



# Paradoxes of the Host-Parasite Relationship

Applying the injunction “Thou shalt not kill” to pathogens brings surprising insights about how they adapt to hosts

Joshua Lederberg

**E**merging infections represent an ongoing threat to human welfare. Some of this threat arises because microorganisms contain an extraordinary apparatus for generating genetic variations, with pervasive gene flow among viruses, bacteria, and other microorganisms. Microbes also grow to immense population sizes, enabling fluctuations in population which speak to the incredible ferocity of natural selection.

The pace of evolutionary change in microbes thus is a million- or billionfold faster than that of their multicellular hosts. In effect for microbes, minutes amount to as much as years, with these calculations driven by natural selection, not the neutral clocks that are favored for phylogenetic trees. Consider how the viral load of humanity has altered in the last two decades.

Consider how dozens of bacterial species are now dominated by drug-resistant hangers-on that were unknown or invisible 30 years ago. These observations underlie my persistent ruminations about the future of infectious disease, about the prospects of our coexistence with the microbial world.

## Natural Selection Raises Basic Questions about Hosts and Microbes

How is that humans are still here, still survivors of such an uneven contest? Most of our evolutionary, and even inscribed, history is bereft of an intelligent understanding of infection, or sci-

entifically well-founded control measures to deal with it. Only more recently can we account for a near-doubling of human lifespan in this century in terms of such controls, embedded in improvements in nutrition, economic status, and sanitation, as well as specific prophylaxis and treatment measures.

But those efforts still hardly seem to answer the question of how humans survive. Of course, proving specific evolution-based, explanatory hypotheses is not so easy, and reconstructing history for any but the most self-evident stories is equally difficult. But arguments based on natural selection processes are the only way to make sense of the boundless potential in organismic physiology. Moreover, this approach does lead to ideas for some otherwise counterintuitive experiments.

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The short-term advantages within an infected host appear to fall mainly to the proliferator—indeed, to the most virulent members of the microbial swarm. Yet, this apparent initial advantage will typically lead to a Pyrrhic victory and limit the eventual fitness of such rogues.

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## Natural Selection Helps To Explain Virulence Modulation

Consider the 1918 influenza pandemic—undeniably the great plague of the 20th century. Yet that deadly viral strain manifestly disappeared

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*Joshua Lederberg is Professor Emeritus and Sackler Foundation Scholar at Rockefeller University, New York, N.Y., and received the Nobel Prize in Physiology and Medicine in 1958. This article, adapted from Lederberg's Centennial lecture during the 100th ASM General Meeting, held in Chicago, Ill., in May 1999, is the final in a three-part series on infectious diseases (see ASM News, January 1999, p. 18, and February 1999, p. 77).*



## Lederberg Reflects on the ASM Centennial, Ira Baldwin

What a pleasure and privilege to be a participant in the 100th birthday party of ASM! I am probably not quite the most senior microbiologist present, but will boast of reading the *Journal of Bacteriology* since 1941 and of having been a member since 1947.

Former ASM president Ira Baldwin, who died last August at the age of 103, barely missed spanning parts of three centuries. He offered very much more than longevity in his contributions to microbiology, and to the Society, of which he was one of the founding pioneers. I recall him fondly for his tenure as my dean and vice-president at the University of Wisconsin, 50 years ago, when he nurtured the then-new science of bacterial genetics by endorsing my appointment there in the face of substantial skepticism.

from terrestrial commerce, and we are hard put to recover even enough of its genes to discover experimentally what accounted for its savagery. On the other hand, tuberculosis is one of the most successful pathogens, with an annual recruitment of many millions of newly infected human hosts. But the growth rate of *Mycobacterium tuberculosis* is so slow as to be exasperating to its students in the laboratory. How do we account for these differences?

Perhaps auxotrophy, or growth factor dependence, which is so prevalent among systemic pathogens, sometimes serves as a strategy to mitigate virulence, rendering a particular disease chronic rather than acute. With current facilities for genetic engineering, this hypothesis is testable. Such testing must be undertaken cautiously, for fear of unleashing new ferocities outside the presumed boundaries that establish long-term evolutionary advantages for any parasite being tested.

The customary view about auxotrophy may still be correct, that it is merely enabled by the parasitic habitat. Auxotrophs are not known to gain a significant advantage when grown in rich media, suggesting that a simple economizing of biosynthesis is not what confers tempered virulence. Anyhow feedback inhibition generally down-regulates biosynthetic metabolism when an organism finds itself in a nutrient-rich milieu. Nonetheless, accumulated intermediates might

serve not only as signalling compounds to temper virulence but also as antibiotics.

