# Parasites Face a Perpetual Dilemma

## The relationships between pathogens and hosts must become delicate balances of adaptation if both parties are to survive

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Parasites always face a dilemma—slow or fast proliferation. If they proliferate rapidly, they risk killing the host. That would be a winning strategy if transmission to a new host is easy, if the vectors are there ready at hand, if the host engages in obliging behavior, or, for instance, if there are mosquitoes around for high-density spread. *Plasmodium falciparum* in northwest Thailand would not likely survive because of its high mortality and morbidity if it were not for the high density of its vectors for spread to new hosts. In nosocomial situations, instead of mosquitoes, health care attendants risk transferring infectious agents from one patient to another in the course of their life-saving ministrations, unless they adhere to the most rigorous hygienic discipline.

Although microorganisms produce many potent toxins, they do not appear to have spread all that widely among other microbial species. Botulinum toxin, one of the deadliest compounds known, is produced in abundance by *Clostridium botulinum*. It probably did not spread to other microorganisms because it is too hot to handle. If it gets into a different microorganism lacking the other properties of the *Clostridium* species, it is more likely to kill the host of that other microorganism more rapidly—meaning a dead end for those transfers.

Thus, there may be specific physiological circumstances in which the usual rules of natural selection do not apply. Consider *Escherichia coli* O157, which is more like a *Shigella* species with a cloak of *E. coli* antigens. The gene for this toxin can inhabit other microbial vectors. This verotoxin is as severe as shiga toxin, and the ecological implications of its appearance in *E. coli* are not clear. In its bovine host it does not seem to be so toxic, and its attack rate is only about 1% in humans. Thus, of individuals infected with *E. coli* O157, only about 1% develop severe disease. In any case, it is doing well enough in its bovine and human hosts that its overall survival does not seem in doubt.

### Slow Proliferation, the Other Side of the Dilemma

If a parasite proliferates slowly, it faces problems from the host immune system, which monitors deviance in the form of new epitope receptors. For most acute infections, the host develops a full-blown immune response within a week or 10 days. Thus, a microorganism that proliferates slowly is vulnerable to that response unless it can deploy additional tactics.

Phase variation is one such tactic, whereby a microorganism can slide from one epitope representation to another. In the case of malaria, the pathogen evades host immunity by means of stealth tactics. Antigenic mimicry, which enables the host to survive its own immune system, can also cover for antigens present on a microbial host.

Parasites also have to compete with commensal microorganisms, which are probiotic. HIV runs into severe trouble by interfering with this system. By itself, HIV would not kill its host. However, by undermining the immune system, it opens the door for other microorganisms, including commensals, which leads to opportunistic infections that ordinarily do not damage the host.

Following this thinking a little further, the infections that occur in the vectors of disease are rarely symptomatic, almost never severely symptomatic. In the case of malaria, the plasmodium does not kill the mosquitoes that transmit it to new hosts. The behavioral anomaly of the

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rabid dog illustrates another pattern of behavior in infected vectors. It serves the purposes of the parasite more effectively.

### Symptoms May Serve Both Hosts and Microorganisms

Very little in biology makes sense absent evolutionary insight. This applies to symptoms perforce. And the issue is not merely abstract, it can also prove practical. For instance, to what extent should we be treating symptoms? Some are life-threatening and must be treated. Others are discomfiting, but treatment may get in the way of a cure.

What about fever? When it is not life-threatening, is it a useful host defense or a means for augmenting a bacterial attack? Put another way, does a bacterium or virus produce pyrogens to promote its own replication? Or is infection-induced fever what Steve Gould calls a spandrel—a side effect of other evolutionary adaptations that have not come to equilibrium?

There is no unequivocal answer to these questions about fever, despite how systematically it is treated. Its impact on a patient's recovery from a febrile illness suggest this subject deserves more attention than it has received.

More generally, when we do not know the impact of a particular physiological response on an infectious disease, perhaps we should address the question of its importance in an evolutionary sense. How did it come to be there? Efforts to answer such questions may open new avenues of thought in examining disease processes. Other symptoms, such as cough, diarrhea, and hemorrhage, may serve the purposes of particular parasites as well as their hosts.

