Pathogens and parasites: insights from evolutionary biology

GREGORY G. DIMIJIAN, MD • The University of Texas Southwestern Medical Center at Dallas

The metaphor of a host-parasite arms race spawns a fertile new approach to understanding the myriad interactions between host and colonist—interactions that constitute the epidemiology and natural history of infectious and parasitic diseases. Sexual reproduction in eukaryotes and prolific “parasexual” gene exchange among bacteria and viruses fuel the arms race by generating genetic diversity, the common currency of effective defense and competition. Emerging and reemerging infectious and parasitic diseases serve as urgent reminders that we are irreversibly altering our global environment. Antibiotic resistance signals our achievement in domesticating microbes that can outwit us. Historical epidemics of infectious diseases add an important dimension to the understanding of our current challenge.

The term parasite comes from para (Greek for alongside) and sitos (Greek for grain, food); parasitos was a guest who came to eat but didn't bring food.

The term pathogen comes from pathos (Greek for suffering) and gen (Greek for genesis, birth). Pathogen usually refers to viruses, bacteria, or fungi that cause disease in host organisms. Unicellular eukaryotic parasites such as pathogenic amoebae are often called either pathogens or parasites.

In this review parasite will signify any organism that lives on or in another, larger host organism, deriving most or all of its nourishment from the host. It often harms the host, without providing services in return (as with a mutualist). Commensal organisms, which derive benefit from the host but cause little or no harm, are included in the meaning of the term. Parasites may alternate between harmful and harmless roles in the same host, and the roles played are often incompletely known. Parasite is thus a general term covering colonists from viruses to helminths, which usually harm the host.

PREVALENCE OF PARASITISM

It has been said that there are 4 “habitats” for organisms on Earth: terrestrial, marine, freshwater, and another organism.

If every multicellular organism we know harbors 1 species of parasite, and often >1 species, and if parasites themselves have parasites, then the sobering possibility exists that there are more parasitic than nonparasitic species of organisms on Earth.

Bacteria, archaea, and fungi have their own viral pathogens, and the closer we look, the
more examples we find of viruses parasitic upon other viruses. The hepatitis delta agent, for example, needs the hepatitis B virus for packaging its nucleic acid in protein. Hepatitis delta virus is thus parasitic upon the host cell and hepatitis B virus (1).

Biology students are taught that organisms occupy ecological niches. It is often forgotten that a host organism may constitute the niche, perhaps more often than not. There may even be a succession of host species at different stages in a parasite's life cycle. Parasites are sometimes useful in deriving the phylogenetic history of their hosts. Ancestors of present-day parasites may have been parasitic on ancestors of their current hosts, and coevolved specializations provide clues to shared ancestry. A new biological “law” has been whimsically proposed: it's easier to steal something than to get it honestly.

**AN EVOLUTIONARY PERSPECTIVE**

Red Queen hypothesis

The *Red Queen hypothesis* is about the host-parasite arms race. It may be the single most powerful paradigm for understanding infectious and parasitic diseases. The hypothesis states that genetic diversity is paramount in staying one step ahead, whether you're a parasite or host (2). For eukaryotes, this means reproducing sexually. With sexual reproduction, genes are reshuffled in every generation. However well adapted a species may be, it must run like the Red Queen just to keep up with its parasites, which are running too, but with a different strategy—short generation times and horizontal gene exchange.

“No, here, you see, it takes all the running you can do to keep in the same place,” the Red Queen said to Alice, in *Through the Looking Glass* by Lewis Carroll.

In the arms race between parasites and their hosts, and between different parasites competing with each other, the fastest way to run is to have lots of different lottery tickets, in the form of different genotypes. Only in this way can a parasite keep its enemy guessing. The great struggle is more with other organisms than with the abiotic environment.

Support for the Red Queen hypothesis is abundant. First, parasites usually attack the most common host phenotype, and organisms with both sexual and asexual phases in their life cycle tend to revert to sexuality when faced with high parasite exposure. Most of our crop plants are genetically uniform because of bottlenecks imposed on them during domestication. A devastating epidemic of southern corn leaf blight ravaged farms throughout North America in 1970, causing the biggest economic losses ever recorded for a single crop in a single year; nothing seemed able to stop the fungus until wild varieties of maize were crossed with cultivated corn, which created varieties resistant to this blight.

Second, genotypic diversity provides survival benefits for a host. An excellent example is the resistance to human immunodeficiency virus 1 (HIV-1) infection that occurs in whites who are homozygous for a mutant allele of the CCR-5 chemokine receptor gene. These individuals, perhaps 1 in 100 whites in the USA, are uniquely resistant to HIV infection by virtue of having a defective receptor. In addition, a mutation in a gene coding for a
chemokine molecule (not a receptor) has been shown to alter the course of HIV infection, with striking increases in longevity if the individual is homozygous for the mutation (3).

Third, the remarkable polymorphism of the major histocompatibility complex (MHC) appears to be generated and maintained by pathogens and parasites. Genes of the MHC code for proteins that deliver peptide fragments of pathogens from the interior of the cell to the cell surface for recognition by T lymphocytes, which may then initiate apoptosis, thus destroying the cell before it replicates a virus. Genes for MHC proteins are among the most polymorphic, and some have >50 alleles. Allelic diversity of this magnitude must be actively maintained by selection or only a few alleles would survive. The MHC has a second unusual feature: instead of the few nucleotide substitutions separating most alleles of a gene, MHC alleles often differ by 100 substitutions. Such variability in 2 dimensions implies strong selection pressure, as might be expected from pathogens and parasites which keep changing their weaponry. There is strong support for the argument that infectious and parasitic diseases are the driving forces for MHC polymorphism.

There is evidence that some mammals select mates on the basis of differences at MHC loci—the greater the differences, the more diverse their progeny would be at these same loci. Smell seems to guide rodents in the choice of a partner differing at MHC loci. There is suggestive evidence in humans of such selective mating, with unconscious guidance by the olfactory sense (a chemistry between partners?).

If sexual reproduction is limited to eukaryotes, how do prokaryotes and viruses achieve genetic diversity?

**Genetic diversity in bacteria**

Despite asexual reproduction, bacteria achieve rapid genetic diversity through horizontal plasmid transfer from one bacterium to another and through insertion of genes by bacteriophages (bacterial viruses, or phages). Such transfers may instantly confer new properties on the bacterium, such as antibiotic resistance or virulence.

Sometimes *Vibrio cholerae*, for example, turns virulent, and a mild initial infection becomes a deadly disease. The gene for cholera toxin is carried by a bacteriophage that infects *V. cholerae* with accessory genes that help it spread through the bacterial population (4). Similarly, the recent deadly epidemic of food poisoning by *E. coli 0157:H7* may have resulted from phage inoculation: the almost identical sequence of toxin genes in *E. coli 0157:H7* with those of *Shigella dysenteriae* type 1 suggests that *E. coli* acquired the genes from *Shigella* by horizontal transfer via bacteriophages.

There are 2 strategies by which phages achieve replication. In one strategy, the synthesis of proteins and DNA is redirected from bacterial cell to viral particle, killing the bacterial host and releasing new viral progeny.

