4

An Arms Race Without End

Every time a nation or a tribe designs a new weapon, a competing nation or tribe will soon devise a counterweapon. Thus spears and swords gave rise to shields and body armor, and radar defenses to the Stealth Bomber. Likewise, the evolutionary origin of a predator's improved hunting technique can be countered by the prey's improved armor, evasive tactics, or other defensive adaptation, which is then met by countermeasures from its predators. If foxes start running faster, rabbits are selected to run even faster so that foxes must run faster still. If foxes' eyesight improves, this selects for rabbits that blend better with the background, which may select for foxes that can locate rabbits by smell, which in turn may select for rabbits that tend to move downwind from foxes. Thus predator and prey coevolve in an escalating cycle of complexity. Biologists have named this idea the *Red Queen Principle* after Lewis Carroll's Red Queen, who explained to Alice, "Now, *here*, you see, it takes all the running you can do, just to keep in the same place."

Like contests between predators and prey, wars between hosts and parasites initiate escalating arms races that require extravagant, harmful expenditures and create extraordinarily complex weapons and defenses. Just as political powers sometimes put more and more of their energies into weaponry and defense to keep from being

dominated by opponents, hosts and parasites must both evolve as fast as they can to maintain their current levels of adaptation. There comes a point where the expense of an arms race is so great that the organism, political or biological, is hard put to meet other basic needs, but the cost of losing it is so great that enormous expenses may nonetheless be maintained. We are in a relentless all-out struggle with our pathogens, and no agreeable accommodation can ever be reached.

The relationships between hosts and parasites are so competitive, wasteful, and ruthlessly destructive that arms-race terminology offers an entirely appropriate framework for describing them. The rest of this chapter explains this point of view, but for an introduction, just try to imagine the magnitude of the personal tragedy that infectious agents have caused throughout human history, until just a few decades ago. The mother of one of the authors (Williams) was orphaned at age nine by meningitis. He has a sister whose best friend died suddenly of acute appendicitis in fourth grade. Our microscopic enemies take no account of individual merit or importance. Shortly before Calvin Coolidge succeeded to the presidency of the United States, his sixteen-year-old son got a blister on his foot while playing tennis but bravely went on playing. The blister broke open and became infected, and in two weeks the boy was dead. As a result, the president of the United States was an ineffective emotional cripple (as even his admirers concede) throughout the ensuing campaign and his one term in office.

The analogy between international arms races and host-parasite coevolution is not exact. The Pentagon can plan new weapons on the drawing board and then try out models and prototypes. It has the benefit of rational planning, fresh starts, and trial-and-error tinkering. In evolution, there are no think tanks systematically devising ways of putting scientific knowledge to new destructive or defensive uses. No plans contribute to evolution, and there can be no fresh starts. *Evolution consists entirely of trial-and-error tinkering.* The slightly different variants of every generation compete in the game of life. Some achieve a higher reproductive output than others, and the population averages shift slightly in their direction. The process is slow and unguided—in some ways misguided—but there is no limit to the precision and complexity of adaptation that the Darwinian process can generate.

PAST VERSUS CURRENT EVOLUTION

Many microbiologists incorrectly assume that hosts and their pathogens are usually in a state of slow evolutionary change toward some optimal future state, usually of active cooperation. This is a grossly unrealistic idea. Both pathogens and hosts must normally maintain close-to-stable equilibria by making trade-offs between competing values, such as growth rates and defensive activities. At equilibrium, a unit of improvement of one adaptation would require more than one unit of loss of another. A leaner rabbit might run faster, but at some point the benefit of still greater speed would not be worth the added risk of starvation. Likewise, our fever response is presumably optimized, at least for historically normal conditions. Higher and more frequent fever would make us less vulnerable to pathogens but would be more than counterbalanced by the costs of tissue damage and nutrient depletion. This will be true as long as the environment stays constant. If circumstances change, some of the optima for both host and pathogen will likely change. If bacterial pathogens are artificially kept in check for many generations, this may select for a decreased fever response, but if our technology fails and we become vulnerable again, we might recover a heightened fever response.

