

References and Notes

1. L. H. Taylor *et al.*, *Philos. Trans. R. Soc. London B*, in press.
2. S. Cleaveland *et al.*, *Philos. Trans. R. Soc. London B*, in press.
3. Office International des Epizooties list A and list B diseases [www.oie.int/eng/maladies/en\_classification.htm].
4. M. C. Whitlock, *Am. Nat.* **148**, S65 (1996); J. D. Fry, *Am. Nat.* **148**, S84 (1996); T. J. Kawecki, *Am. Nat.* **152**, 635 (1998).
5. C. Combes, A. Theron, *Int. J. Parasitol.* **30**, 299 (2000).
6. J. Blancou *et al.* [*Bull. Acad. Natl. Med. (Paris)* **181**, 301 (1997)] report that rabies virus taken from foxes has a LD<sub>50</sub> (number of virus particles to which hosts must be exposed to cause 50% mortality) 10<sup>5</sup> to 10<sup>6</sup> times greater for cats and dogs than for foxes.
7. W. Bitter *et al.*, *Nature* **391**, 499 (1998).
8. K. Morimoto *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 3152 (1998).
9. J. H. M. Simon *et al.*, *EMBO J.* **17**, 1259 (1998); L. L. Kuo *et al.*, *J. Virol.* **74**, 1393 (2000); E. H. Hartland *et al.*, *Infect. Immun.* **68**, 4637 (2000).
10. Y. A. Smirnov *et al.*, *Acta Virol.* **44**, 1 (2000); D. J. Alexander, I. H. Brown, *Rev. Sci. Tech. Off. Int. Epizoot.* **19**, 197 (2000).
11. C. P. Conner *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 4641 (1998).
12. T. Binz *et al.*, *Virus Res.* **34**, 281 (1994).
13. S. C. Weaver *et al.*, *J. Virol.* **73**, 4316 (1999).
14. B. H. Hahn *et al.*, *Science* **287**, 607 (2000).
15. J. Seale, *J. R. Soc. Med.* **82**, 519 (1989).
16. M. A. Nowak *et al.*, *Science* **254**, 963 (1991); S. Morand *et al.*, *Proc. R. Soc. London B* **263**, 119 (1996); D. T. Haydon, M. E. J. Woolhouse, *J. Theor. Biol.* **193**, 601 (1998); S. Gupta, N. Ferguson, R. Anderson, *Science* **280**, 912 (1998).
17. P. A. Cane, *Trends Microbiol.* **1**, 156 (1993); S. Wain-Hobson, *Trends Microbiol.* **4**, 135 (1996); J. P. Horst, *Trends Microbiol.* **7**, 29 (1999); J. W. Drake, J. J. Holland, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 13910 (1999); G. Rudenko, *Curr. Opin. Microbiol.* **2**, 651 (1999).
18. Examples include: *E. coli* O157 in cattle, 10<sup>6</sup> bacteria per g feces; *Diphyllobothrium latum* in humans, 10<sup>6</sup> eggs per female per day; *Plasmodium chaubaudi* in mice, 10<sup>7</sup> gametocytes per ml blood; *Brucella melitensis* in cattle, 10<sup>12</sup> bacteria per g placental tissue; *Toxocara canis* in dogs, 10<sup>7</sup> eggs per day; and foot-and-mouth disease virus in pigs, 10<sup>10</sup> to 10<sup>12</sup> virus particles exhaled per day.
19. Many authors suggest that exposure to a few compatible pathogens, or even just one, may result in infection [R. L. Ward, E. W. Akin, *CRC Crit. Rev. Environ. Control* **14**, 297 (1984); W. A. Cafruny, D. E. Hovinen, *J. Virol. Methods* **20**, 265 (1988); D. A. Blewett *et al.*, *Water Sci. Technol.* **27**, 61 (1993); P. Suttmoller, D. J. Vose, *Rev. Sci. Tech. Off. Int. Epizoot.* **16**, 30 (1997); A. R. McLean, C. J. Bostock, *Philos. Trans. R. Soc. London B* **355**, 1043 (2000)].