With the second strategy, determined by a genetic switch in the phage, the phage DNA is integrated into the bacterial chromosome without harming the host. The bacteria continue to
thrive and multiply, and the virus lives with its host cell, but no virus particles are synthesized. The host may acquire new properties from the phage DNA, such as antibiotic resistance or virulence factors. In such cases, phage infection may be useful to bacteria. After a period of time, in response to signals such as a toxic agent that harms the host bacterium, the phage excises itself from the host chromosome and “bails out,” replicating itself and lysing the host.

As with other infectious agents, phages show host specificity. The phage that kills the Shiga bacillus, for example, does not infect staphylococci.

Bacteriophage lambda is a lysogenic virus of *E. coli*, which can choose either the integrated or the lytic pathway described above. In the recently sequenced *E. coli* genome, many phage genes were found, including the entire integrated genome of bacteriophage lambda. This provides concrete evidence of a fluid bacterial genome that takes in and embraces foreign genes, some of which may confer either virulence or antibiotic resistance.

Phages have been found that have lost some genes essential for their replication but that were nevertheless incorporated into bacterial cell genomes. Does this provide “spare parts” for related phages integrated in the same genome? The bacterial genome is a mercurial zoo of interacting genes, both domestic and foreign (5). Or perhaps we get it wrong: if “foreign” genes eventually become “domestic,” our categories may be too hard and fast.

As a defense against harmful phages, bacteria have evolved restriction enzymes—weapons that disarm viral DNA by chopping the genome of an invading virus to bits before it can take over the bacterial replicative machinery. Restriction enzymes have been purified from hundreds of bacterial species. Each enzyme cuts DNA at a specific run of 4 to 8 base pairs. We use the enzymes as scissors in the laboratory; the molecular biologist Robert Pollack calls them “plowshares beaten from the swords of an invisible war between bacteria and their viruses” (6).

Microsatellite repeats constitute another defense of bacteria. These highly variable segments of the bacterial genome undergo slipped-strand mispairing, in which the newly forming DNA strand slips with regard to its template strand, scrambling downstream sequences and producing highly variable new genes. These code for changed proteins that may confer new resistant properties on the pathogen.

*E. coli* has still another trick up its sleeve. Increased mutation rates have been found in populations of *E. coli* that are subjected to new environmental conditions. It seems that the bacteria can accelerate their adaptation to stress or new environments by temporarily increasing their mutation rates. This has been called “directed mutation” and “adaptive evolution” (7).

**Genetic diversity in viruses**

RNA viruses lack proofreading enzymes for correcting the transcription of their RNA into DNA. As a result they have a high rate of point mutations, producing “antigenic drift.”
Consider HIV. In a human host the virus replicates 24 hours a day from day 1. It causes the host to manufacture the enzyme reverse transcriptase, which transcribes viral RNA into DNA for insertion into the host nucleus. The relatively low fidelity of reverse transcriptase, coupled with a lack of proofreading enzymes, enables the development of virtually limitless genetic variation, just like sexual reproduction does for eukaryotes. An asymptomatic host can harbor 106 genetically distinct variants of HIV, and an AIDS patient may host more than 108, among which drug-resistant mutants are likely to occur.

Ten billion virions are produced daily in established HIV infection. If each contains, on average, 1 mutation in the 9.2-kilobase HIV genome, a replication-competent virus with every possible single drug-resistance mutation is likely to be generated daily.

High virus load in a host triggers an immune response that inhibits the dominant strain, allowing other strains to multiply within the host. These are the very Darwinian dynamics that we see in antibiotic resistance, when we administer antibiotics and knock out a susceptible strain of a pathogen, enabling takeover by resistant strains.

**Recombinant viral genomes**

As if this variability is not enough, different globally circulating strains of HIV-1 can apparently hybridize, forming new mosaic strains even at the onset of infection. HIV, like all retroviruses, is diploid. Each virion contains 2 RNA strands. If a cell is infected simultaneously with 2 strains of a retrovirus, 1 RNA strand from each strain can be encapsulated into a single “heterozygous” virion. When this virion subsequently infects a new cell, the reverse transcriptase may jump back and forth between the 2 RNA templates and cause “crossing over,” as occurs in meiosis in eukaryotes when gametes are formed. All subsequent progeny of the virus will be of this recombinant genotype, created by “vertical” gene exchange (from parent to progeny). It may be an important retroviral evolutionary strategy and could be considered a form of primitive sexual reproduction.

Several other families of viruses, including influenza viruses, have segmented genomes that enable reassortment of segments during the course of coinfection with 2 different strains of a virus. Novel recombinant strains result, just as with retroviruses. Influenza viruses have 8 RNA molecules called segments. If 2 different strains infect 1 host, progeny virus particles may be formed with segments from different parent strains. This genetic reassortment occurs in pigs, which become infected by both human and avian strains. Pigs seem to be “mixing vessels” where genetic exchange occurs between avian and human strains. The new strains then move into human populations. Pigs also seem to be mixing vessels for Japanese encephalitis virus strains, which colonize wild birds and humans. *Culex* mosquitoes willingly provide transmission services among avian and mammalian hosts.

Because fresh manure from pigs and ducks is used around the world as fertilizer for fish ponds, there is concern that fish farming (aquaculture) might spread new influenza virus strains to fish and humans. In the worst of practices, Thailand has a pig-hen-fish culture in which hens are in cages above the pigs, which consume the hen feces, and the pig pens are directly above fish ponds into which the pigs defecate.
Fortunately not all viruses are highly changeable. Poliovirus, for example, retains a highly conserved structure even though it is subject to the same error rate as influenza viruses. Nucleotides occupying the first 2 positions in each codon scarcely change at all; any mutations here must be strongly eliminated by natural selection. As a result a relatively small quasispecies cloud is created. In contrast, in the immunodeficiency viruses, about 70% of all 3 codon positions are variable, resulting in a very large quasispecies cloud.

**Antibiotic resistance**

Thirty years ago, a triumphant surgeon general of the USA, celebrating the antibiotic revolution, informed the nation that the book of infectious diseases was closed. In the decades since, antibiotic resistance has become one of the most urgent challenges in medicine. Like pesticide resistance, it is a prime example of human selection (domestication). Acting as agents of selection, we kill off susceptible bacterial strains, leaving resistant strains to take over.

Administration of antibiotics to humans and other animals is only one way we set the stage for antibiotic resistance. Half of the volume of antibiotics produced annually in the USA is used to treat farm animals (8). Antibiotic-resistant enteric bacteria are found in food when they survive the production processes. If we consume such food without thorough cooking, we may become ill with an infection that is not only resistant to antibiotics but possibly worsened by treatment that kills off other bacteria.

Another way occurs when hospitals discard antibiotics in the trash. The antibiotics often end up in landfills, where they eventually enter groundwater and streams. Microorganisms in the environment are exposed to them.

Emergence of multidrug resistance has been found in *Yersinia pestis* from Madagascar. The responsible genes are on a plasmid that appears to have come from intestinal enterobacteria. How can interspecies plasmid transfer occur? If *Y. pestis* organisms mix with enteric bacteria in a blood-borne infection, or in the gut of a flea that ingested blood infected with both microorganisms, plasmids may conceivably cross species boundaries (9).