In all of this book's other chapters we deal mainly with features of human biology established by long-term historical processes. In the present chapter we will discuss evolutionary changes that can occur within the next year, or perhaps maybe even next week. Because pathogens reproduce so rapidly, they also evolve rapidly.

Some of our defenses against disease, such as sickle cell hemoglobin, have evolved markedly in the last ten thousand years, during which we have had perhaps three hundred generations. The species as a whole has evolved significantly higher resistance to a few epidemic diseases such as smallpox and tuberculosis in the last few centuries, perhaps a dozen generations. Compare this to a bacterium's three hundred generations in a week or two and the even faster reproduction of a virus. Bacteria can evolve as much in a day as we can in a thousand years, and this gives us a grossly unfair handicap in the arms race. We cannot evolve fast enough to escape from microorganisms. Instead, an individual must counter a pathogen's evolution-

ary changes by altering the ratios of its various kinds of antibody-producing cells. Fortunately, the number and diversity of these chemical weapons factories are enormous and at least partly compensate for our pathogens' great evolutionary advantage.

From an immunological perspective, an epidemic may change a human population dramatically. Those individuals who have contracted a disease and recovered will likely be immune to reinfection because they harbor vastly increased concentrations of the lymphocytes that make the antibodies that are most destructive of that particular pathogen. Adult immunity to childhood diseases such as mumps depends not on changing human gene pools but on changing the concentrations of different kinds of antibodies within each individual.

Small size gives our pathogens another advantage: their enormous numbers. Each of us carries around (mostly in our digestive and respiratory systems) more bacterial cells than there are people on Earth. These enormous numbers mean that even improbable sorts of mutations will occur with appreciable frequency and that any mutant bacterial strain with even the most minute advantage over the others will soon prevail numerically. We can expect our pathogens' quantitative characteristics to evolve rapidly to whatever values are optimal for present circumstances.

In some catastrophic epidemics, a human population can evolve a higher level of resistance to an infectious disease in mere months. When Europeans first arrived in the New World, for example, some European diseases quickly killed as much as 90 percent of a Native American community in a short time. If the Native Americans' vulnerability had had any genetic basis, the genes of the lucky few who survived the epidemic would have become proportionately more frequent, and we could say that the population, in this limited sense, evolved a higher resistance. This is an extreme example. More often, a human gene pool will be little changed by an epidemic, while the pathogen's features may evolve dramatically.

Bacterial Resistance to Antibiotics

Perhaps the greatest medical advance of this century, and one of the greatest of all time, was the discovery that toxins produced by fungi could kill the bacteria that cause human disease. While arsenic compounds had been used for syphilis

since Paul Ehrlich introduced them in 1910, the antibiotic era did not really begin until Alexander Fleming noted one day in 1929 that bacteria in his petri dishes would not grow properly in the vicinity of contaminating colonies of the mold *Penicillium*. Why should this have been? Why did the most effective antibiotics come from molds? Antibiotics are chemical warfare agents that evolved in fungi and bacteria to protect them from pathogens and competitors. They were shaped by millions of years of trial-and-error selection to exploit the special vulnerabilities of bacteria but to be nontoxic to the fungi.

A wide variety of fungal and bacterial products that are safe for most people can devastate the bacteria that cause tuberculosis, pneumonia, and many other infections. For several decades now, these antibiotics have given economically advanced societies a golden age of relief from bacterial disease. A combination of public health measures and antibiotics made the death rates from infectious disease fall so rapidly that in 1969 the Surgeon General of the United States felt justified in announcing that it was "time to close the book on infectious disease."

Like other golden ages, this one may be short-lived. Dangerous bacteria, most notably those that cause tuberculosis and gonorrhea, are now more difficult to control with antibiotics than they were ten or twenty years ago. Bacteria have been evolving defenses against antibiotics just as surely as they have been evolving defenses against our natural weaponry and that of fungi throughout their evolutionary history. As Mitchell Cohen of the Centers for Disease Control and Prevention put it recently, "Such issues have raised the concern that we may be approaching the post-antimicrobial era."

