented by k_1) cannot eradicate *H. pylori* colonization; this is consistent with a presumed lack of natural immunity to *H. pylori*. However, as the value of k_1 increases, the time required for steady state to develop

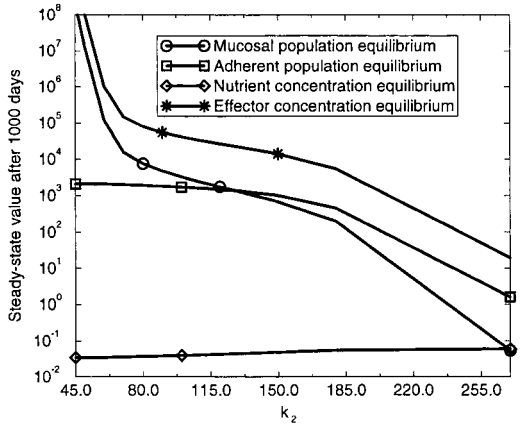

FIG. 3. Strength of host response. This figure represents the change in the steady-state value of the system at 1000 days as k_2, the parameter that measures the strength of host response, is varied. For each value of k_2, a steady state for the system (Eqs. **1–5**) is obtained. Thus, as we vary the parameter (x axis), the steady-state value of the microbial populations (y axis) changes. Each vertical slice of the graph indicates a value of k_2 and then determines the corresponding system values for the populations. We consider k_2 to be a *bifurcation parameter* as the model has very different behaviors for different choices of values (see Section 3).

is longer, and the steady state occurs at a lower level. Conversely, decreasing k_1 allows the microbial population to sooner reach a higher steady-state level (not shown).

The relative impact on the host response of the free-living (M) population in relation to the adherent (A) population is represented by k_3. This more properly may be considered as a microbial characteristic rather than a host characteristic. For example, for some strains, the M population may colonize the host with greater proximity to the tissues than do others (26). If all else were equal, the strains colonizing in greater proximity would be predicted to have a greater impact on the host response (higher k_3), which ultimately would limit total bacterial numbers. Differences among strains in their pro-inflammatory efficiency, for example, could counterbalance variations in proximity. Interestingly, even with $k_3 = 1$, the M population decreases but does not disappear. Thus, *H. pylori* could tolerate very close proximity to the host, if necessary. However, low M populations might reduce the ability for transmission to new hosts.

The role of the other key parameters in the model was explored in detail (Table 1). The washout rate, μ_M, has a strong effect on the dynamics. With increased μ_M, the mucus population is washed out completely, and colonization cannot persist; with decreased μ_M, the bacterial population grows without bounds. In contrast, changes in the *H. pylori* growth rate, r_M or r_A, had little effect on the bacterial population size. The value of c represents the rate that *H. pylori* produces effector molecules, such as urease, to induce inflammation. As expected, when c is increased, there is a large response in the bacterial population. Also as anticipated, our numerical studies indicate that the size of the bacterial population is very sensitive to the value for β, which represents the amount of nutrient produced in relation to the effector concentration. This was expected, as it is the finely tuned feedback model that allows for *H. pylori* persistence.

4. Strain Variation

Naturally occurring *H. pylori* strains may be of the *cagA*$^+$ or *cagA*$^-$ genotype (27), and colonization by *cagA*$^+$ organisms increases the risk of development of both peptic ulceration and adenocarcinoma of the distal stomach (28). *cagA*$^+$ strains induce higher levels of inflammation (28–31) and colonize at approximately a 5-fold higher density than do *cagA*$^-$ strains (22). If we assume that *cagA*$^+$ strains have small increases in their intrinsic ability to induce inflammation, as has been shown *in vitro* (32), then to compare the kinetics of *cagA*$^+$ and *cagA*$^-$ strains, the appropriate mathematical parameter to explore is β, which governs the conversion of effectors into nutrients based on the host response. We observe numerically that the model is sensitive to very small increases in β (Table 1), which is consistent with *cagA*$^+$ strains producing the predicted result: that of higher colonization levels (21).