Vancomycin-resistant enterococci are a frightening example of antibiotic resistance. Long-term treatment with vancomycin, especially when administered prophylactically, has contributed not only to the development of resistance, but also to bizarre new strains of bacteria, vancomycin-dependent enterococci. Continued administration of the antibiotic has brought about selection for strains that not only tolerate it but actually need it. In such cases withdrawal of the antibiotic may reverse the infection!

In our quest for solutions, we may begin to turn to antimicrobial strategies used by other organisms. A striking example has just been found in leafcutter ants (10), which are among the few organisms in nature that cultivate their own food. Fungus gardens maintained by the ants enable the breakdown of cellulose in the leaves harvested. The fungus is vulnerable to attack by a parasitic fungus of a different genus, and the ants carry around a bacterium of the genus *Streptomyces*, which produces antibiotics targeted to suppress the parasitic
fungus. Perhaps it is not coincidental that many of our antibiotics have been derived from this same bacterial family. The tripartite mutualism appears to be highly evolved and of ancient origin, perhaps tens of millions of years old. In the probable arms race between pathogen and host, how do the ants keep their antimicrobial defense current?

**Natural selection and the medical disease model**

How can big, lumbering eukaryotic hosts hope to keep up in the arms race with much simpler, tiny pathogens that reproduce in vast numbers in no time, with virtually unlimited variation? Eukaryotes are not only slow to reproduce; they are also much more complex than microbes, and uncorrected errors in replication are more likely to be harmful to their highly integrated organ systems. The best current answer is this: sexual reproduction succeeds in generating the requisite diversity, albeit moving at a snail's pace in comparison to microbial generation times.

Inbreeding, however, can deplete the genotypic diversity of a sexually reproducing species. That crisis is faced by many wild species today. Cheetahs are so inbred that allografts are not rejected. They are at risk of having too little diversity to escape a critical epizootic infectious disease. Feline immunodeficiency virus is the counterpart of HIV, causing the immune system of cats to collapse. If it ever spreads through a population of cheetahs, they may all be wiped out. The same dilemma is faced by crop plants, which have been inbred to a dangerous level of genetic uniformity.

The outcome of natural selection is a change in allele frequencies. We talk of “strategies” for want of a better term. There is no teleology, purpose, or design in the natural selection model. Richard Dawkins has compared natural selection to a blind watchmaker (11). The analogy is good if by “blind” we mean not only sightless but also completely unknowing of the outcome of his choices. Natural selection can create complex structures one step at a time, provided that each step confers a survival or reproductive benefit on the genes that work together to make up the organism. An allele with even a slight advantage can enjoy greater future representation over time.

No one has captured the historical importance of the discovery of natural selection more poignantly than Helena Cronin (12):

An awesome gulf divides the pre-Darwinian world from ours. Awesome is not too strong a word to describe the achievements of Charles Darwin and Alfred Russel Wallace. The theory of natural selection revolutionized our existence where previously science had stood silent.

Medicine has been slow to incorporate evolutionary theory in the study and teaching of disease etiology. One of the resulting shortcomings in our medical disease model is host-centrism. If we adopt a colonist-centric view instead, we begin to think differently about the dynamics of the arms race and how to approach disease. The colonist is doing what any other organism is doing: finding a means of surviving and replicating its genes in the face of ever-present competition. Any genes that compete successfully will be around to try again.
A colonist-centered view changes our interpretation of virulence. The virulence hypothesis states there is a positive relationship (coupling) between a pathogen's virulence and its ease of transmission between hosts, maintained by natural selection. This important hypothesis, championed by Paul Ewald, professor of biology at Amherst College, will be explored in greater depth in a future review. The final level of virulence is likely to be found in the trade-off between within-host competition (with other colonists) and ease of transmission, possibly resulting in host illness and death.

If host death can be avoided, a pathogen may achieve spread to other hosts over a longer period of time. Herpes simplex virus type 1 can multiply and spread without causing lesions or symptoms, in effect hiding its own tracks, temporarily becoming a commensal organism, until it causes host illness again. The virus is so successful that virtually 100% of human adults have antibodies to it.

Is host disease a clumsy blunder on the part of a pathogen or parasite? Or is it an artifact of the parasite's “imperative” to reproduce rapidly enough to outcompete other parasites? Is there a trend over evolutionary time for virulence to decrease? These unanswered questions are among the most pressing issues in host-parasite studies today.

**HIV/SIV phylogeny**

In early 1999, an important link between human and simian immunodeficiency viruses was made. The link provided an instructive example of a pathogen getting a foothold in a new host species when the door is opened wide (13).

The 4 subspecies of chimpanzees, which live in discrete regions of tropical rain forest from the west coast of Africa to the shores of Lake Tanganyika in Tanzania, are healthy carriers of different strains of SIVcpz (simian immunodeficiency virus chimpanzee), a retrovirus related to human immunodeficiency viruses. Researchers identified similarities in nucleotide sequences in HIV-1 and the SIVcpz strains, carried by only 1 of the 4 chimpanzee subspecies, *Pan troglodytes troglodytes*. This subspecies lives in several countries bordering the coast of equatorial West Africa, where human HIV-1 infections have been recorded for the longest time. Its natural range coincides uniquely with areas of HIV-1 endemcity.

This important finding identifies *Pan troglodytes troglodytes* as the primary reservoir of the SIVcpz lineage that crossed the “species barrier” to humans and evolved into HIV-1. All strains of HIV-1 known to infect humans are closely related to only this one SIVcpz lineage. At some point in the early 20th century, this SIV lineage was given the opportunity to make the crossing and to become established in humans. It may have made many crossings before becoming established; in fact, the HIV phylogenetic tree suggests that at least 3 different crossings were made, resulting in the current HIV-1 viruses infecting humans around the world (Figure 1).

Why did these successful transspecies crossings occur when they did? To our knowledge, chimps and hominids have coexisted in equatorial Africa for hundreds of thousands of
years. The reason for these crossings may be the same as that for Ebola infection. Until humans invaded the rain forest in large numbers, moving in and out with unprecedented global mobility, viruses apparently crossed species with only limited consequences, soon to be forgotten. Earlier in the century, small-scale epidemics of devastating illnesses apparently occurred with some regularity in anyone's lifetime in tropical African rain forests, but they disappeared as mysteriously as they had come. Field workers from the Centers for Disease Control and Prevention (CDC) reached these conclusions while studying the history of Ebola-like outbreaks prior to the 1976 Ebola epidemic in Zaire (now the Democratic Republic of Congo) and southern Sudan.

There are 2 major types of HIV, HIV-1 and HIV-2. Each has many subtypes. The RNA sequences of the 2 viruses are very different, with an average similarity of only 60%. HIV-2 produces the same clinical AIDS syndrome as HIV-1, but onset of disease is later and viral load is lower (14, 15). The efficiency of heterosexual transmission of HIV-1 is up to 5 times greater than that of HIV-2; this may be one reason why there is no HIV-2 pandemic. HIV-2 is the predominant virus in West African countries and has spread very little to other areas of the world.

HIV-2 appears to have crossed to humans from sooty mangabey monkeys in West Africa. These monkeys, like chimpanzees, have been hunted for food, and they are also kept as pets. A strain of SIVsm (simian immunodeficiency virus sooty mangabey) closely related to HIV-2 has been found in sooty mangabeys whose natural habitat coincides with the epicenter of the HIV-2 epidemic today.