Indeed we may. Consider staphylococcal bacteria, the most common cause of wound infection. In 1941, all such bacteria were vulnerable to penicillin. By 1944, some strains had already evolved to make enzymes that could break down penicillin. Today, 95 percent of staphylococcus strains show some resistance to penicillin. In the 1950s, an artificial penicillin, methicillin, was developed that could kill these organisms, but the bacteria soon evolved ways around this as well, and still new drugs needed to be produced. The drug ciprofloxacin raised great hopes when it was introduced in the mid-1980s, but 80 percent of staphylococcus strains in New York City are now resistant to it. In an Oregon Veterans' Administration hospital, the rate of resistance went from less than 5 percent to over 80 percent in a single year.

In the 1960s, most cases of gonorrhea were easy to control with penicillin, and even the resistant strains responded to ampicillin. Now 75 percent of gonococcal strains make enzymes that inactivate ampicillin. Some of these changes were apparently a result of standard chromosomal mutation and selection, but bacteria have another evolutionary trick. They are themselves infected by tiny rings of DNA called plasmids, which occasionally leave a part of their DNA behind as a new part of the bacterial genome. In 1976, it was discovered that the bacteria that cause gonorrhea had gotten the genes that code for penicillin-destroying enzymes via plasmids from *Escherichia coli*, bacteria that normally live in the human gut, so that now 90 percent of the gonorrheal bacteria in Thailand and the Philippines have become resistant. Similarly, the gene that caused antibiotic resistance in a strain of *Salmonella flexneri* that caused a 1983 outbreak of severe diarrhea on a Hopi Indian reservation was traced back to a woman who had been taking long-term antibiotics to suppress an *E. coli* urinary tract infection.

The list of threats we face from antibiotic-resistant bacteria is long and frightening. A plasmid-mediated ability to prevent binding of erythromycin has made over 20 percent of pneumococcal bacteria resistant to treatment with that drug in France. Some strains of the cholera now threatening thousands in South America are resistant to all five previously effective drugs. Amoxicillin is no longer effective against 30 to 50 percent of pathogenic *E. coli*. It appears that we are indeed running, together with the Red Queen, as fast as we can just to stay in the same place.

Perhaps most frightening of all, one third of all cases of tuberculosis in New York City are caused by tuberculosis bacilli resistant to one antibiotic, while 3 percent of new cases and 7 percent of recurrent cases are resistant to two or more antibiotics. People with tuberculosis resistant to multiple drugs have about a 50 percent chance of survival. This is about the same as before antibiotics were invented! Tuberculosis is still the most common cause of death from infection in developing countries, causing 26 percent of avoidable adult deaths and 6.7 percent of all deaths. TB rates in the United States fell steadily until 1985 but have increased 18 percent since then. About half of these cases resulted from impaired immune function in people with AIDS, the rest from increased opportunity for contagion and drug-resistant pathogens.

Increasing tolerance to antibiotics is the most widely known and appreciated kind of pathogen evolution. Since their discovery in the

1950s, an enormous number of studies have established many medically important conclusions:

1. Bacterial resistance to antibiotics arises not by the gradual development of tolerance by individual bacteria but by rare gene mutations or new genes introduced by plasmids.
2. Gene mutations can be transmitted by plasmid infection or other processes to different species of bacteria.
3. The presence of an antibiotic causes the initially rare mutant strain to increase and gradually replace the ancestral type.
4. If the antibiotic is removed, ancestral strains slowly replace the resistant forms.
5. Mutations within a resistant strain can confer still greater resistance, so that increasing the dose of an antibiotic may be effective only temporarily.
6. Low concentrations of an antibiotic, which may retard bacterial growth only slightly, will eventually select for strains that resist the slight retardation.
7. Mutations that confer still higher levels of resistance arise in such partially adapted strains more often than in the original nonresistant strain.
8. Resistance to one antibiotic may confer resistance to another, especially if the two are chemically related.
9. Finally, the disadvantage of resistant strains in the absence of an antibiotic is gradually lost by further evolutionary changes, so that resistance can prevail even where no antibiotics have been used for a long time.