20. J. W. Drake, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 7160 (1991).
21. D. S. Kettle, *Medical and Veterinary Entomology* (CAB International, Wallingford, UK, ed. 2, 1995).
22. M. E. J. Woolhouse *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 338 (1997); G. Hide *et al.*, *Parasitol. Today* **12**, 50 (1996); C. C. Lord *et al.*, *Med. Vet. Entomol.* **10**, 19 (1996).
23. W. L. Kellogg, *Am. Nat.* **47**, 129 (1913).
24. For example, the orders Diptera, Siphonaptera, Hemiptera, Phthiraptera, and Acari all contain species that act as vectors of pathogens from a variety of taxa.
25. Virulence is defined as a reduction in host fitness associated with infection by a pathogen.
26. G. Dwyer *et al.*, *Ecol. Monogr.* **60**, 423 (1990); J. J. Bull, *Evolution* **48**, 1423 (1994); M. Lipsitch, E. R. Moxon, *Trends Microbiol.* **5**, 31 (1997).
27. S. C. Stearns, Ed., *Evolution in Health and Disease* (Oxford Univ. Press, Oxford, 1999).
28. R. M. Anderson, R. M. May, *Infectious Diseases of Humans: Dynamics and Control* (Oxford Science Publications, Oxford, 1991).
29. R. W. Ashford, *Belg. J. Zool.* **127**, 85 (1997).
30. Single-host pathogens too can occur as outbreaks in isolated host subpopulations [C. J. Rhodes, R. M. Anderson, *Nature* **381**, 600 (1996)].
31. M. J. Keeling and C. A. Gilligan [*Nature* **407**, 903 (2000)] describe a model of the dynamics of a vector-borne zoonotic disease, bubonic plague, which reproduces outbreaks in one host population (humans) as a consequence of small changes in the epidemiology of endemic infection in another host population (rats).
32. L. R. Taylor, *Nature* **189**, 732 (1961).
33. G. E. Hutchinson, *Am. Nat.* **93**, 145 (1959); T. de Meeus *et al.*, *Parasitol. Today* **14**, 10 (1998).
34. R. Timms, A. F. Read, *Trends Ecol. Evol.* **14**, 333 (1999).
35. For example, *Schistosoma haematobium* is a predominantly human parasite, whereas the congeneric *S. japonicum* infects a wide range of host species, including humans. Similarly, one subspecies of *Trypanosoma brucei*, *T. b. gambiense*, is a predominantly human parasite, whereas another subspecies, *T. b. rhodesiense*, infects a wide range of hosts, including humans.
36. W. O. Kermack, A. G. McKendrick, *Proc. R. Soc. London A* **115**, 700 (1927).
37. *Escherichia coli* O157 data, from the Scottish Centre for Infection and Environmental Health (www.show.scot.nhs.uk/scieh/), exclude sporadic cases and cases from the same household. Ebola data are from ProMed (www.promedmail.org), and *S. aureus* data are from Health Canada (www.hc-sc.gc.ca).
38. Details available from the authors on request.
39. We gratefully acknowledge colleagues at the Centre for Tropical Veterinary Medicine for valuable discussions, and the Wellcome Trust for financial support.