The ability of simian viruses to jump host species provides a model for human pathogens in general, all of which have ultimately evolved from preexisting pathogens or commensals of other species.

CONTEMPORARY issues in INFECTIOUS AND PARASITIC DISEASES

The principal killers today

Three parasites stand out today as causing the greatest human mortality. One is a bacterium, one a protozoan, and one a virus.

*Mycobacterium tuberculosis* infects almost one third of the world's population (at least 1.7 billion of the world's 5.9 billion people) and causes 3 million deaths annually.

Malaria parasites (*Plasmodium spp.*) cause at least 3 million human deaths every year. Many surely go unreported, especially deaths of rural children in developing countries.

HIV-1 causes over 3 million deaths annually and is spreading at an accelerating rate throughout Africa and Asia. In 1998, about 6 million seroconversions were reported, and some 35 million people were infected. Two thirds of all new cases of AIDS occur in sub-Saharan Africa, where the World Health Organization reports 5500 funerals every day for people who have died of AIDS. Several African countries may achieve zero population
growth early in the 21st century.

Five million people are infected with both HIV-1 and tuberculosis, three quarters of whom live in Africa (16).

**Diarrheal diseases and their spread**

Diarrheal diseases cause >3 million deaths annually—>8000 per day. The most lethal players in these diseases appear to be *Campylobacter jejuni, Vibrio cholerae, Shigella dysenteriae, Salmonella typhi, E. coli 0157:H7*, and rotavirus.

Over half of the chickens and turkeys examined in grocery stores in the USA in 1997 were contaminated with *Campylobacter jejuni*, and some 20% of the strains were resistant to fluoroquinolone antibiotics. These very antibiotics are given to chickens in their drinking water to prevent *E. coli* infection! The Food and Drug Administration's approval in 1995 of a fluoroquinolone for use in poultry drinking water has provided an opportunity for resistance to develop to all antibiotics of that class, which includes ciprofloxacin.

Rotavirus infection is the most important cause of severe childhood diarrhea worldwide, killing an estimated 870,000 children each year. In the USA it is the single most important cause of hospitalization for childhood diarrhea, mainly in children from 6 months to 2 years of age. By 4 years of age most children have been infected and are immune to the severe dehydrating syndrome (17). Rotavirus multiplies in the gut with such efficiency that its genome dominates the RNA content of stool. A child with rotavirus diarrhea may excrete 1 trillion infectious particles per mL of stool; as only 10 particles constitute an infective dose, person-to-person transmission perpetuates endemic disease. Human wastes are more menacing than nuclear wastes, as feces kill far more people than do radioactive substances.

Small round-structured viruses, also called SRSVs or Norwalk-like viruses, may be the major cause of viral gastroenteritis among adults worldwide (18). Outbreaks due to contaminated water systems and wells have been reported, as well as person-to-person spread, as in restaurant epidemics and consumption of infected oysters. Aerosolized vomitus has been proposed as a mode of transmission.

For the Third World, water can be a deadly drink. In slums near Bombay, India, water pipes are cracked and run in ditches filled with sewage. The biggest slum in the world may be Dharavi, a vast shantytown in Bombay, where hundreds of thousands of people live in hovels connected by tiny meandering alleys. Sewage runs in the paths along with the rats. Water purification in modern cities may be one of the most significant public health advances of all time (*Figure 2*).

On a river just outside Phnom Penh, Cambodia, is one of the most wretched slums in the world, a putrid slope of mud and excrement that is home to tens of thousands of people packed in rickety shacks on the bank of the river. There are latrines of a sort, open toilets behind half-barrels. Fish are bred in fenced-in waters below the toilet platforms.
Cholera bacteria are found in inland coastal areas and estuaries and thrive in seawater as well. *Vibrio cholerae* is autochthonous in brackish estuarine ecosystems, meaning that it survives there on its own, forming a dormant, spore-like stage that can withstand unfavorable environmental conditions. It often colonizes copepods. A single copepod can carry 104 cells of cholera bacteria, and in untreated water several copepods may be ingested in a glass of water. The history of cholera reveals a strong association with the sea; the great pandemics have followed coastlines around the world.

For example, in 1991 a freighter from South Asia emptied its bilges off the coast of Peru. Along with the wastewater came a strain of cholera that reproduced well in the unusually warm coastal waters with abundant pollution. The bacterium made its way into shellfish and humans, and spread in an epidemic killing at least 5000 people. The unchlorinated water supply in Peru's cities carried the cholera strain and delivered it right into people's houses, dripping from their water faucets.

Rita Colwell, director of the National Science Foundation, found that the El Tor strain of cholera is equipped to survive inside algae for long periods, becoming dormant and greatly reduced in size. It is revived by moving it into the laboratory, elevating the temperature, decreasing the salinity, and adding nitrogen, transforming it into an active pathogen. A hallmark of the El Tor strain is its ability to move in the open oceans as a silent passenger aboard marine algae. With plankton blooms in spring and fall, bacterial numbers increase exponentially along with the algal cells. Colwell showed rural Indians how to strain their drinking water through sari cloth, removing the copepods that serve as vectors of cholera bacteria (19).

Colwell also discovered a stew of viruses, plasmids, transposons, and bacteria at sewage sites in the Chesapeake Bay, all undergoing rampant genetic exchange and ingested by mollusks, which humans consider delicacies.

In the USA, some surprising water supply disasters have occurred. In 1993, some 400,000 residents of Milwaukee became ill with cryptosporidiosis, and the city's AIDS population faced a mortal threat as a result. The contamination resulted from a low water level and chlorine-resistant *Cryptosporidium parvum* (a protozoan) that got through the filtration system. Also in 1993, some 35,000 residents of New York City had to switch to boiled water when *E. coli* 0157:H7 made its way into the water supply, surviving chlorination and a faulty filtration system.

In 1997, 25 million pounds of US beef were recalled because of contamination with *E. coli* 0157:H7, and the huge company of Hudson Foods closed its doors.

Alfalfa sprouts are a new source of concern because of the ease with which seeds are contaminated with *Salmonella* and other bacteria. A common-source outbreak in Oregon and British Columbia in 1995 was traced to *Salmonella enterica* (Newport) contamination, resulting in a protracted international epidemic spread over many months. Alfalfa sprouts are a well-suited vehicle for salmonellosis, as the seeds are stored for months or years under cool, dry conditions in which the bacteria are stable. During the 3- to 5-day sprouting
process, *Salmonella* populations may increase by 3 or 4 orders of magnitude, decreasing little or none during subsequent refrigeration. From farm to table, many opportunities exist for contamination of seed or sprouts. Crops can be contaminated by dirty water, runoff, and excreta of rodents or ruminants. *Salmonella* organisms may reside in seed crevices and between cotyledon and testa even after chemical treatment. Irradiation is an untested treatment that may prove more effective (20).

Listeriosis is a food-borne infection that can be dangerous in pregnancy and in AIDS patients. The causative bacterium, *Listeria monocytogenes*, is found in soil and healthy animal carriers and can contaminate meats, cheeses, and manure-fertilized vegetables. Of nearly 2000 people infected yearly in the USA, some 400 to 500 die.