Certainly hemorrhage must be treated, but perhaps a mild cough may be left untreated because it helps to eliminate some of the infectious load. Of course, the aerosol that accompanies a cough also promotes dissemination of the pathogen to other hosts. Thus, cough perhaps should be treated as a public health measure rather than as a therapeutic measure for a given individual. Diarrhea is another symptom that sometimes benefits the pathogen as well as the host. It helps to eliminate the parasite. However, the large volumes of fluid that cholera induces seem a special adaptation to enhance the dissemination of this parasite.

Other symptoms of infectious disease, such as malaise, headache, other pain, and itching, have different implications. Without pain receptors, individuals easily injure themselves. Thus, pain plays an indispensable role, even in infectious disease. Of course, there is no reason not to treat it. Yet, with the exception of chronic long-term leprosy, which induces anesthesia, no other infectious disease seems capable of blunting the sense of pain, let alone inducing a sense of euphoria. Imagine such pathogens, whose hosts would welcome them and infect themselves with them.

Perhaps scratching sometimes increases circulation in a given area. Certainly it can help to spread an infection, suggesting that the irritation of an itch can benefit the parasite and may be another adaptation in disease physiology.

### Death of the Host Rarely Benefits a Parasite

The death of the host is almost never to the advantage of the parasite. Whenever that happens there is a breakdown in the contract that could have had a better outcome for both sides.

Analyzing zoonotic interactions provides insights into other evolutionary relationships. When zoonoses break away from their ordinary hosts, they may have a very severe impact on their new hosts. The hantavirus is an outstanding recent example. The virus does not appear to cause any significant pathology to its rodent carriers—certainly nothing that compares with what happens in its human host.

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Most zoonotic transfers simply do not work, or work so poorly that we pay no attention to them. Many zoonotic transfers are neutral, such as when ferrets are infected with the influenza virus. However, we tend to focus when a zoonotic transfer has enormous pathologic implications for the host. For instance, the filiviruses seem to belong in this latter category. Although HIV seems to fit the category, the simian immunodeficiency viruses, which are far less virulent for their natural hosts than HIV is in humans, do not.

One accommodation—maternal immunity—

between host and parasite is not genetic but physiological. The outbreak of canine distemper among lions of the Serengeti provides an example. The population of 4,000 lions a decade ago is reduced to 3,000, which have some immunity that can be communicated by mothers to their cubs. At first, the variant of canine distemper devastated the lions, but it will eventually stabilize further as newer cubs accommodate the pathogen more fully against the background of maternal immunity. Meanwhile, these quasi-hereditary cycles do not involve genes as such, but depend on the propagation of maternal immunity, partial immunity on the part of the offspring, and more easy adaptation to infection by the host.

### Contemplating Interplanetary Zoonoses

Perhaps the most extreme, albeit hypothetical concerns over zoonoses switching hosts revolve around planetary quarantine discussions that began with the Sputnik launch in the late 1950s. When the space program moved toward interplanetary travel, concerns focused on samples from Mars contaminating Earth, although the possibility of the converse is perhaps greater because we are sure that Earth harbors proliferating organisms. Expert committees, including several convened by the National Academy of Sciences, developed an international convention for conserving the microbial integrity of celestial bodies, which includes sterilization protocols for spacecraft. Whether a microorganism from Mars exists and could attack us is more conjectural. If so, it might be a zoonosis to beat all others.

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On the one hand, how could microbes from Mars be pathogenic for hosts on Earth when so many subtle adaptations are needed for any new organisms to come into a host and cause disease? Dozens if not hundreds of bacterial genes need to work in concert to enable a microorganism to be a pathogen. On the other hand, microorganisms make little besides proteins and carbohydrates, and the human or other mammalian immune systems typically respond to peptides or carbohydrates produced by invading pathogens.

Thus, although the hypothetical parasite from Mars is not adapted to live in a host from Earth, our immune systems are not equipped to cope with totally alien parasites: a conceptual impasse.

### Mitochondria, Other Examples of Ultimate Symbionts

The ultimate symbionts—and perhaps the ultimate attenuated pathogens—are the mitochondria. This one-time bacterial invader from probably 2.5 billion years ago entered progenitor eukaryotic cells to introduce the oxidative machinery that enables such cells to use other substrates with high efficiency. Who serves whom? Mitochondria require a huge amount of raw material to be active at peak efficiency. Or, in metaphorical terms, we work hard to shovel coal into the mitochondrial furnaces that are found in every cell of the body.