VIEWPOINT

# Why We Don't Get Sick: The Within-Host Population Dynamics of Bacterial Infections

Bruce R. Levin and Rustom Antia

To pathogenic microparasites (viruses, bacteria, protozoa, or fungi), we and other mammals (living organisms at large) are little more than soft, thin-walled flasks of culture media. Almost every time we eat, brush our teeth, scrape our skin, have sex, get bitten by insects, and inhale, we are confronted with populations of microbes that are capable of colonizing the mucosa lining our orifices and alimentary tract and proliferating in fluids and cells within us. Nevertheless, we rarely get sick, much less succumb to these infections. The massive numbers of bacteria and other micro- and not-so-micro organisms that abound and replicate in our alimentary tract and cover our skin and the mucosa lining our orifices normally maintain their communities in seemingly peaceful coexistence with the somatic cells that define us. Why don't these microbes invade and proliferate in the culture media within the soft, thin-walled flask that envelops us? Why don't they cause disease and lead to our rapid demise?

For several microparasites, and for bacteria and viruses in particular, we have a good part of the answers to the question of why we don't get sick. There is a plethora of detailed,

but almost exclusively qualitative, information about the genetics, molecular biology, development, biochemistry, cell biology, and physiology of the nonspecific and specific immune defenses that protect mammals from bacterial infections (*1*) and the virulence factors bacteria use to evade these defenses, sequester iron and other nutrients essential

for their replication, and cause disease (*2, 3*). Although these details are fundamental to understanding the mechanisms of pathogenesis, by themselves they are not sufficient. Knowing why we don't get sick and, by default, knowing why we do, ultimately comes down to a quantitative understanding of the processes responsible for the rise, dissemination, fall, and evolution of the populations of infecting microparasites and those of the somatic cells of the mammalian defenses.

There have been several quantitative studies of the within-host population dynamics of microparasite infections using mathematical models. The majority of these have been for viruses such as human immunodeficiency virus (HIV) and its interaction with the specific immune system (*4–6*). There have also been few studies of the within-host population dynamics of other microparasites such as protozoa (*7, 8*) and bacteria (*9, 10*). Although there are certainly exceptions, for example,

Department of Biology, Emory University, Atlanta, GA 30322, USA. E-mail: blevin@emory.edu; rantia@biology.emory.edu

(9) and (10), taken at large, at this time, our quantitative understanding of the within-host population dynamics of microparasite infections is limited and would not have satisfied Lord Kelvin (11).

Here we consider the within-host population dynamics and evolution of invasive bacterial infections and that of the somatic cells responsible for controlling the proliferation of these bacteria. We focus on those elements of the population biology of bacterial infections that we believe have to be elucidated in a quantitative way to understand bacterial pathogenesis and virulence and why some infected individuals get sick and others do not.

**Invasion, Colonization, Persistence, and Disease**

Infection and disease, like everything else in life, are continuous processes. Nevertheless, as with other complex continuous processes, it is convenient and, perhaps because of the limitations of our imaginations, necessary to study and describe the within-host population dynamics of bacterial infections as a sequence of more-or-less discrete stages.

**Stage 1: Invasion, Proliferation, and Colonization**

Systemic (invasive) infections commence with a population of bacteria traversing our skin and/or mucosal linings and entering our blood, somatic cells, and intercellular spaces and fluids (12). At this earliest stage of the infection process, we are passive, and our defenses are those that are on all the time and do not require signaling or specific instructions to respond to the invasion by a population of microparasites. Nevertheless, despite the successful passage through this first station of the gauntlet, the infecting population of bacteria is likely to be cleared. This may occur for a variety of reasons including the following: (i) the entire invading population is killed by phagocytic cells, such as neutrophils, or circulating bacteriocidal compounds, such as complement, (ii) the density of bacteria traversing the integument is collectively too low to condition the tissue to allow their population to grow, or (iii) the mutations or phase shifts required to get across the mucosa or survive in the blood (13–15) do not occur (16). All of these reasons include a strong stochastic element, which could be one reason why only a fraction of individuals exposed to microparasites get productive infections (17).

**Stage 2: The Nonspecific, Constitutive Host Responses**

When a population of infecting bacteria passes through the skin or mucus membranes and replicates, its densities will

