ever 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 anti-
biotics 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 consuming 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**