The implications of these findings for medical practice are now widely appreciated. If one antibiotic doesn't alleviate your disease, it may be better to try another, instead of increasing the dose of the first. Avoid long-term exposure to antibiotics; taking a daily penicillin pill to ward off infection is accepted therapy for some conditions, such as infection of vulnerable heart valves, but has the incidental effect of selecting for resistant strains. Unfortunately, we may often be exposed to this side effect without knowing it, by con-

suming meat or eggs or milk from animals routinely dosed with antibiotics. This is a hazard that has recently provoked conflict between food producers and public health activists. The problem of antibiotic use in farm animals needs to be more widely recognized and carefully evaluated in relation to whatever economic gains may be claimed. As Harold Neu, professor of medicine at Columbia University, says in concluding his 1992 article "The Crisis in Antibiotic Resistance," "The responsibility of reducing resistance lies with the physician who uses antimicrobial agents and with patients who demand antibiotics when the illness is viral and when antibiotics are not indicated. It is also critical for the pharmaceutical industry not to promote inappropriate use of antibiotics for humans or for animals because this selective pressure has been what has brought us to this crisis." Such advice is unlikely to be heeded. As Matt Ridley and Bobbi Low point out in a recent article in *The Atlantic Monthly*, moral exhortations for the good of the many are often welcomed but rarely acted upon. To get people to cooperate for the good of the whole requires sanctions that make lack of cooperation expensive.

Viruses don't have the same kind of metabolic machinery as bacteria and are not controllable by fungal antibiotics, but there are drugs that can combat them. An important recent example is zidovudine (AZT), used to delay the onset of AIDS in HIV-infected individuals. Unfortunately, AZT, like antibiotics, is not as reliable as it once was because some HIV strains are now (no surprise) resistant to AZT. HIV is a retrovirus, a really minimal sort of organism with special limitations and special strengths. It has no DNA of its own. Its minute RNA code acts by slowly subverting the DNA-replicating machinery of the host to make copies of itself. The cells it exploits include those of the immune system. The virus can hide inside these cells, where it is largely invulnerable to the host's antibodies.

A retrovirus's lack of self-contained proliferation machinery is both its weakness and its strength. It reproduces and evolves more slowly than DNA viruses or bacteria. Another weakness is its low level of reproductive precision, which means that it produces an appreciable number of defective copies of itself. This functional weakness can be an evolutionary strength, however, because some of the defective copies may be better at evading the host's immune system or antiviral drugs. Another strength of retroviruses is their lack of any easily exploited Achilles' heel in their simple makeup.

It takes months or years for HIV to evolve resistance to AZT, in marked contrast to the few weeks it takes bacteria to evolve significant levels of resistance to some antibiotics. Unfortunately, HIV has a long time to evolve in any given host. A single infection, after years of replication, mutation, and selection, can result in a diverse mixture of competing strains of the virus within a single host. The predominant strains will be those best able to compete with whatever difficulties must be overcome (e.g., AZT or other drug). They will be the ones that most rapidly divert host resources to their own use—in other words, the most virulent.

Short-Term Evolution of Virulence

The evolution of virulence is a widely misunderstood process. Conventional wisdom has it that parasites should always be evolving toward reduced virulence. The reasoning assumes, correctly, that the longer the host lives, the longer the parasites can live and the longer they can disperse offspring to new hosts. Any damage to the host on which they depend will ultimately damage all dependent parasites, and the most successful parasites should be those that help the host in some way. The expected evolutionary sequence starts with a virulent parasite that becomes steadily more benign until finally it may become an important aid to the host's survival.