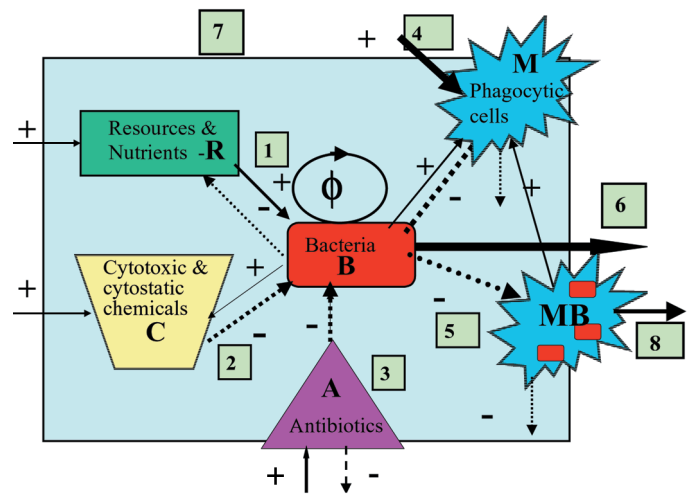
eventually reach a level where it will be recognized by our constitutive defenses and an inflammatory response will be initiated. Chemical signals, cytokines, will be generated, diffuse from the site of the infection, and recruit phagocytic cells (primarily neutrophils and monocytes) and bactericidal chemical defense (including complement and lysozyme) to the site of the infection. These constitutive defenses are nonspecific. They recognize invasion by bacteria through molecules unique to these prokaryotes (such as proteins initiated by formyl-met-leu-phe) but are unable to distinguish different species and strains of bacteria. Whether the specific immune system is or is not informed about the foreign intrusion at this early stage of an inflammatory response is not clear. The invading bacterial population may be cleared before the assistance of the specific immune response is induced or required (18).

From a population dynamic–ecological perspective, the control of the replication of the bacterial population at this stage is analogous to that of a predator-prey system. The bacteria are the prey and the phagocytic cells the predators, which along with

nutrient limitation, complement, lysozyme, other chemical defenses, and introduced antimicrobial agents can halt the growth of the bacterial population and lead to its clearance. At a qualitative level, the basic elements of this process have been studied in considerable detail and are well described in textbooks (see Fig. 1). Yet at a quantitative level, the interactions between components of the constitutive immune and infecting populations of bacteria have barely been considered.

To understand these processes at a quantitative level, the diagram presented in Fig. 1 would have to be expressed as a mathematical model (19). In the analysis of this model, of particular concern is the relative roles of nutrient limitation, complement, and other defensive chemicals and of the different populations of phagocytic cells in controlling the rate of proliferation or demise of the bacterial population as measured by their effect on the value (and sign) of  $\phi$ . Of practical interest is how different regimes of antibiotic use facilitate the control of the infection in a way that accounts for the host response, as well as the pharmacokinetics and pharmacodynamics of the antibiotics (20–23). Another focus of this analysis might be to as-

**Fig. 1.** A model of the population dynamics of an inflammatory response and control of a proliferating population of bacteria by the nonspecific immune response. Solid arrows with plus signs denote a positive effect on the growth of the noted population or increase in the concentration of bactericidal chemicals, and broken arrows with minus signs denote negative effects. The parameter  $\phi$  is the net or realized growth rate of the bacterial population. If  $\phi > 0$ , the density of the population is increasing, and if  $\phi < 0$ , it is in decline. In a mathematical model of this process, the arrows in this diagram would be represented by functions whose values will change in the course of time and with the density of bacteria [see (19)]. 1, The intrinsic growth rate of bacteria is proportional to the concentration of available resources and nutrients. 2, The proliferating bacterial population will stimulate the production of complement and other agents that kill them or make them more susceptible to phagocytosis and increase the rate of the migration of phagocytic cells into the site of the infection. 3, From a population dynamic perspective, antibiotics supplement the host defenses by reducing the rate of growth and/or killing the bacteria. 4, Through signaling, via an array of cytokines, the action of which is stimulated by the proliferating population of bacteria, phagocytic cells (primarily neutrophils and monocytes) would enter the site of the infection at higher rates and become increasingly voracious. In this model, these changes would be reflected in increases in their rate of migration and in the rate at which they take up free bacteria and kill those they have engulfed. 5, Although depicted as a single population, several different populations of phagocytic cells would be involved in this process: neutrophils, monocytes, and macrophages. Individual phagocytes can take up a number of bacteria. 6, Dissemination of bacteria via blood and other fluids. 7, The formation of an abscess. As time proceeds, puss (debris, dead bacteria, and phagocytic cells) will build up and the site of the infection can become walled off by membranes of host cells, and the rate of dissemination of bacteria from that site is thus reduced. 8, Macrophages will migrate to the site of the infection to clean up the debris and participate in the feeding frenzy of the other phagocytic cells present. Some of these macrophages along with free bacteria and parts thereof will make their way to the germinal centers as either free antigen or antigen-presenting cells and induce the specific immune response.



