Who Speaks for the Microbes?

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In discussing emerging infectious diseases, the focus is often on the clinical effects of the host-parasite relationship, i.e., the impact on the health and survival of humans and animals, rather than the examination of the biology of the pathogen. It seems fitting to take a moment to reflect on how pathogens "got that way in the first place." Thus, while we discuss emerging infections, it is worthwhile to consider that from the beginning of recorded history—in books or the pictographs of ancient cultures—infectious diseases have been the leading cause of illness and death. Even today, because of infectious diseases most of the world's population does not have the luxury of living long enough to succumb to the chronic diseases of aging.

What were and what remain the reasons that infectious diseases are still the leading cause of death? I believe there are four answers. 1) The presence of human populations was and is large enough to sustain and amplify parasites. We have lived in communities large enough to perpetuate parasites for only about 10,000 years, barely a blink of the eye in the time frame of evolution, which means that most of the well-known infectious diseases adapted to humans are very recent in the evolutionary sense. The black death of the 14th century, just 700 years ago, led to the death of approximately one quarter to one third of the human population of what was then the Western world. We may never understand the full implications of the plague outbreaks of the Middle Ages. The resistance of some caucasian populations to the recent scourge of HIV actually may reflect the genetic consequences of plague survival 20 generations ago. 2) Poverty, with its crowding, unsanitary conditions, and often malnutrition, has led to an increased susceptibility to infection and disease. 3) War, famine, civil unrest, and, indeed, epidemic disease have led to a breakdown in public infrastructure and the increased incidence of infectious diseases. 4) The domestication of animals, beginning about 12,000 years ago, was another important factor. The actual large-scale domestication of animals has slowed and has been replaced by the encroachment of human populations into the domain of animal species all over the globe. It is little wonder that our deliberate destruction of predators and the outgrowth of human populations into virgin land with its attendant destruction of habitat led to the emergence of new diseases such as Lyme disease and murine typhus (spread now by opossums and cat fleas in our slums, instead of by the more classic rat and rat flea vector—"sic transit gloria mundi").

The Enemy Is Us

The cartoon character Pogo, invented by Walt Kelly, once announced to his companions that "the enemy is us." I believe that many of what we refer to as emerging diseases are characterized better as "diseases of human progress." Thus, many major public health crises of the past 2 decades have been infectious in origin. Many, like the outbreaks of Lyme disease and murine typhus, are a natural consequence of human meddling. Similarly, the appearance of infections, like Legionnaires' disease, can be traced to more subtle differences in human behavior and social conventions that have an effect on the microbial world. Thus, the aerosolization of water, now so prominent in the Western world from the widespread use of showers instead of baths to the spraying of produce in large markets to air conditioning, likely has played an important role in the emergence of Legionnaires' disease and also of *Mycobacterium avium* infection in both healthy and immunocompromised persons.

Legionella pneumophila, the Legionnaires' bacillus, is found in nature as an infectious agent of predatory protozoa. Introduction of this organism, often as part of an aerosol of potable water into the alveolus of the lung, results in the microorganism's finding a new niche in the macrophage instead of in its usual host *Acanthamoeba* or *Hartmanella.* More absorbent tampons helped select for a new disease, toxic shock syndrome.

While pathogenic traits of the disease-causing microbes are of consequence, humans and their technology and social behavior have played a major role in providing pathogenic microbes with new venues for their wares. Food poisoning by *Escherichia coli* O157, *Campylobacter*, and *Salmonella* emerged more from food technology and food distribution networks than from any fundamental change in the virulence properties of the bacteria. In a sense, we have provided these bacteria with a moveable feast.

What Is a Pathogen, Anyway?

Medicine views pathogens as microorganisms capable of causing disease. The emphasis is on disease, not the microorganism. However, from the microbial standpoint, being pathogenic is a strategy for survival and simply one more remarkable example of the extraordinary diversity of the microbial world. Humans are a home to a myriad of other living creatures. From mouth to anus, from head to toes, every millimeter of our cells exposed to the outside world is inhabited by a rich biology. From the mites that may inhabit the eyebrows to the seething cauldron of more than 600 species of bacteria that inhabit the large bowel, we are a veritable garden of microorganisms. Most of these microorganisms are not only innocuous but play a useful, yet unseen, role in our lives. They protect against the few harmful microorganisms that we encounter each day; they provide vitamins and nutrients and help digest food. We have harbored them so long in our evolution that they are even a necessary part of the developmental pathways required for the maturation of intestinal mucosa and the immune system.