This germ's-eye perspective could help to address an important issue. After all, the death of the host is not the primary marker of the microbe's fitness. It is an accident of collateral damage. In this context, humans survive because it is not to a pathogen's advantage to eliminate its hosts. Instead, the teleonomic aim of pathogens, the driver of their natural selection, is to domesticate their hosts.

The most successful parasites are the ones that persist in healthy or near-healthy hosts, and promote and exploit their behavior for two principal goals: (i) to ensure continued carriage and viability and (ii) to promote efficient dissemination to other hosts. These propositions have been articulated by others, including Theobald Smith, Frank Burnet, Rene Dubos, and Lewis Thomas.

To a large degree, however, these ideas have not percolated deeply into the thinking of those who set public health policies and develop research strategies for investigating infectious diseases. Those policies tend, instead, to be permeated with Manichean images of the struggle between good and evil, or life and death—against which the appropriate response is to employ sterilizing hygiene or other means of eradication. Bacteriophobia probably delayed the interdisciplinary movements of genetics and molecular biology into microbiological studies.

For instance, the Manichean view probably also is responsible for the egregious delay (1884–1959) in the discovery that cholera is an exocrine-acting disease. Thus, its “toxin” is not intrinsically cytotoxic, but acts very much as a hormone on the host, leading to fluid secretion.

### Giving Microbes the Benefit of the Doubt

The alternative approach of peaceful coexistence with pathogens brings more questions than answers. Attempting to think of these questions with a germ's-eye perspective demands that, in almost every encounter, we ask about the pathogen's role in defining the rules of engagement. As these roles may coincide with the host's long-term interests of surviving and also multiplying, it may be difficult to disentangle which partner is driving the outcome. But, for a change, let's



give the microbes the benefit of the doubt, at least as a preliminary hypothesis and perhaps in defiance of common sense. Even if wrong, this deviant perspective may open new lines of experimentation.

One unusual line is to query how a particular pathogen moderates its virulence, in contrast to the main line of pathogenesis research that focuses on hypervirulence. To be sure, mortality is a convenient measure, and the one that is least problematical to extrapolate to other hosts. However, parasite maintenance and dissemination are more important for fitness, and morbidity is the more prevalent outcome of disease than mortality.

However, this approach requires more effort, as there is a whole array of symptoms of infection—notably fever, malaise, inflammation, diarrhea, cough, and other mucous effusions. The latter are patently fountains of dissemination. Of course, parasites attack or undermine host defenses—at least locally, if not systemically. Hence, an overshoot in local toxicity that, for example, provides *Corynebacterium diphtheriae* a foothold in the throat occasionally may prove lethal to the host.

However, systemic neurotoxins outside the near-saprophytic clostridia are rare among microbial pathogens. As bottom feeders these microbes may well violate the Sixth Commandment, as they profit from the nutrient-rich carcasses raining down on their major habitats. The milder, more successful transgressors content themselves with stealing nutrients from their still-living hosts.

Among disease symptoms, fever has been the most controversial, and may be a mixed bag. Some argue that, if fever did not have an adaptive function, it is unlikely that this energetically expensive phenomenon would have persisted for millions of years in vertebrate hosts. This argument discounts the odds that fever may be adaptive for some parasites. Because bacterial cell wall lipopolysaccharides seem uniformly pyrogenic, fever may well represent an early and generalized host adaptive response to bacterial infection.

Nonetheless, because viruses have such diverse mechanisms of promoting (or defeating)

cytokines, each case has to be examined independently of the next. Indeed, viral pyrogenicity, and other cytokine activations, may favor the long-term survival of the virus by attenuating bacterial superinfections that would otherwise compromise the host.

Such reasoning carries implications for treatment of fever. Recalling the therapeutic use of inoculation malaria in the treatment of syphilis before the wonder drugs, the case for symptomatic treatment of fever (barring febrile seizures in children) is a weak one. On the contrary, warming patients to induce cryogenic reflexes may be a better strategy than is actively cooling them or administering antipyretic drugs.

Is it possible that the interferon reaction which we attribute to the host defense against influenza is also a protection against superinfection by other viruses, competing with the influenza virus either in local habitat or for survival of the host? Other pathogens, including lentiviruses and *Helicobacter pylori*, elaborate antibacterial peptides. Moreover, treating superinfections with antibiotics targeted at sterilizing the gut often leads to dire consequences for patients.

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### Immune System Is a Study in Darwinian Processes

One triumph of modern biologists has been their elucidation of the adaptive immune response as a Darwinian process of diversification and selection among somatic cells. Although these basic principles are reassuringly applicable to the entire vertebrate world, achieving a comprehensive understanding is complicated by the bewildering diversity of cell types, in apparent defiance of Occam's razor.