There are several things wrong with this seemingly reasonable argument. For example, it ignores a pathogen's ultimate requirement of dispersing offspring to new hosts. This dispersal, as noted in the previous chapter, frequently makes use of host defenses, such as coughing and sneezing, that are activated only as a result of appreciable virulence. A rhinovirus that does not stimulate the host to defend itself with abundant secretion of mucus and sneezing is unlikely to reach new hosts.

Another error in the traditional view is the assumption that evolution is a slow process not only on a time scale of generations, but also in absolute time. Such a belief arises from a failure to appreciate the capacity for rapid evolution of any parasite that will go through hundreds or thousands of generations in one host's lifetime. If the

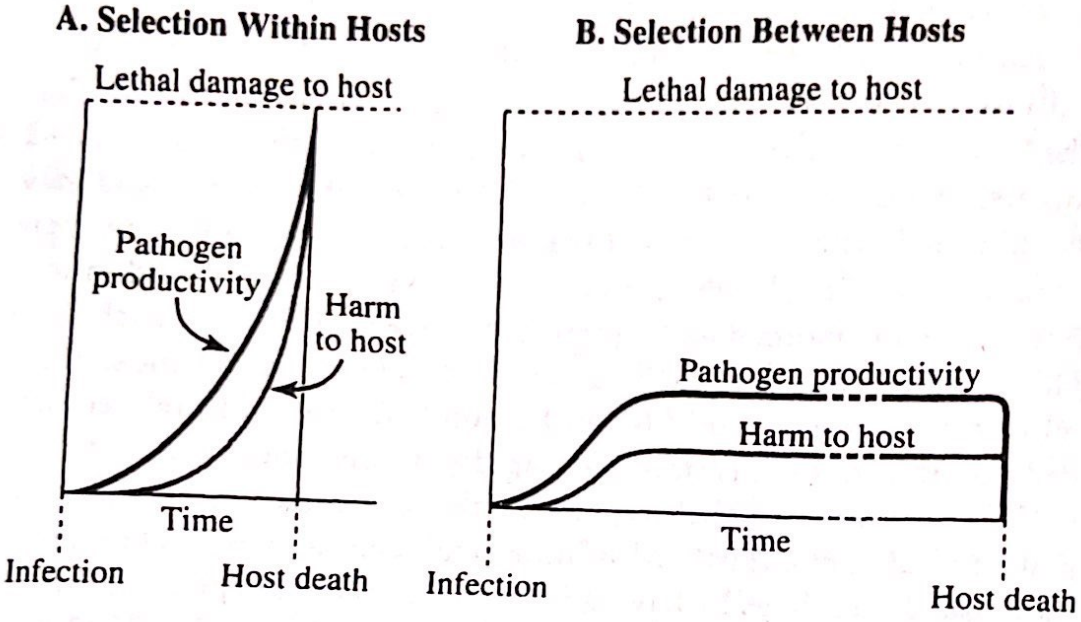
virulence of the amoeba that causes dysentery is too low or too high for maximizing its fitness, the virulence can be expected to evolve quickly toward whatever level is currently ideal. We should not expect the present virulence of any pathogen to be in transit from one level to another unless conditions have changed recently. By "recently," we mean last week or last month, not the last ice age, which is what an evolutionary biologist often means by "recently."

Yet another flaw in the conventional wisdom is its neglect of selection among different parasites within hosts, as we just implied in our discussion of HIV. What good would it do a liver fluke to restrain itself so as not to harm the host if that host is about to die of shigellosis? The fluke and the *Shigella* are competing for the same pool of resources within the host, and the one that most ruthlessly exploits that pool will be the winner. Likewise, if there is more than one *Shigella* strain, the one that most effectively converts the host's resources to its own use will disperse the most progeny before the host dies. As a rule, all else being equal, such *within-host selection* favors increased virulence, while *between-host selection* acts to decrease it. A recent comparative study of eleven species of fig wasps and their parasites confirmed that increased opportunities for parasite transmission are associated with increased parasite virulence.