Protozoa which cause gastroenteritis include *Giardia lamblia* (giardiasis), *Entamoeba histolytica* (amebiasis), *Toxoplasma gondii* (toxoplasmosis), *Cryptosporidium parvum* (cryptosporidiosis), and *Cyclospora cayetanensis* (cyclosporiasis). A 1996 epidemic of *Cyclospora cayetanensis*, a spore-forming protozoan first reported in 1986, involved 1465 cases in 20 states and stemmed from contaminated Guatemalan raspberries (21).

*Toxoplasma gondii*, a parasite prevalent in wild and domestic animals worldwide, is transmitted through the food chain by carnivorous feeding and scavenging. Wild and domestic cats constitute a major host reservoir. An estimated 15% to 85% of adult humans are chronically infected with the protozoan and are typically asymptomatic. In stark contrast, toxoplasmosis is often fatal in AIDS patients. Strains of differing virulence exist around the world. A water-borne urban epidemic of *T. gondii* gastroenteritis occurred recently in Canada.

**Macroparasites (helminths and ectoparasites)**

Helminths, unique among parasites in not multiplying within the host, cause more morbidity than mortality. They include tapeworms (flatworms) and nematodes (roundworms). Tapeworms may grow to 30 feet in length, filling the entire intestine of a vertebrate host. Whale tapeworms may be 100 feet long!

Hookworms (nematodes) are so common that they inhabit the small intestine of 20% of the entire human population! With their sharp teeth, they bite into the intestinal wall and live off of ingested blood. Each individual worm ingests a small amount of blood each day, but when 100 or 1000 worms cohabit a single small intestine, they enjoy about a cup of blood daily. For a child the consequences can be severe malnutrition and mental retardation. Children born where intestinal helminths are endemic can expect to harbor worms for most of their life, owing to repeated exposure and limited immunity. An individual worm may live almost as long as its host!

Not all helminths are intestinal. *Trichinella*, which causes trichinosis (trichinellosis), is a nematode that takes up residence in skeletal muscle and is acquired by ingesting undercooked meat from almost any mammal, including swine, fox, wolf, deer, rat, dog, cat, cougar, lion, leopard, jackal, and hyena. *Schistosoma* is a trematode flatworm that causes
schistosomiasis (bilharzia), taking up residence in the veins of gut and liver and releasing thousands of eggs daily that form cysts in liver, brain, and lung.

The importance of ectoparasites can hardly be overestimated. Fleas carry plague, lice transmit typhus, ticks spread Lyme disease and Rickettsial diseases, and mites cause scabies in humans and sarcoptic mange in dogs. Chiggers are the larval stages of tiny mites.

The human body louse can build up in epidemic proportions in no time—10,000 on a man's shirt. Head lice were so common in the Middle Ages that heads were shaved and wig collections were popular; the lice simply moved to the wigs.

The crab louse, which dwells in the groin, can survive for short periods off the host, so some people worry about toilet seats. A poem found on a bathroom wall (22) reads:

Don't bother to hover,
or stand on the seat;
the crabs in this place
can jump 30 feet!

Human ectoparasites are usually arthropods—either insects (lice, fleas, bed bugs) or arachnids (ticks, mites, chiggers). The leech, an annelid, is an exception. Arthropod ectoparasites of mammals are all bloodsucking, but avian feather mites feed on the feathers themselves. One parrot harbors 15 species of feather mites, each living on a particular part of a particular feather on the bird's body.

Hans Zinsser (23) reminds us of the narrowness of our host-centric views. He writes (paraphrased):

If lice can dread, the nightmare of their lives is the fear of some day inhabiting an infected rat or human being. To the louse, we are the dreaded emissaries of death. He leads a relatively harmless life…then, out of the blue, an epidemic occurs; his host sickens, and the only world he has ever known becomes pestilential and deadly. His host may survive, but the ill-fated louse is doomed. In 8 days he sickens, in 10 days he is in extremis, and on the 12th he gives up his little ghost.

HISTORICAL PERSPECTIVES

A new ecology for microorganisms

Prior to food production, human pathogens could survive only if they had a reservoir in other animals or if they could maintain themselves in scattered human groups by means of a carrier state (like typhoid bacilli), latency (like herpesviruses), or delayed onset of illness (like HIV).

Beginning about 10,000 years ago, in different places and at different times, agriculture and animal breeding by early humans brought about radically changed ecologies for microbes
capable of crossing the “species barrier.” Even the earliest examples of food production permitted the support of 10 to 100 times the human population densities that had relied on hunting and gathering. The growth of settlements into large communities and complex societies was accompanied by crowding, garbage accumulation, and sewage. Some farming communities spread their own feces as fertilizer.

The growth of settlements provided a red carpet for the evolution of pathogens causing crowd diseases with respiratory, enteric, or vector-borne spread. Agents like the measles and poliomyelitis viruses could now be maintained in a population, instead of dying out in a smaller community where they would kill or immunize most of the population.

Europeans and Asians have lived intimately with dogs, pigs, cows, goats, horses, and chickens for thousands of years. The pathogens and parasites of these animals have had daily access to human hosts and have been free to evolve into strains that could better exploit their new “habitat.”

The most virulent malaria parasite for humans, *Plasmodium falciparum*, seems to fit this picture. A study of ribosomal RNA sequences of avian, rodent, and human *Plasmodium spp.* suggests that falciparum malaria is a recent infection of humans, acquired laterally from an avian source coincident with the onset of an agriculture-based lifestyle. Consistent with this interpretation is the finding that if the level of transmission drops below a critical point (as in small human populations), *P. falciparum* malaria is slowly and irrevocably eliminated (24).

Stored food in early human communities guaranteed that rats and mice would live alongside us, as they have ever since. As vectors of disease, they occupy our dwellings and accompany us to sea on ships. These rodents are so adaptable that they are almost impossible to eliminate.

Bubonic plague was spread through Eurasia in the 14th century by rats and their fleas.

**The great dying or Black Death**

In 1346, Europe, northern Africa, and the nearer parts of the Middle East had a total population of about 100 million people. In the course of the next few years, one fourth of them died from the plague. The disease put an end to the population rise of medieval society. Within 4 years, Europe alone lost 20 million people. The epidemic may have spread to Europe in flea-infested furs from plague-ridden Central Asia.

The time from onset of symptoms to death was usually 5 days. The name *bubonic plague* derives from the large, painful swellings (buboes) in lymph nodes of axilla, neck, or groin. Three days after the appearance of buboes, victims were overwhelmed by high fever and became delirious. The buboes grew until they burst and were so painful that they were said to arouse the moribund to a state of frenzy. Pneumonic plague, spread by respiratory droplets, was more rapidly fatal. Some victims went to bed well and died before morning, and doctors who became infected at the bedside died the same day.
Bubonic plague and pneumonic plague spread through crowded cities like a raging fire without a firebreak, consuming whole cities. The bubonic form moved relentlessly from one building to the next by means of rats and fleas; the pneumonic form raced from person to person in closed quarters by means of respiratory droplets.