certain the rates at which free bacteria, bacterial antigens, macrophages, and other somatic cells displaying bacterial antigens migrate from the site of the infection and induce a specific immune response.

The model depicted in Fig. 1 is relatively general and its purpose is primarily heuristic. The form and magnitude of the functions depicted by the solid and broken arrows vary depending on the bacterial species and strain. The values of these functions and how they respond to changes in the density of the bacterial population depend on the mechanisms these bacteria have to sequester iron and other nutrients, subvert host defenses, and survive and replicate in the phagocytic cells (their virulence determinants). For example, encapsulated strains of bacteria, such as those of *Streptococcus pneumoniae* will, in the absence of a specific immune response be less susceptible to phagocytosis than those without capsules. Some species of bacteria such as *Listeria monocytogenes* and *Legionella pneumophila* are rapidly taken up by macrophages and other phagocytic cells and, like *Mycobacterium tuberculosis*, can survive and replicate within these phagocytes.

### Stage 3: Specific Immunity

If bacteria are not rapidly cleared during the first two stages of the infection, and perhaps if even if they are, the specific immune defenses will be induced. These defenses include the production of cytotoxic T lymphocytes (CTL, which consist predominantly of CD8 T cells) that are specific for infected host cells and the humoral response, involving circulating antibodies that are specific for the infecting bacteria and parts thereof. The generation of both the cell-mediated and humoral immune responses is population dynamic and evolutionary processes and has been considered as such for some time (24–36).

The effect of this escalation of the host response is a profound increase in the rate at which free bacteria, as well as viable bacteria within macrophages and other somatic cells are killed. The circulating antibodies bind to antigens on the surface of the bacteria to cause opsonization, making them considerably more liable to phagocytosis (including those with formerly refractory capsules). The induction of additional complement pathways will further reduce the rate of growth of free bacteria and, ideally, make the value of  $\phi$  in Fig. 1 negative. A further reduction in the bacterial population will come from the CTLs killing macrophages and other somatic cells that bear viable bacteria. To incorporate the response of the specific immune system into a mathematical model that includes the constitutive defenses, the set of equations for the population dynamics of the specific immune response would need to be coupled with those

specified in Fig. 1 for the inflammatory response. The functions, i.e., the arrows in Fig. 1, that govern the rate of proliferation of the bacteria would then take into account the changes in the concentration of specific antibody and densities of cytotoxic T cells. The questions of interest for this more comprehensive model of the host defenses would be extensions of those outlined above for the inflammatory response, i.e., to evaluate the contribution of circulating antibodies and CTLs in controlling the rate of proliferation or demise of the infecting bacterial population, as measured by their effect on the value and sign of  $\phi$ .

An important secondary effect of the induction of the specific immune response is the generation of immune memory (37–40) and thus immunity to subsequent infection by bacteria of that antigenic ilk and their endo- and exotoxins. When those bacteria traverse the integument a second time, their rate of clearance will be accelerated, because of the rapid ascent of the specific immune response.