As with many other applications of evolutionary theory, careful quantitative reasoning is needed to understand the balance between natural selection within and between hosts. The graph on the next page is a naive representation of what we have in mind.

An adequate theory of the evolution of virulence must take into account the rate of establishment, in a given host, of new infections; the extent to which these competing pathogens differ in virulence; the rate of origin of new strains by mutation within a host; and the extent to which these new strains differ in virulence. From such considerations it should be possible to infer the expected levels of virulence for a given pathogen, assuming that conditions stay the same, which they never really do. The most important changes would be those that alter the means by which a pathogen reaches new hosts. If dispersal depends not only on a host's survival but also on its mobility, any damage to the host is especially harmful to the pathogen. If you are so sick from a cold that you stay home in bed, you are unlikely to come into contact with many people that your virus might infect. If you feel well enough to be up and about, you may be able to disperse it far and wide. It is very much in a cold virus's interest to avoid making you

FIGURE 4–1. SELECTION WITHIN AND BETWEEN HOSTS. *A* shows the effects of an extremely virulent pathogen, which would be favored by natural selection *within* a host. It exploits its host to maximize the current rate of dispersal of new individuals to new hosts. It may kill the host quickly, but while the host lives it does better than any competing pathogen. *B* shows the effects of a pathogen that is favored by selection *between* pathogen communities of different hosts. It maximizes its long-term total productivity (rate of reproduction times duration, graphically the area under the production curve). Host death in *B* is most likely from something other than the pathogen.



really sick. By contrast, the malaria agent *Plasmodium* gets no benefit from the host's feeling well. In fact, as shown by experiments with rabbits and mice, a prostrate host is more vulnerable to mosquitoes. People in the throes of a malarial attack are not likely to expend much effort warding off insects. Mosquitoes can feast on them at leisure and spread the disease far and wide.

This evolutionary perspective suggests that diseases spread by personal contact should generally be less virulent than those conveyed by insects or other vectors. Do the facts fit this expectation? They do indeed. Among Paul Ewald's important discoveries is the truth of this generalization and its importance for public health. He has shown that diseases from vector-borne pathogens tend to be more severe than those spread by personal contact and that mosquito-borne infections are generally mild in the mosquito and severe in vertebrate hosts. This is to be expected because any harm to the

mosquito would make it less likely to bite another vertebrate. For gastrointestinal pathogens, the death rate is lower for direct, as compared to waterborne, transmission, as long as really sick hosts can effectively contaminate the water supply. As pure water became the norm in the United States early in this century, the deadly *Shigella dysenteriae* was displaced by the less virulent *Shigella flexneri*. As water was purified in South Asia during the middle of the century, the lethal form of cholera was steadily displaced by a more benign form, and the transition took place earliest at the places where water was first purified.

An unsanitary water supply is only one example of what Ewald calls *cultural vectors*. The history of medicine shows repeatedly that the best place to acquire a fatal disease is not a brothel or a crowded sweatshop but a hospital. In hospitals, large numbers of patients may be admitted with infectious diseases normally transmitted by personal contact. People who are acutely ill do not move around much, but hospital personnel and equipment move rapidly from such people to others not yet infected. Inadequately cleaned hands, thermometers, or eating utensils can be quite effective cultural vectors, and the transmitted diseases may rapidly become more virulent.

Take, for instance, the streptococci that can cause uterine infection in women after childbirth. Most nineteenth-century women knew that they risked their lives by having their babies in the hospital, but some still did so. Viennese physician Ignaz Semmelweis noted in 1847 that women in a clinic staffed by medical personnel contracted childbed fever three times as frequently as those in a clinic staffed by midwives. On investigating, he found that doctors came directly from doing autopsies on women who had died from childbed fever to do pelvic examinations on women in labor. Semmelweis proposed that they were transmitting the causative agent and showed that infections were less frequent when examiners washed their hands in a bleach solution. Was he thanked for his wonderful discovery? No. He was dismissed from his post for suggesting that doctors were causing the deaths of patients. He became more and more frantic in his efforts to save the thousands of women who were dying unnecessarily, but he was ignored, and finally, at age forty-seven, he died in an insane asylum. Nowadays, we all accept the need for hygiene in hospitals, but whenever it becomes lax, conditions are perfect for selecting for increased virulence, as in the virulent hospital-acquired (versus community-acquired) infantile diarrhea studied by Paul Ewald.