Table 1. Effect of variation of several key biological parameters on the mucosal *H. pylori* population from Eqs. **1–5**

Parameter	New value	Effect on M-population from change*
μ_M	0.95	$\rightarrow 0$
	0.8	5-fold increase
	0.7	$\rightarrow \infty$
r_M, r_A	13.3	2% decrease
	25	no change
c	1.017	20% increase
	1.057	65% increase
	1.207	$\rightarrow \infty$
β	0.09	1.4-fold decrease
	0.102	2.4-fold increase
	0.105	$\rightarrow \infty$

*Change in steady state value of the *H. pylori* population. New values represent changes in the default parameter values. $\rightarrow 0$, washout; $\rightarrow \infty$, unbounded growth.

5. Competition

Humans may be simultaneously colonized with *cagA*$^+$ and *cagA*$^-$ strains (33, 34). If we assume that there is competition for adherence sites, then each strain must have a compensatory advantage over the other to permit co-existence in a specific niche. For example, if certain strains were more motile *in vivo*, thus better resisting peristaltic loss (the effective loss-rate for that strain would be decreased; Table 1), they could compete with strains that produced inflammation (and allowed release of nutrients) more efficiently. Identification of *H. pylori* strains with different colonization characteristics has been reported (26).

To extend the model Eqs. **1–5** to represent a two-strain competition, it is necessary to double the number of equations representing the microbial populations, M and A together with the addition to the equations for the corresponding effectors, E, and subsequent nutrient production, N. The host response equation, (Eq. **5**), is changed via the sum of all the bacterial populations. Thus, the new equations are identical to those in Eqs. **1–4** but now include subscripts indicating species 1 or species 2, and in Eq. **5** they replace the $M + A$ terms with the four new subspecies (not shown). We now can consider the dynamics of competing bacterial populations under the following scenarios: two strains of equal or differing properties, two different strains, or hybrid strains that were created via horizontal gene transfer.

Although organisms with differing characteristics, based on any of the three scenarios above, cannot co-exist indefinitely in this model, they may do so for a period of months (Fig. 4*A*) or years (Fig. 4*B*), before one or more is eliminated. Thus, development of microheterogeneity permits the creation of a pool of competing organisms; such diversity may increase survival possibilities for the total population as environmental conditions change. This suggests that each strain must have its own, essentially non-overlapping, niche for steady state to occur, otherwise exclusion of one population may occur. Although steady state cannot be reached, after elimination of one strain, another strain may be acquired (by mutation or exogenously), and competition dynamics can iterate for the lifetime of the host. Alternatively, since *H. pylori* are naturally competent (35, 36), there may be horizontal gene transfer between the competing strains to create hybrids (24, 37, 38). A host in whom there is competition for resources (e.g., adherence sites, nutrients) would result in selection for hybrids that can more efficiently sequester these resources than can their parental strains. The current model encompasses any of these possibilites under these general principles of competition.

Another possibility is that two strains colonize the stomach but one is able to adhere and the other is not; thus, they do not compete at all for adherence sites. According to our model, this cannot occur because without an adherent population, *H. pylori* will be eliminated. It was not possible to obtain simultaneous steady-state solutions for both populations in this model of competing *H. pylori* strains, unless the strains have virtually identical colonization characteristics. This result implies that colonization niches for *H. pylori* are exclusive and indicates that selection will occur when mutation leads to phenotypic heterogeneity; the recent observations of *H. pylori* clones that show microheterogeneity (34, 39, 40) indicate that competition for a niche occurs.

6. Host Variation: Immunodeficiency

As mentioned, the host response could include either (or both) innate or specific immune responses as well as other host mechanisms that respond to the introduction of a microbial colonizer. As such, an important scenario to consider is when immunodeficiency supervenes during persistent *H. pylori*