Most microbes are commensal; that is, they "eat from the same table." Others are either commensal or transient microbes that are opportunistic; they can cause disease if one (or more) usual defense mechanism, evolved to restrict microorganisms from normally sterile inner organs and tissue, is breached by accident, by intent (as in surgery and, increasingly, in gunshot wounds), or by an underlying metabolic or even infectious disorder. Nevertheless, a small group of microorganisms often causes infection and overt disease in seemingly healthy persons.

Many of the microorganisms, for example, the typhoid bacillus, gonococcus, tubercle bacillus, and treponema of syphilis, are adapted exclusively to humans; others, for example, *Salmonella* Typhimurium, can regularly cause disease in humans, animals, birds, and reptiles. The distinct difference between commensal, opportunistic, and pathogenic microbes is that pathogenic microbes have evolved the genetic ability to breach cellular and anatomic barriers that ordinarily restrict other microorganisms. Thus, pathogens can inherently cause damage to cells to forcefully gain access to a new, unique niche that provides them with less competition from other microorganisms, as well as with a ready new source of nutrients.

For microorganisms that inhabit mammals as an essential component of their survival tactic, success can be measured by their capacity to multiply sufficiently to be maintained or be transmitted to a new susceptible host. This is true for commensal and pathogenic organisms alike. However, if the pathogen gains a new niche free of competition and rich in nutrients, it also faces a more hostile environment designed by evolution to restrict microbial entry and, indeed, to destroy any intruders that enter these protected regions. Thus, pathogens have not only acquired the capacity to breach cellular barriers but also, by necessity, have learned to circumvent, exploit, and subvert our normal cellular mechanisms for their own selfish need to multiply at our expense.

How Did Pathogens Get That Way?

Recent advances in bacterial genetics, molecular biology, and microbial genomics have led to a better understanding of the evolution of bacterial pathogenicity. In genera that have both pathogenic and nonpathogenic organisms, the nonpathogenic bacteria frequently possess one (or more) large genetic insert that contains genes exclusively associated with the pathogenic phenotype. Indeed, in gram-negative enteric bacteria, pathogenic traits are commonly found as large inserts of DNA in the chromosome, as are plasmids dedicated to the pathogenicity of the host microbe. Certain qualities of these DNA inserts suggest that they were acquired by horizontal gene transfer from one microbe to another and that the ultimate origin of these virulence genes was a microbe very different from the organism in which these genes now reside. These "pathogenicity islands" have been the subject of a number of recent articles. However, the evolution of pathogenicity is not the product of a slow, plodding process as much as it is the product of a large single genetic event that had a profound influence on the biology of the microorganism. Thus, the divergence of *Salmonella* from an ancestor that also gave rise to *E. coli* resulted when the organism received a large pathogenicity island that encoded a contact-dependent secretory system, which gave the host bacterium the ability to cross epithelial barriers. Later on in evolution, some *Salmonellae* received another pathogenicity island that provided the host bacterium with the ability to survive within phagocytic macrophages; finally, other *Salmonellae* that infect only warm-blooded animals eventually inherited a plasmid that appears to permit systemic spread and, perhaps, some degree of host animal preference. These genetic events occurred over millions of years of evolution and were undoubtedly rare, perhaps occurring only once in evolution.

The success of these genetic changes also depended on subsequent selective pressures and genetic fine-tuning by mutation and other genetic mechanisms. Nevertheless, the molecular fossil record in the DNA of contemporary pathogens leads to the inevitable conclusion that microbial evolution is still dynamic and that these periodic genetic upheavals in microbes affecting their pathogenicity can occur at any time. To underestimate the evolutionary potential of microorganisms and their ability to survive, even in the face of enormous pressures to eradicate them and their effects on humankind, would be a mistake.

Infectious agents will emerge so long as there are microorganisms. Humans help the evolutionary process sometimes unwittingly and sometimes by arrogance or ignorance. Antibiotic resistance on a global scale in what seems such a short time comes as no surprise. Does feeding animals antibiotics to promote growth have any effect on human microbes and the health of the human population as a whole?

Rachel Carson's book Silent Spring, which documents the devastating effects of insecticides (e.g., DDT) on the health of a number of living creatures far removed from the insects that were the target, was easily understood. Yet, application of a selective pressure on the microbes of the planet with antibiotics, a pressure that dwarfs the use of DDT in its scope, as well in the number of species that are affected, still remains a subject of debate after 50 years. Is it because we could see the effects of DDT in the pictures of fragile eagle eggs but not in the unseen microscopic world? As Pasteur said, the microbe will endure. Perhaps the fate of the last human is to be consumed by its own microorganisms.

Suggested Bibliography

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