It is widely believed that HIV is a new pathogen, perhaps originating from a monkey infected with simian immunodeficiency virus (SIV). However, evidence now suggests that monkeys might have acquired SIV from people with HIV. While HIV may have been present in some humans for many generations, AIDS is apparently a new disease, resulting from the evolutionary origin in recent decades of highly virulent HIV strains. AIDS may have arisen because of changed sexual behavior resulting from the socioeconomic disruption of some traditional societies. Large numbers of prostitutes serving hundreds of men per year were so effective at spreading infection that host survival became much less important to virus survival. Those strains that most rapidly exploited their hosts came to prevail within the hosts, and even the highly virulent strains had plenty of opportunity to disperse to new hosts before the old ones died.

In Western countries, AIDS appeared initially as a disease mainly of male homosexuals because their large numbers of sex partners greatly accelerated sexual transmission, and of intravenous drug users because the drug users' needles were effective vectors. As in Africa, the most virulent HIV strains prevailed over the less virulent because between-host selection for lower virulence was greatly weakened. Even highly virulent viruses had abundant opportunities to reach new hosts before the original host died. Conversely, the use of clean needles and condoms can not only curtail the transmission of the virus, *it can also cause the evolution of lower virulence.*

Costs and Benefits of the Immune Response

As described in the previous chapter, natural selection has given us a fiendishly effective system of chemical warfare. For every invading pathogen there will be a worst-case scenario as to what kind of molecules it might encounter. Our immune systems have been shaped over a hundred million years to make the pathogen's worst nightmares come true. Unfortunately, every effective weapon can sometimes be dangerous to the one who wields it.

The immune system can make two kinds of mistakes: failing to attack when it should and attacking something when it shouldn't. The first kind of mistake results from inadequate response, so that a disease that should have been nipped in the bud becomes serious. The second kind of mistake results from mounting too aggressive a response to minute chemical differences. Autoimmune diseases such as lupus erythematosus and rheumatoid arthritis could be the result. The average person's degree of sensitivity and responsiveness is presumably close to what has historically been the optimum: enough to counter pathogens but not so great as to attack the body's own structure.

Given that we have this chemical superweapon—immunity—how can we possibly remain vulnerable to infectious diseases? Once again, it is because the infectious agents can evolve rapidly and become better adapted by natural selection. Those variants that are least vulnerable to immunological attack will be those whose genes are best represented in future generations. So the pathogens may evolve one or another kind of defensive superweapon. Molecular mimicry, mentioned in the last chapter, is one such weapon.

Escalating Deception

Scientists first developed the concept of mimicry to describe the patterns on butterflies' wings. For instance, the viceroy butterfly looks almost exactly like the monarch butterfly, which birds do not attack because they want to avoid the toxins the monarch caterpillar gets from eating milkweed leaves. The viceroy has no such toxins, but birds mistake it for its bitter lookalike and likewise shun it. Examples are now also known in many other animal groups. Any edible species that by chance resembles a toxic species will have an advantage, and selection will make this *mimic* species look increasingly like the toxic *model*. This is bad for the model because predators that eat the edible mimic learn to go after the model as well. This sets up an arms race between the mimic, which evolves an ever closer resemblance to the model, and the model, which evolves to be as different as possible from its edible neighbors. Some environmental circumstances favor the mimic to such an extent that really detailed resemblances between unrelated species may evolve. We notice such mimicry easily because we per-

ceive so much of the world visually. Detection of chemical mimicry requires more subtle techniques, but there is no reason to think it less common than visual examples.