### Why We Get Sick and Succumb to Bacterial Infections

Although bacteria may be the cause of disease, infection alone does not explain why we get sick and succumb to bacterial infections. Even when a mammal dies of a bacterial infection, the biomass of bacteria responsible is usually negligible. Ironically, the same defense mechanisms that prevent the proliferation of bacteria (and other microparasites) are also responsible for much of the virulence of those infections. When the density of bacteria gets large enough, the infection will be recognized as heat and pain, a fever will ensue, and there will be malaise. Although the apparent (and probably the evolved role) of the inflammatory response is to control the proliferation of microparasites, it is a two-edged sword in other ways. In some tissues and organs, such as the cerebral spinal fluid, a massive inflammatory response in itself could be detrimental and even lethal. While attempting to control the proliferation of the bacteria and rid the host of endo- and exotoxins they produce, there could be a massive killing of somatic cells by what is well described as “friendly fire” (41). A perverse side effect of these processes can be permanent physical impairment or even the death of the host. Thus, the host may succumb to an infection even when the defensive gauntlets of the constitutive and specific immune response are effective in stopping the proliferation of the infecting population of bacteria.

#### References and Notes

1. For a population biologist-friendly review of these defenses, see J. K. Spitznagel, in *Mechanisms of Microbial Disease*, X. Schaechter, M. G. Medoff, B. J. Eisenstein, Eds. (Williams & Wilkins, Baltimore, MD, ed. 2, 1993), pp. 90–114; H. K. Zeigler, in *Mechanisms of Microbial Disease*, M. Schaechter, G. Medoff, B. I.

- Eisenstein, Eds. (Williams & Wilkins, Baltimore, ed. 2, 1993), pp. 114–153; W. E. Paul, Ed., *Fundamentals of Immunology* (Lippincott, Williams & Wilkins, Baltimore, MD, ed. 4, 1999).
2. B. B. Finlay, S. Falkow, *Microbiol. Mol. Biol. Rev.* **61**, 136 (1997).
3. H. Ochman, N. A. Moran, *Science* **292**, 1096 (2001).
4. M. A. Nowak, R. M. May, *Virus Dynamics: Mathematical Principles of Immunology and Virology* (Oxford Univ. Press, Oxford, 2000).
5. A. U. Neumann et al., *Science* **282**, 103 (1998).
6. M. B. Gravenor, A. R. McLean, D. Kwiatkowski, *Parasitology* **110**, 115 (1995).
7. M. J. Blaser, D. Kirschner, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 8359 (1999).
8. P. C. Falk et al., *Trends Microbiol.* **8**, 321 (2000).
9. K. Murali-Krishna et al., *Immunity* **8**, 177 (1998).
10. K. M. Kerksiek, E. G. Pamer, *Curr. Opin. Immunol.* **11**, 400 (1999).
11. “I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it: but when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science, whatever the matter may be.” William Thompson (Lord Kelvin) (1824–1907). Of course, we wouldn’t say that.
12. In itself this is a considerable achievement. The integument of a mammal and the associated fluids and cilia are formidable defenses in their own right and are, doubtless, the primary reason that the bacteria and other microparasites that abound in the world around us, on us, and within us rarely cause disease. Save for trauma including the proboscis of biting arthropods, it is difficult for a microbe to get through the skin of a mammal. Although not as impermeable as skin, the mucosa of the alimentary tract and nasal pharyngeal passages and other orifices have formidable defenses of their own. Included among these are our microbial allies, the established populations of our commensal bacteria in these habitats. Their communities, and by default the mucosa in which they reside, are protected from colonization by potential pathogens by a home team advantage in the competition for space and nutrients and a variety of competitive allelopathic mechanisms, such as bacteriocins and microcins and predation by phage, protozoa, and nematodes.
13. J. W. S. Gerns, S. Falkow, *Infect. Immun.* **59**, 1325 (1991).
14. F. P. DeVries, A. VanDerEden, J. P. M. Putten, J. Dankert, *Infect. Immun.* **64**, 2999 (1996).
15. M. P. Jennings et al., *Microbiology* **145**, 3013 (1999).
16. If the colonizing population of the ancestral capsulated strains is too small, a sufficient number of unencapsulated variants (mutants) may not be generated and invasion will not take place. This indeed, may well be one of the reasons for the observations that systemic infections are caused by very few of the colonizing bacteria (42–44). These situations where a genetic change in the microparasite population is needed to establish systemic infection virulence could well be a consequence of short-sighted evolution of the microparasite in the host, rather than an adaptation for the maintenance of the microparasite in the community of hosts (45).
17. It has been suggested that because of the stochastic nature of the early phase of infections, vaccines that are only partially effective could reduce the probability of infection (46).
18. It may well be that although the infection is cleared by the constitutive defenses, an adequate specific immune response may be induced to generate immune memory. This, for example, may account for why older adults who have never experienced invasive diseases by commensal organisms such as *H. influenzae* and *N. meningitidis* are much less susceptible to bacterial meningitis than younger individuals.
19. For an example of a mathematical model of this type and a consideration of the motivation for its development, its predictions, and its role in an experimental study of a bacterial infection, see [www.ecf.net/phagocyte.html](http://www.ecf.net/phagocyte.html).
20. W. Craig, *Eur. J. Clin. Microbiol. Infect. Dis.* **12**, S6 (1993).