An account from Messina, Italy, described the arrival and initial progress of the disease:

At the beginning of October, in the year of the incarnation of the Son of God 1347, twelve Genoese galleys…entered the harbor of Messina. In their bones they bore so virulent a disease that anyone who only spoke to them was seized by a mortal illness and in no manner could evade death. The infection spread to everyone who had any contact with the diseased….Soon the corpses were lying forsaken in the houses. No ecclesiastic, no son, no father and no relation dared to enter, but they hired servants with high wages to bury the dead. The houses of the deceased remained open with all their valuables, gold and jewels….When the catastrophe had reached its climax the Messinians resolved to emigrate. One portion of them settled in the vineyards and fields, but a larger portion sought refuge in the town of Catania. The disease clung to the fugitives and accompanied them everywhere where they turned in search of help (25).

Another account reads:

In many places in Siena [Italy] great pits were dug and piled deep with the multitude of dead. And they died by the hundreds, both day and night, and all were thrown in those ditches and covered with earth. And as soon as those ditches were filled, more were dug. I, Agnolo di Tura…buried my five children with my own hands….And so many died that all believed it was the end of the world (25).

Boccaccio wrote in the *Decameron*, “One man shunned another . . . kinsfolk held aloof, brother was forsaken by brother . . . and scarcely to be believed, fathers and mothers were found to abandon their own children to their fate, untended, unvisited as if they had been strangers” (26).

People burned all manner of incense: juniper, laurel, pine, beech, lemon leaves, rosemary, camphor, and sulphur. There was no end to the talismans, charms, and spells that could be purchased from the local wise woman or apothecary. The cure of sound was another superstition. Towns rang church bells to drive the plague away. Some towns fired cannons, which made a comfortably loud din.

In 1348, the pope sought the opinions of the medical faculty in Paris. The good professors opined that the disaster was caused by a particularly unfortunate conjunction of Saturn, Jupiter, and Mars in the sign of Aquarius that had occurred in 1345. This conjunction caused hot, moist conditions, which caused the earth to exhale poisonous vapors. (This blame on “vapors” is reminiscent of beliefs about malaria, which was named for “bad air” in English and “marsh” in French and Spanish [*paludisme*, French, and *paludismo*, Spanish, both from the Latin *palus*, for marsh]).
The physicians' report went on to recommend the following:

No poultry should be eaten, no waterfowl, no pig, no old beef, altogether no fat meat. . . . It is injurious to sleep during the daytime. . . . Fish should not be eaten, too much exercise may be injurious . . . and nothing should be cooked in rainwater. Olive oil with food is deadly. . . . Bathing is dangerous. . . (25).

From Italy came this advice, from the pens of educated men:

In the first instance, no man should think of death. . . . Nothing should distress him, but all his thoughts should be directed to pleasing, agreeable and delicious things. . . . Beautiful landscapes, fine gardens should be visited, particularly when aromatic plants are flowering. . . . Listening to beautiful, melodious songs is wholesome (25).

If the plague was a manifestation of divine anger, then Christians should do all they could to assuage that anger. From this reasoning was born the flagellants, bands of fanatics who wandered through towns and countryside doing public acts of penance, inflicting all sorts of punishments upon themselves. Many others also viewed the pandemic as God's punishment to sinners, but when priests were not spared, the grip of the Catholic Church was weakened, and the door to Protestantism opened wider.

As ever in Europe, when a crisis arose, the Jews were targets of blame. They were accused of bringing on the plague by poisoning the water and practicing witchcraft, and they suffered the outrage of angry mobs over a wide geographic area.

With all of these opinions and superstitions about the cause of the plague, there is no mention of rodents, the animal reservoir of the plague, or of fleas, the vector which carries the plague to other mammals, including humans.

The art of the later Middle Ages poignantly depicted the devastating effects of the plague. Paintings and graveyard sculptures showed skeletons performing a danse macabre in the midst of the living, along with decomposing bodies, half flesh and half bone.

By 1350 the plague had largely passed out of western Europe. In the space of 2 years, 1 out of every 3 people had died. The Black Death marked a dividing line between the central Middle Ages, with medieval culture in full bloom and at its greatest strength, and the later Middle Ages, with cultural decline and chronically reduced populations.

Plague struck again in subsequent centuries. Between 1600 and 1650 the population of Italy fell from 13.1 million to 11.4 million because of the plague. In Venice an average of 600 bodies were collected daily on barges.

During the plague of London in 1664 to 1665, many draconian measures were introduced out of ignorance and desperation. The lord mayor of London contributed to the spread of the disease by ordering the extermination of all cats and dogs in the city. Rat populations expanded as a result! People were locked into their homes if a family member died of the
plague in the house. City watchmen patrolled the street to prevent occupants from escaping. Inside, many perished of thirst or starvation rather than the plague.

Plague is still with us. It is widespread among small mammal populations in the Rocky Mountains. Occasionally, a rat or squirrel in Dallas dies of plague. Old abandoned cabins with rats and their fleas are dangerous places. When a human acquires plague, the disease may progress very quickly. Once in a while, a hunter or student staying in an old cabin gets plague and all too often dies of it. Two young people died in 1996 from rapidly progressing septicemia and respiratory distress syndrome before the diagnosis was made. Both had been exposed to fleas from infected prairie dog colonies, one in Arizona, the other in Colorado (27). In 1997, a Madagascar strain of *Yersinia pestis* was found to carry a plasmid conferring multidrug resistance, possibly acquired from enteric bacteria.

**Spread of diseases by water**

William McNeill, in *Plagues and Peoples* (28), argues that diseases were historically spread more easily by sea than by land. Movement by sea could attain an average of >100 miles per day, and shipboard travel could carry an infection across thousands of miles of water. Coastal cities of the Mediterranean came to constitute a single disease pool.

There was the ever-present terror of a disease outbreak at sea. A sailor in good health might fall ill at sea and serve as a source of infection to all on board. The peculiar affinity of *Aedes aegypti* mosquitoes for water casks meant that mosquitoes could remain on shipboard for months at a time. It might seem to the frightened crew that yellow fever appeared out of nowhere in the middle of the ocean. Because of its high lethality, few survived with immunity. A voyage lasting for months could be haunted by an unending chain of fatal cases of yellow fever, and no one knew who would be next. In comparison, during overland travel, persons falling ill could be left behind without the terrible decision of whether to throw them overboard alive.

From the 16th to the 18th centuries, one of the most devastating diseases on long sea voyages was scurvy, a lethal disease caused by vitamin C deficiency. To its victims it was as mysterious as yellow fever, coming from out of the blue, inviting superstitions and any spurious “explanations” one could contrive. Few physicians today would recognize the symptoms of scurvy—swollen and bleeding gums with loosened teeth, spontaneous hemorrhages in any part of the body, slow wound healing, and anemia, which progressed to death. Scurvy wasn't attributed to dietary deficiency until 1753, when the Scottish naval surgeon James Lind showed that it could be both cured and prevented by drinking the juice of oranges, lemons, or limes.

The power of 2 diseases, one infectious and contagious, the other nutritional and noncontagious, to confuse, terrify, and kill reminds us of a different age when medical knowledge was far in the future.

Even when microbes had been discovered in the late 19th century, enlightenment was still far away. Physicians found it hard to accept the role of germs in disease since they were so
ubiquitous. Germs were all over the body of healthy as well as sick people, so how could one incriminate them in illness? Furthermore, the growth of unusual bacteria in secretions of the sick could just as well be the consequence, rather than the cause, of the illness. In a thoughtful book, Nancy Tomes chronicles the golden age of bacteriology in the late 19th and early 20th centuries, when the germ theory of disease captivated the lay public and provoked inappropriate measures to avoid the new invisible enemies (29).