The molecular mimicry shown by pathogens turns out to be at least as subtle, complicated, and full of surprises as the visual mimicry shown by butterflies and other animals. Deceptive resemblances to human proteins are shown by the surfaces of various parasitic worms, protozoa, and bacteria. If there is any deficiency in the mimicry of human tissues by a bacterium, we can expect it to evolve an improvement rapidly. Pathogen surfaces may have a complex sculpturing of convexities and concavities, and the molecular forms most readily recognized by antibodies are hidden in crevices. As noted in the last chapter, some pathogens alter their exposed molecular structures so rapidly that the host has difficulty producing newly needed antibodies fast enough. This is rapid change without evolution, because the same pathogen genotype codes for a variety of molecular structures.

Mimicry may not only permit pathogens to escape from immunological attack but also make active use of hosts' cellular processes. For instance, streptococcal bacteria make molecules similar to host hormones that have receptor sites on cell membranes. In effect, the bacterium has a key to the lock on the door that normally admits a hormone. Once inside the cell, the bacterium is shielded from immunological and other host defenses. The host has an endosome-lysosome complex that can attack pathogens within its cells, but molecular mimicry and other countermeasures protect the pathogen there too.

Novel Environmental Factors

Before leaving infectious disease, we will anticipate a theme of Chapter 10 by noting the large proportion of epidemics that have resulted from novel environmental circumstances. We have already mentioned how changed social conditions may have initiated the AIDS epidemic, but the same is true for many other plagues. Richard Krause, of the National Institutes of Health, reports that early measles and smallpox epidemics spread along caravan routes in the second and third centuries and

killed a third of the people in some communities. Bubonic plague, the black death, had long festered in Asia, but became epidemic only when Mongol invaders brought it to unexposed populations in Europe who lived with large populations of flea-infested rats. While we like to imagine that such events are in the past, AIDS continues to spread alarmingly, and the causes of other sudden outbreaks of infection are unknown. The Ebola virus ravaged parts of Africa in the 1980s, killing half of those who became ill, including most of the doctors and nurses who cared for the patients. It stopped as suddenly as it started, for reasons that remain unclear.

Some infectious diseases stem directly from modern technology. Legionnaires' disease arose from an organism that was able to grow and be dispersed from the water in a hotel air-conditioning system. Toxic shock syndrome arose when a new superabsorbent tampon material allowed enough surface area and oxygen for the growth of unusually large concentrations of toxic staphylococcal bacteria. Lyme disease became a problem only when deer populations multiplied adjacent to new suburbs. Influenza has become a major threat since mass worldwide transportation began spreading new strains that contain new genes. It is often called the *Asian flu* because new strains so often originate on Asian farms, where people, ducks, and pigs (some strains are called *swine flu*) live in such close proximity that genes from one influenza strain can easily be passed from one to another.

Tuberculosis became epidemic in Europe with the rise of large, crowded cities. Unsanitary practices and poverty are always cited as causes, but we wonder if the disease didn't become epidemic simply because large numbers of people began spending large amounts of time together indoors. Air exhausted from a TB ward reliably produces infection in guinea pigs but no longer causes infection if it is briefly exposed to ultraviolet light. A single sneeze can produce a million droplets, which settle to the ground at a rate of only about one centimeter per minute in still air. In the open air they would be dispersed or killed by sunlight, but indoors they might last for weeks, as they no doubt did in 1651, when tuberculosis caused 20 percent of all deaths in London.

Finally, we note that epidemics can result from the best of intentions. Polio was not an epidemic disease that caused paralysis until the early twentieth century. Before that time, most children got the disease in the first years of life, when it usually produces only mild effects. By midcentury, improving sanitation delayed the infection

until late childhood, when it can be much more severe. Mononucleosis is also less severe at earlier ages. In each of these examples, a disease became a serious problem only when its mode of transmission was changed by novel environments. We will return in Chapter 10 to other novel environmental factors and their role in disease.