21. G. L. Drusano, W. A. Craig, *J. Chemother.* **9**, 38 (1997).
22. *Antimicrob. Agents Chemother.* **41**, 365 (1997).
23. M. Lipsitch, B. R. Levin, *Int. J. Tuberculosis Lung Dis.* **2**, 187 (1998).
24. A. R. McLean, M. M. Rosado, F. Agenes, R. Vasconcello, A. A. Freitas, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 5792 (1997).
25. M. Oprea, A. S. Perelson, *J. Theor. Biol.* **181**, 215 (1996).
26. Z. Agur, G. Mazar, I. Meilijson, *Proc. R. Soc. London Ser. B* **245**, 147 (1991).
27. R. Mehr, A. Globerson, A. S. Perelson, *J. Theor. Biol.* **175**, 103 (1995).
28. M. A. Fishman, A. S. Perelson, *J. Theor. Biol.* **173**, 241 (1995).
29. A. A. Freitas, B. Rocha, *Annu. Rev. Immunol.* **18**, 83 (2000).
30. R. J. De Boer, A. S. Perelson, *Int. Immunol.* **9**, 779 (1997).
31. T. P. Arstila *et al.*, *Science* **286**, 958 (1999).
32. V. Detours, A. S. Perelson, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 5153 (1999).
33. L. A. Segel, R. L. Bar-Or, *J. Immunol.* **163**, 1342 (1999).
34. D. Wodarz, M. A. Nowak, C. R. Bangham, *Immunol. Today* **20**, 220 (1999).
35. T. B. Kepler, A. S. Perelson, *J. Theor. Biol.* **164**, 37 (1993).
36. C. Kestmir, R. J. De Boer, *J. Immunol.* **163**, 2463 (1999).
37. A. A. Freitas, B. B. Rocha, *Immunol. Today* **14**, 25 (1993).
38. R. Ahmed, D. Gray, *Science* **272**, 54 (1996).
39. R. Antia, S. S. Pilyugin, R. Ahmed, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 14926 (1998).
40. D. Wodarz *et al.*, *Philos. Trans. R. Soc. London Ser. B* **355**, 329 (2000).
41. D. C. Krakauer, M. Nowak, *Proc. R. Soc. London Ser. B* **266**, 1069 (1999).
42. G. G. Meynell, B. A. D. Stocker, *J. Gen. Microbiol.* **16**, 38 (1957).
43. G. G. Meynell, *J. Gen. Microbiol.* **16**, 396 (1957).
44. E. R. Moxon, P. A. Murphy, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 1534 (1978).
45. B. R. Levin, J. J. Bull, *Trends Microbiol.* **2**, 76 (1994).
46. D. Wick, S. G. Self, *Math. Biosci.* **165**, 115 (2000).
47. The authors wish to thank F. Baquero, J. Bull, D. Generaux, D. Relman, I. Stojilkovick, and R. Zappala for useful comments and suggestions, most of which we agree with but lament in not having the space to develop them here. This endeavor was supported by grants from the U.S. National Institutes of Health GM33782 and AI40662 (B.R.L.) and GM 54268 (R.A.) and from the Wellcome Trust (B.R.L.).