Symbiosis is not always so mutually accommodating. For example, bacterial plasmids confer valuable functions, such as drug resistance, on the bacteria that they inhabit. But many plasmids also encode a toxin with a longer lifespan than the also encoded antitoxin. Any bacterium contemplating divorce that drops such a plasmid faces the effects of the long-lasting toxin. Thus, only those cells in the population that continue to carry the plasmid are free to proliferate. Again, who serves whom in these kinds of complicated relationships?

Carl Woese of the University of Illinois, Champaign-Urbana, has been instrumental in revising our picture of how organisms are related based on the criterion of 16S RNA sequence variations. In terms of fundamental housekeeping machinery, however, multicellular organisms are far less divergent than are the microorganisms. That is not to say that there have not been extraordinary evolutionary changes going on within the multicellular branch, but they have to do with growing brains and eyes and branches and flowers—not cellular physiology.

Despite this general understanding of how species are related, we lack clues about some very germane questions. For instance, where do viruses come from? Although suspected of originating from some kind of cellular organelle, the evolutionary provenance of eukaryotic viruses is unknown.

Exploring this question will be complicated. For instance, surely in prokaryotic systems and probably also among eukaryotic systems, viral genomes can integrate into host chromosomes with ease. Among the prokaryotes, this integration involves double-stranded DNA viruses, which have the same fundamental structure as the bacterial chromosome. They can be integrated, mobilized, and live as viruses or as bacterial genes, making it impossible to say which came first. Even if a cluster of genes in a bacterium suggested an emerging virus, it might instead be the relic of a very old virus reemerging. On this important issue, our fundamental knowledge is very primitive.

### Prions Make an Unusual Case for Agents of Infectious Disease

Recently, prions have emerged as a new model for agents of infectious disease, and there is a great deal that we do not understand about them. Stanley Prusiner of the University of California, San Francisco, and his collaborators have persuaded some very important people that the prions are pure proteins.

Trying to understand how a pure protein can propagate itself offers some major challenges to our fundamental understanding of how biological information is transmitted. Prusiner and others suggest that the prion protein is a conformational modification of a normal protein coded for by an endogenous gene, a part of the normal genome. That protein arises from a gene that is not an essential gene. For instance, mice in which that gene is knocked out show some functional disorders but survive.

However, according to Prusiner's model, no sequence information is imparted to the normal prion to convert it to the infective agent. Instead, there is merely a change in its conformation. This model represents a totally new paradigm for infectious disease, and its implications are far-reaching.

One implication is that other natural forces that could cause the prion to convert from normal to infectious, and from benign to disease-causing. Proteins adopt new conformations under physical and chemical stress, denaturation, and renaturation. Maltreatment of normal prion protein might then generate infectious protein de novo—what we would recognize as "spontaneous" Creutzfeldt Jacob disease. The rendering of sheep offal used for cattle feed might have made it more infectious in triggering the mad cow disease in Britain. These are merely speculations, but the prion paradigm is so radical that its implications need careful review—and experimental tests now hindered by the cumbersomeness of assays for infectivity.

### Emerging Infectious Diseases: Policy Considerations

What are we going to do about new, mutant, and recombinant strains? Can we anticipate major new outbreaks? How should we be defending ourselves? Fortunately, help is available in the form of one marvelous innovation after another in many fields, including prophylaxis, vaccine development, and understanding pathogenic phenomena. The genomics work on bacteria is having wonderful payoffs and may justify the human genome project all by itself with its insights into microbial evolution and potential targets for vaccines and antibiotics.

At a strategic level, we have the basic technical knowledge to control foodborne epidemics, waterborne epidemics, and even sexually transmitted diseases. However, technical knowledge is not well developed for preventing airborne transmission of infectious agents. Often, something as elementary as a face mask represents our best available technology. We need to design both the means and the doctrine by which even a vicious airborne, aerosol epidemic of influenza virus could be slowed enough to allow other resources to come into play. Tens or even hundreds of millions of lives might be at stake.