War and conquest

Hans Zinsser reminds us that the effects of a succession of epidemics upon a state are not measurable in mortality alone. More wars in history may have been won or lost by disease epidemics than by weapons or the skill of military leaders. As armies dispersed and soldiers returned to their home towns, they “lighted fuses of infection that flickered along through villages and cities wherever chance sparks lighted on inflammable material” (23).

Perhaps 95% of the Aztec, Maya, and Inca civilizations were casualties of diseases introduced to the Western Hemisphere after 1492—smallpox, measles, influenza, plague, yellow fever, typhus, mumps, and tuberculosis. These diseases were weapons of conquest, spreading from tribe to tribe far in advance of the Spaniards, who came upon ghost settlements abandoned after most inhabitants had died and others had fled in terror of the disease.

One military outcome of disease was the defeat of Napoleon's army in 1812. Napoleon's forces numbered >600,000, compared to Russia's 250,000. The French made excellent progress en route to Moscow until typhus broke out. This was a new epidemic for the French army. As the troops advanced, the epidemic spread. By the start of the first battle, 80,000 soldiers were dead or disabled. By comparison, the Russians had some degree of immunity and fewer became ill.

The French finally began a retreat when the weather turned cold, later in the winter than they had intended. They had <100,000 men remaining without protection from the cold. Soldiers took the clothes off of their fallen comrades and put them on, increasing the probability that they would infect themselves with typhus-carrying lice. By the time Napoleon's army returned home, only 3000 of the original 600,000 had survived, and most of those were sick with typhus.

World War I was another victory for typhus, which at first raged unchecked, killing 150,000 in 6 months. The International Red Cross interrupted the spread with a massive delousing campaign, using over a million pounds of insecticide.

In World War II, in contrast, one of the few wars in history in which infectious diseases claimed fewer lives than weapons did, DDT was sprayed liberally by the US military.

“Spanish flu”

The “Spanish flu” pandemic of 1918 found its way to every nation on the planet. Within 16
months it had killed >20 million people worldwide, more lives than were lost in all the battles of World War I, which raged at the same time. In fact, the 600 miles of trenches in France and Belgium occupied by crowded troops may have contributed to the establishment of the extremely virulent strain of the flu among the soldiers.

The pandemic swept through North America and Europe and as far as the Alaskan wilderness and the remotest islands of the Pacific. Most deaths occurred among young adults, a group that usually has a low death rate from influenza. Lungs of acutely ill victims filled with fluid, as if they had drowned. Pathologists described samples of lung tissue that sank like a rock in water, instead of floating, as normal lung tissue does.

The Spanish flu produced the most striking single demographic event of the century, depressing the average US life expectancy in 1918 from 52 to 39 years (Figure 3).

The viral strain disappeared with the end of the epidemic. Since then, there have been many attempts to recover traces of it from exhumed bodies of victims. From a body disinterred in Brevig Mission, Alaska, and in tissue samples preserved from soldiers in World War I, fragments of the 1918 strain have been isolated. The latest attempt was in a remote cemetery on an island above the Arctic Circle north of Norway, where the permafrost is perennial.

The pathologist who acquired the tissue samples from Alaska has instructed his family to move to their remote mountain cabin in the event of another flu pandemic, which he feels is sure to occur. His recommendation is not without precedent. In 1918, a village not far from Brevig Mission stationed armed guards at the village perimeter with orders to shoot anyone who tried to enter. The village escaped the pandemic unscathed.

Four less severe influenza pandemics occurred in the following years: 1900; 1957 (“Asian flu”); 1968 (“Hong Kong flu”); and 1977 (“Russian flu”). Many influenza experts feel we are overdue for the next severe pandemic.

Flu viruses are pantropic, causing illness across species in humans, horses, pigs, seals, and birds. Southern China is an influenza epicenter where new strains of influenza viruses originate in a large population of pigs, people, and ducks. Genetic reassortment occurs among strains, with pigs serving as intermediate hosts or “mixing vessels.” Although most influenza pandemics have originated in China, other parts of the world may contribute to genetic reassortment in flu viruses. An epidemic of flu in Mexican chickens in 1993 and 1994 raised concerns about global spread, and human flu strains have been found in pigs bred in Italy (30).

Birds, especially ducks and other waterfowl, constitute a vast, mobile reservoir of flu viruses that replicate in their intestines and are excreted in their droppings. Lakes and streams along migration routes may periodically teem with flu viruses. In 1997, a virulent strain of influenza virus jumped directly from birds to humans for the first time. With 18 proven human cases, many severe or fatal, the danger of novel influenza viruses became frighteningly apparent (31).
Why are pigs in China the “mixing vessels” for new subtypes of influenza A viruses every year? Is it because they are raised in close proximity to wild and domestic birds? No one knows. But the CDC has funded nearly a dozen flu labs in China in hopes of guessing correctly which subtypes to use for the flu vaccine each year.

Influenza is not an eradicable disease, because many subtypes exist in the aquatic bird reservoir, and the virus is a master at mutating and reassorting gene segments annually. Strains to which humans have no immunity appear suddenly.

**Smallpox**

Over the span of human history, the smallpox virus may have killed more people than any other pathogen or parasite. Three hundred million deaths in the 20th century are attributed to smallpox, 3 times more deaths than occurred from all the wars of the century and considerably more deaths than caused by AIDS. Smallpox changed the outcome of wars throughout history, from the Spanish invasion of North America to multiple wars in Europe over many centuries.

Smallpox was eradicated in 1977 through global vaccination programs organized by the World Health Organization, under the leadership of Donald Henderson. Just the year before, in 1976, the worldwide number of cases had approached 10 million. In October 1997, we celebrated the 20th anniversary of the last naturally occurring case of smallpox.

Two features of smallpox made eradication possible. Its only host is humans, so it was not inaccessible within a wildlife reservoir. Also, the virus is not maintained in the human population by healthy carriers or chronically ill patients. Unfortunately, the virus is still alive and well in biological warfare arsenals of an unknown number of nations.

Some of the earliest historical records of vaccination describe experiments with material from smallpox lesions. Although Edward Jenner is credited by many sources as being the first to vaccinate against smallpox, there were earlier attempts in China and elsewhere to protect against smallpox by using exudate from cowpox lesions, apparently by ad 1000 or even earlier. Chinese records describe the use of cotton plugs impregnated with cowpox material inserted in the nose.

Jenner's achievement is nevertheless noteworthy. In 1796 he carried out an experiment on an 8-year-old boy, making 2 cuts in the boy's arm and working into them a small amount of serum from a cowpox lesion. The boy developed a mild fever and soon recovered. Six weeks later, Jenner repeated the inoculation, using exudate from lesions of a smallpox victim; the boy remained healthy. Vaccination was named after the cowpox virus, *Vaccinia*. It would be three quarters of a century before Pasteur would clarify the biology of immunization, using vaccines for anthrax and rabies.