VIEWPOINT

# Commensal Host-Bacterial Relationships in the Gut

Lora V. Hooper and Jeffrey I. Gordon\*

One potential outcome of the adaptive coevolution of humans and bacteria is the development of commensal relationships, where neither partner is harmed, or symbiotic relationships, where unique metabolic traits or other benefits are provided. Our gastrointestinal tract is colonized by a vast community of symbionts and commensals that have important effects on immune function, nutrient processing, and a broad range of other host activities. The current genomic revolution offers an unprecedented opportunity to identify the molecular foundations of these relationships so that we can understand how they contribute to our normal physiology and how they can be exploited to develop new therapeutic strategies.

The first draft of our complete DNA sequence represents a historic event in our quest for self-knowledge (1, 2). Knowing our genotype highlights the need to understand how environmental factors interact with our genetic traits to influence health and predispose us to illness. In the midst of the current revolution in comparative and functional genomics, it is therefore appropriate to consider another form of self-knowledge: the contributions of our microbial partners to our biology. From birth to death, we are colonized by a vast, complex, and dynamic consortium of microorganisms that may outnumber our somatic and germ cells (3). The Nobel laureate Joshua Lederberg has suggested using the term “microbiome” to describe the collective genome of our indigenous microbes (microflora), the idea being that a comprehensive genetic view of *Homo sapiens* as a life-form should include the genes in our microbiome (4).

Bacteria have inhabited Earth for at least 2.5 billion years (5). As a result, our predecessors have had to adapt to a biosphere dominated by microbes. However, we have minimal knowledge of how coevolution with indigenous microorganisms has shaped our genome and microbiome, as well as our physiology and postnatal development. For example, the human genome encodes 223 proteins with significant homology to bacterial but not eukaryotic proteins, suggesting that they were acquired through horizontal transfer of bacterial genes (1). Unfortunately, the components of our microbiome remain poorly defined. Like most complex ecosystems, enumerating membership in the various microbial societies that reside on our body surfaces has been hindered by the fact that most societal members cannot be cultured *ex vivo*. Moreover, most microbial genome-sequencing projects have focused on pathogens. Those that have embraced nonpathogens have turned to Archaea to understand the evolutionary diversification of prokaryotes and eukaryotes or to extremophiles to examine their adaptations to harsh environments and their potential for performing commercially applicable chemistry (6).

Interactions between bacteria and their hosts can be viewed in terms of a continuum between symbiosis, commensalism, and pathogenicity, with symbiosis and commensalism grouped under the general heading of mutualism (Fig. 1). “Symbiosis” refers to a relationship between two different species where at least one partner benefits without harming the other and is typically centered on metabolic capabilities that allow either or both partners to exploit an otherwise unavailable or poorly utilizable nutrient foundation (7, 8). The term “commensal” comes from the medieval Latin “commensalis,” meaning “at table together,” and generally refers to partners that coexist without detriment but without obvious benefit. A pathogenic relationship results in damage to the host. Symbiosis and commensalism have been viewed as potential outcomes of a dynamic “arms race” (9) initiated when a pathogen encounters a vulnerable host. In this race, a change in one combatant is matched by an adaptive response in the other. In some settings, the arms race evolves toward attenuation of virulence and peaceful coexistence, with or without frank codependence (symbiosis). In other circumstances, the pathogenic relationship is sustained by the development of effective countermeasures that bypass the host’s innate or adaptive defenses (Fig. 1). Ewald has coined the term “evolutionary epidemiology” to underscore how a comprehensive analysis of disease prevalence and spread must include the set of adaptive responses of host and pathogen to one another and their outside environment over time (10). He and others have emphasized that the concept of obligate evolution of parasites (pathogens) to benignness should be rejected on the

Department of Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, MO 63110, USA.

\*To whom correspondence should be addressed. E-mail: jgordon@molecool.wustl.edu