The complexity embodied in the immune system serves as a reminder that evolution involves tinkering, with frequent remolding of existing widgets or, in many cases, the development of careless redundancy. Nevertheless, host defense strategies are highly diversified, making it hazardous to extrapolate about their details from one species to another. At least the major systemic features of response to infectious disease appear to have become established about 200



million years ago, prior to the emergence of mammals and birds.

Specialists contend that, about 450 million years ago when jawed fish were confronted with massive infections, they developed the adaptive immune system upon which the human system is patterned. Perhaps the fish grew so large that the costs of out-reproducing the parasites became prohibitive. At any rate, the fish contain the origins of our immune system.

Meanwhile the immune system of the birds—more precisely, of chickens—resembles that of mammals in almost every detail. The chicken immune system contains specialized elements, such as the Bursa of Fabricius, although its IG-V sequence potential is more limited than that of mammals. However, those differences do not appear to influence the quality of the eponymous B-cell response (B from Bursa).

Although few other species have been studied, biologists have been quick to generalize from mice to men, disregarding the details of environmental stresses and how they shape the selective milieu in which a species lives. The mouse, with its short life span and large reproductive potential, typically enjoys a more microbe-ridden habitat than does the primate or human. However, in densely populated areas, these habitats may converge, with humans and mice eating from the same granaries.

Because most laboratory studies are done using inbred mouse strains, which tend to be far removed from wild populations both in provenance and in genetic uniformity, we might uncover some surprises by studying the immune systems of wild rodents and other carrion eaters. In general, we can anticipate some surprises if more in the way of natural history of species being studied were imported into the molecular genetics laboratory.

#### **Genetic Mechanisms Moderate Infectious Diseases, Cancers**

Unlike the microbial world, with its system for promiscuously exchanging genetic materials, speciation in multicellular organisms constrains recent innovation to narrow branches of the phyletic tree. Our choice of model organisms for disease study is intrinsically biased to mal-

adapted zoonoses: we favor the models that exhibit fulminating, lethal disease with the inoculation of one or a few propagules, and perhaps by unnatural routes.

These extreme cases may be very poor models for natural disease in the human, with typically moderated morbidity, low case fatality, and prevalent carrier states. Of course, humans face opportunistic infections, with many immunocompromised individuals at risk for a whole range of such diseases. These examples may be expected to break the standard rules, which allow for pathogens to exploit the host's immune system as part of its strategy in mitigating virulence. That same line of paranoid thinking leads us to look for epitope presentation by the microbe as being tuned to preserve the balance in moderated infection—except when it does not do so.

Another distinctive feature of most multicellular organisms is diploidy. Microbial pathogens are usually haploid, but have options that blur this limitation, such as gene amplification and variable copy number of plasmids. Diploidy is customarily explained as allowing for the momentary banking of mutational component advances, against future possibilities of change in environment or genetic background.

To this I add another possible role for diploidy: it may stabilize the somatic genotype, and help ensure that this state remains domesticated in the service of the organism. One apparent corroboration of this notion is the drastic consequences we suffer following heterozygous deletion of so called “tumor suppressor” genes. The haploid state apparently exposes the organism to the risk of cancer from a single mutation in any such gene. The applicability of this idea could be put to the test by comparing parthenogenetic haploid frogs with their autodiploids. Alternatively, haploid plants could be studied as part of a broader effort to understand neoplasia in plants.

#### **Curious Analogy between Cancer and Rogue Virulent Microbes**

In several ways, cancer is analogous to the rogue virulent microbial cell in an otherwise domesti-

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cated swarm of microorganisms in a single infected host. That rogue, like the cancer cell, may dominate the host soma, and bring about the demise of both; unlike cancer the rogue microorganism is transmissible, and in crowded populations may sustain an epidemic even of a lethal infectious disease.

Extrapolating this analogy still further, pathogens—like hosts in relation to cancer—perhaps moderate their mutation rates to reduce the incidence of rogue outbursts. There are other explanations, but one wonders why wild populations of some viruses such as those which cause measles and polio have not developed vaccine-indifferent variations. Or have we simply not looked closely enough for those variants?

Many fungi have an alternative means of moderating their virulence, namely by adopting attenuating mycoviruses. These are double-stranded RNA viruses that behave much like plasmids but disseminate by hyphal fusion. With their help, some strains of *Endothia parasitica* can coexist with their chestnut tree host; while other hypervirulent strains have gone on to near extinction of their hosts and themselves. Lethality as an outcome of infection must be viewed as an imbalance, perhaps arising from collateral factors—atypical weakness or genetic idiosyncrasy on the part of the host, or comorbidity.

In principle, human immunodeficiency virus (HIV) never directly kills its host, but lethality arises from adventitious secondary infections. Thus, HIV can be considered a zoonosis, but one out of balance in the human species in the sense that it induces too much immunosuppression (thus representing an example where the details of phyletic variations in the immune regulatory network prove significant). Perhaps HIV may yet evolve towards reducing that vulnerability, and in fact perhaps even to evoking further resistance to secondary infections.