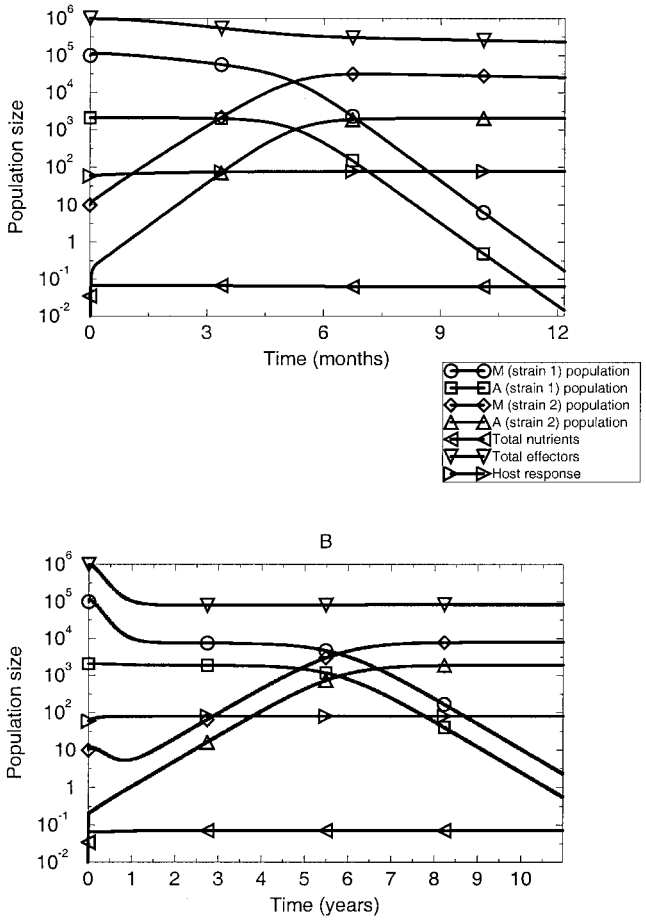

FIG. 4. Competition dynamics. The model (Eqs. **1–5**) is extended to represent two different genotypes of *H. pylori*, identified as strain 1 and strain 2. This is achieved in the system by doubling the number equations representing the microbial population, namely M and A, together with the corresponding nutrients and effectors, N and E, respectively. Strain 1 is already present in steady state when strain 2 is introduced (either by mutation or exogenously). In this model, strain 2 is a better swimmer than strain 1 (which has a $\mu_{M_1} = .85$). If $\mu_{M_2} = .79$ (*A*), strain 2 is able to outcompete strain 1 quickly (within 1 year); if $\mu_{M_2} = .84$ (*B*), it can outcompete strain 1 slowly (over 10 years). All other parameters for the two populations are the same as the default values listed in Table 2 (at www.pnas.org). In either case, there is a time frame whereby both populations are present in the stomach (transient co-existence).

colonization. Clinical studies indicate that *H. pylori* colonization and HIV infection often co-exist (41). Although the clinical and pathological consequences of the interaction are not well-defined in the literature (41, 42), there does not appear to be any striking deviation from characteristics in HIV-negative hosts. This observation is consistent with an autoregulated model of colonization, as we have proposed (2–4), and diminution of k_1 or k_3 in the current model has little effect on the steady-state equilibrium. Diminution of k_2 has a significant effect, and decreasing k_2 below the steady-state values transits to a dynamic whereby the bacterial populations grow without bound (see Fig. 5, published as supplemental data at www.pnas.org). This is not consistent with the observed maintenance of *H. pylori* in the face of HIV infection. This observation suggests that there exists a lower limit on k_2 values in humans, in relation to the indigenous microbial flora, that is maintained despite most immunodeficiencies. Such a limit may imply selection for humans who are able to contain their indigenous microbial populations and could presumably reflect our long co-evolution (3). Similarly, in HIV infection, there are only selected instances of deficiency in responding to other autochthonous organisms (43).

7. Discussion

Persistent parasites, by definition, have developed mechanisms for thwarting host responses. In parallel, there also has been selection for hosts that respond appropriately to their microflora, neither permitting their unlimited proliferation nor eliminating symbionts. Hosts have several mechanisms for dealing with microbial invaders. One response is to eliminate the agent altogether. When this is not possible, for example due to microbial evasion strategies, our model indicates that down-regulation of the host response is beneficial to the host. For *H. pylori* and humans, the equilibrium reached includes an inflammatory response that appears necessary for the microbe but is not overly harmful to the host (2, 3). It has been suggested that ultimately, microbes and their hosts compete for nutrients (44). Hosts often possess innate properties to limit microbial nutrition, such as iron-sequestration mechanisms. We propose that the key function of the host to *H. pylori* is to limit the nutrient supply to the organism, thus curtailing the microbial population. The role of the host response to limit microbial access to nutrients is a model that may have applicability beyond *H. pylori* and may help explain granuloma formation in tuberculosis, for example ref. 45. This concept suggests the paradigm that when hosts are unable to eliminate a particular parasite, there is selection for host responses that directly or indirectly restrict nutrient uptake by the parasite, or reduce its ability to affect adjacent tissues.