The monkeypox virus, a “first cousin” of the smallpox virus, causes symptoms nearly identical to smallpox. A 1997 outbreak of monkeypox in the Democratic Republic of Congo (formerly Zaire) is an omen that smallpox may be back in a new guise. Monkeypox, which
may be an emerging infectious disease, may be more dangerous than smallpox, because it has a reservoir in wild animals: monkeys, squirrels, and rats. The 1997 civil war in the Democratic Republic of Congo may have contributed to the crossing of the species barrier, as the war resulted in starvation, which led to increased hunting of animals that carry the virus (32).

**EMERGING AND REEMERGING INFECTIOUS AND PARASITIC DISEASES**

Humans have carved paths into remote wilderness areas throughout history, but today's invasion of tropical forests is different (Figure 4). Immunologically naive human immune systems are being exposed to new viruses, bacteria, and eukaryotic parasites, unlike earlier explorers who had grown up in geographically proximate areas and possessed a measure of immunity to parasites of other animals. Unlimited global travel is bringing people from far away to lands they have never visited before and taking them far away again, in an instant of time, easily within the incubation period of infectious diseases.

The same danger is faced by wild animals raised in captivity and then returned to the wild. With no prior exposure to the pathogens and parasites in the wilderness to which they are “returned,” their immune systems are naive and unable to cope with endemic diseases. Zoos are now attempting to raise captive animals in preserves close to the wilderness into which they will be released, in hopes that the animals will develop natural immunity to endemic pathogens during the period of captivity.

There is evidence that HIV has infected small numbers of people in remote regions of central Africa at least since the 1960s or 1970s, and that it has remained confined. In major African cities it has become epidemic. Along the Congo River, the CDC found a clear pattern of HIV dispersal radiating from river inns, where prostitution was a regular business. The incidence of disease became higher with proximity to the city of Kinshasa. The CDC concluded that an urban center is a kind of ecosystem that can amplify infectious diseases.

Hantaviruses apparently do little harm to their usual hosts, which include many different rodent species around the world. When we inhale dust containing dried rodent excreta, we risk becoming ill with hantavirus pulmonary syndrome or hemorrhagic fever with renal syndrome. Airborne transmission between human hosts may be emerging, as suggested by apparent person-to-person spread in 1996 in Argentina.

Legionnaire's disease, which struck in August 1977, remained a complete mystery for 5 months. All attempts by the CDC to isolate a bacterial, viral, fungal, or parasitic organism failed. Finally, a CDC researcher incubated, in chicken egg yolk, some frozen lung tissue from a cadaver, then injected it into hamsters instead of mice. The hamsters developed the same symptoms as the patients with Legionnaire's. Patients who had recovered from the disease had antibodies that reacted positively with the yolk sac isolates. A bacterium was finally isolated. Since then, *Legionella* has been found in aerosol-generating systems around the world, including cooling towers, air conditioning systems, respiratory therapy equipment, whirlpool baths, even water pipes. Recently it was found in an ultrasonic mist machine in a grocery store. The bacterium has probably been in the environment for a long
time and has only recently been recognized.

Plague is, in a sense, a reemerging disease around the world. The last plague pandemic began in Hong Kong in 1894 and spread throughout the world, establishing many endemic foci. In 1994 it reappeared in epidemic form in India, Malawi, and Mozambique. It is increasing in developed countries as well, and newly evolved genes conferring resistance to multiple antibiotics have been found to be carried by a plasmid (9).

Emerging diseases may come from a breakdown in geographic isolation between 2 species (Figure 5). The epidemic of morbillivirus that killed one third of Serengeti lions in 1994 is believed to have spread from domestic dogs from local villages.

The changing ecology of murine typhus in southern California and Texas over the past 30 years demonstrates the effects of suburban expansion. In suburbia the classic rat-flea-rat cycle of *Rickettsia typhi* has been replaced by a “semidomestic” or “peridomestic” animal cycle involving free-ranging cats and dogs, opossums, raccoons, and squirrels. Fleas found on these animals are picked up by household pets and brought into homes, and may carry pathogenic organisms (33).

One of the most remarkable emerging pathogens is *Pfiesteria piscicida*, a highly dangerous dinoflagellate which has formed local “red tides” in coastal waterways of the eastern USA (34). *Pfiesteria* emerges from a dormant encysted form in response to nutrient enrichment from the excreta of a school of fish and quickly becomes transformed into toxin-producing ameboid and flagellated forms. These rapidly reproduce by feeding upon the fish, forming a “bloom” in the estuary. Their potent neurotoxin has caused blurred vision, headaches, and memory loss in exposed fishermen and laboratory personnel working with cultures of the organism. Blooms have recently occurred in waters enriched with nutrient runoff from the land, where sewage, agricultural fertilizer, and excreta from hog and chicken farms are indiscriminately discharged into the water. *Pfiesteria* is a frightening example of a pathogen/predator that can turn genes on and metamorphose into killing forms that multiply in vast numbers.

Toxic algal blooms produced by >50 dinoflagellate species are becoming common in nutrient-enriched coastal waters around the world, as more soil, fertilizer, and sewage wash off the land.

An outbreak of an unidentified and rapidly progressing disease produces the same panic today as we read about in historic accounts of the Black Death. There is a sense of helplessness and of time running out, as if an airplane were falling out of the sky. A healthy young patient dies as his lungs fill rapidly with fluid. Medical personnel are devastated at the futility of their intervention. Another patient dies with devastating speed. Those caring for the patients fear for their own lives as well. Modern medicine is in abeyance.

Zinsser describes the spread of typhus in the 17th century, using an analogy of a fire (23):

> Once thoroughly established west of the Balkans, typhus began to spread in all
For diseases like AIDS, Ebola, and malaria, against which we have little defense and as yet no vaccines, Zinsser's description may be ominously accurate. Malaria and other tropical diseases could spread northward with global warming, along with their vectors. Anopheline mosquitoes capable of transmitting malaria are found in all 48 contiguous states of the USA.

A new epidemic disease has an unknown potential for spread, no matter how small the earliest outbreak may be. A future mutation could conceivably enable the Ebola virus to spread by an airborne route. Predicting the ultimate impact of a disease in the early days of its emergence is next to impossible, no matter how well we think we understand the pathogen.

**SUMMARY**

For a host's defense against parasites, for a parasite's defense against its host, and for a parasite's competitive edge with other parasites, genetic diversity seems to be the common currency in the arms race. Diversity is achieved in eukaryotes through sexual reproduction and in bacteria and viruses through myriad mechanisms of gene mixing and transfer.

Domestication of plants and animals through human history provides a model for understanding natural selection, with humans as the selecting agent. The same model provides an explanatory framework for antibiotic resistance, which emerges in microbes exposed to antimicrobial agents. In a population of diverse strains of a microbe, some strains will be resistant by coincidence, and these will proliferate. Diversity (different lottery tickets) provides the parasite with an advantage.

Even though humans are not special hosts, we are laying out a red carpet for pathogens and parasites. New and unique ecologies are being provided for microbes: the human population explosion; city crowding; uncontrolled filth in developing countries; global mixing of people, microbes, and vectors; the provision of common sources of food and water, through which microbes can instantly spread; the invasion of remote wilderness areas by people who travel widely; the use and abuse of antibiotics in medicine and animal husbandry; multiple-partner sex with global mixing; reused needles and syringes; and specialized environments such as hospitals.

**References**


Figure 1

Figure 2
Figure 3

Figure 4

Figure 5