The very high abundance of human endogenous retroviruses (HERV) in the human genome can be taken as evidence that other retroviruses are pacified. Perhaps they even confer a positive advantage to human fitness. At a minimum the fitness of HERV, like that of any parasite, depends on its capacity to coexist without gravely compromising its hosts.

At any rate, the endpoint of natural selection is, in theory, the domestication of the host, with

long-term chronic habitation and facilitated transmission to other hosts. There will be exceptions to this general rule, including:

- very efficient transmission by vectors, overriding short residence time;
- subacute infection where, e.g., human behavior with respect to sexually transmitted diseases ensures transmission within the envelope of survival; and
- bottom-feeders, like the anaerobic clostridia which can proliferate on dead meat; no wonder these microbes are uniquely imbued with the most lethal systemic neurotoxins.

### Paying Attention to Zoonoses

Many serious emerging infections are zoonotic transfers, including HIV, hantavirus, plague, and tickborne rickettsioses. In many of these cases human infection is incidental to the natural history of the microbe. Probably most interspecies transfers are totally innocuous, hence invisible. Many others will be neutral. We pay close attention to those where the microbe-host balance is disrupted by the change in genomic environment, has not yet reached new equilibrium, and manifests a rule-breaker.

It likely takes as delicate fine-tuning for a microbe to moderate itself as it does to take on the defensive barriers of a new and strange host. New zoonoses are not alien encounters, as the microbe involved usually has a history of successful parasitosis in another species—even if that experience is as distant as transovarian propagation in a tick.

These earthly encounters raise questions for those concerned about interplanetary travel and ensuing exposure to microbes that might be found on other celestial bodies. If Martian microorganisms ever make it here, will they be totally mystified and defeated by terrestrial metabolism, perhaps even before they challenge immune defenses? Or will they have a field day in light of our own total naivete in dealing with their “aggressins”?

It was not a Martian, but a distant kingdom of bacteria, that initiated the ultimate symbionts: the mitochondria that confer oxidative metabolism on all eukaryotic cells. Mitochondria now seem to provide an unalloyed benefit to such cells. But the lives of aerobic eukaryotes are dominated by a never-ending quest for fuel to



stoke those mitochondrial furnaces. And we dare not relax more than minutes in gulping the air needed to maintain the fires, while we endure some of the toxic side effects of oxygen radicals.

### **Each Individual Is a Complex Superorganism**

The mitochondria and the HERVs are reminders that each individual constitutes a complex superorganism—embracing also a huge population of pathogenic and commensal flora decorating every mucosal and epidermal surface. Each of those constituent relationships is complicated. If it would not compromise beneficial symbionts, we might consider ridding ourselves of pathogens. But what of unforeseen consequences that are embedded in the complex evolutionary history between us and pathogens?

Paul Ewald of Amherst College, Amherst, Mass., Kyle Cochrane of the Massachusetts Institute of Technology, Cambridge, and Gregory Cochrane point to several human genetic phenomena that go against the grain of evolutionary doctrine. For example, why does natural selection not seem to work against host genetic factors affecting depression, obesity, substance abuse, and behaviors eventuating in infertility or sexually transmitted diseases? They would therefore attribute these disorders to infectious agents. Before invoking a Darwinian drive in another genome, pleiotropic effects of the host genome need to be ruled out. The relevant genes that give rise to deleterious behaviors might enhance fitness in other contexts—for example,

under conditions of extraordinary trauma and stress.

In any case, to be understood, these and undoubtedly other traits have to be projected back to early human evolutionary history. Our genomes probably have not reached a fully stable equilibrium. But what use is all this philosophy for understanding infectious disease?

At a research level, we need to pay much closer attention to ecological relationships among various microorganisms, whether they are called commensals or pathogens, and their multicellular hosts. A major component of that research effort would be to study how microbes sustain their chronicity, both in their defenses against host immunity and in the moderation of their own virulence. In an immediately practical vein, interbacterial interference, more commonly known as probiotic therapy, could be a fount of prophylactic practice and of antibiotic discovery. Yet, its study is largely neglected.

At a more general health policy level, several widely embraced public health goals need to be carefully reexamined, including: (i) the wisdom of eradicating specific diseases such as smallpox, polio, or measles, absent measures to ensure the sustained maintenance of some level of immunity in the herd, and (ii) an insistence on hygiene approaching sterility, which may undermine benefits that come from sustained stimulation of the immune system. Humans also face a risk if they make themselves hothouse flowers, a risk like others associated with our technology-dependent civilization—but none with graver implications for human durability.