This model considers populations of microbes, nutrients, and effectors, as well as the host response. Because we model this deterministically (i.e., through the use of differential equations) rather than stochastically, in essence, we average over all possible outcomes for each of the populations rather than consider each plausible outcome separately; hence fractional values for the different population-size values are possible.

Our model of *H. pylori* persistence also considers issues of microbial competition. Experimental studies have documented co-colonization by different strains (33, 46), as well as the emergence of both clonal variants of a single strain (34, 39, 40), and recombinants of different strains (37). *H. pylori* strains appear to be highly diverse (47, 48). As in other biological systems, there is clearly selection for microbial fitness, and an important aspect of selection is the ability to interact with the host. Differential susceptibility to host response can lead to the ascendency of clonal variants and recombinant progeny over their parental strains. The current model incorporates this biological feature.

Host responses have developed to protect hosts from pathogens. But among host–microbial interactions, not all are antagonistic, and examples of mutualism abound (44). In such cases, the selective pressures on the genes controlling host responses differ from those in antagonistic relationships. In mutualistic relationships, the selection has been toward responses leading to equilibria that permit successful reproduction of both life-forms. From an immunological viewpoint, the equilibrium values must lie between complete immunity (elimination of the microbe) and complete tolerance (death of the host).

We speculate that such has been the case for *H. pylori* and humans, and the development of this equilibrium model is consistent with this concept. Intrinsic to this model are the concepts of host recognition and down-regulation of the host response (3) which permits equilibrium to be achieved.

The model teaches us that the value of k_2, the capacity of the host to respond to *H. pylori*, is critical in determining the colonization level and that there is a lower limit of k_2 below which the bacteria grow without control and an upper limit of k_2 beyond which equilibrium (colonization) cannot occur (i.e., bacteria are successfully removed from the system). What do these observations imply? First, the broad range of k_2 values

leading to colonization is consistent with the heterogeneity of human response genes. Second, the lower limit suggests that there is a universal response and that the genes controlling this could be deeply embedded in our evolutionary development. A k_2-related lower limit may be relevant to the host response to other indigenous biota. The infrequency of opportunistic infections from the indigenous bowel microflora in AIDS, for example, indicates that the protective responses that monitor these populations remain intact. Third, the upper limit indicates that there is a range of host responses that can lead to clearance of *H. pylori*. This may depend on the particular bacterial strain or on the state of the host at the time of exposure.

In this model, k_1, representing the growth rate of the host response, does not affect whether or not *H. pylori* colonization can occur, but it does affect the time it takes to reach steady state and the sizes the steady-state populations will reach. Variability in k_1 reflects the polymorphism of human responses, but it does so differently than that of the capacity, k_2. This may be interpreted such that the age at which a host is exposed to a microbe has an important bearing on the outcome of the interaction (49–51). For *H. pylori* in particular, differences in presumed acquisition age are associated with differences in clinical expression of the colonization (52). Values of k_2 may reflect, among other phenomena, age-related differences in the host response to modulate inflammatory responses to microbial stimuli. The particular k_2 value in any host represents both age-related and exogenous effectors of the host response and, by governing inflammation, would have important bearing on the long-term outcome of the host–microbial interaction.

In conclusion, the model proposed examines the events in the colonization of a persistent microbe from the time of its introduction to the host. Modeling of the host response as an agent to control microbial populations when elimination is not possible suggests a possible solution to the dilemma of the transition from initial colonization to persistence. That the model is flexible to both host and microbial perturbations (via the rate constants) suggests not only that it can improve our understanding of *H. pylori* dynamics but also that the central features may be generalizable to other persistent microbial carriage states (e.g., malaria, HIV).

This work was supported in part by Grant R01 DK 50837 from the National Institutes of Health, by the Medical Research Service of the Department of Veterans Affairs, and by Astra-Merck, Inc.

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