

# The Evolution of Virulence

*Human behavior appears to influence whether pathogens evolve into benign or harmful forms. Health policy should therefore include evolutionary considerations*

by Paul W. Ewald

Some pathogens, such as those that cause cholera, smallpox, tuberculosis, malaria and AIDS, have quite severe effects. Others rarely inflict any damage beyond a cold or a sore throat. Recent studies suggest there are several evolutionary reasons for these varying levels of virulence. They include a pathogen's mode of transmission as well as its ability to survive outside a host organism for long periods. Human behavior may also play a significant, largely unrecognized role in the evolution of pathogens because it often determines the route and timing of transmission.

Understanding the forces that shape changes in virulence could become a powerful tool for medicine. By examining these variables, evolutionary biologists have already been able to predict patterns of morbidity and mortality in several diseases—including cholera, dysentery and AIDS. Using such an approach, medical scientists may be able to anticipate alternative evolutionary courses of pathogens and to tailor treatment and social behavior accordingly. They might even be able to transform virulent adversaries into mild ones.

Until recently, the understanding of how virulence evolves has generally been limited to one view. Most physicians and medical writers have concluded, unjustifiably, that the evolution of



host-parasite relations ultimately leads to benign coexistence. Their opinion is based on the idea that parasites that do not harm their hosts have the best long-term chance of survival: they thrive because their hosts thrive.

Some biologists, however, have arrived at a different conclusion. Evolutionary theory holds that what is best for a species may differ from what is best for its component individuals and that what is best for these individuals is defined by which genes are passed along most successfully. Even if a pathogen reproduces so extensively that it causes its host to become gravely sick, its host-impairing instructions may still win out over the less damaging instructions of a less aggressive competitor. The more virulent pathogen would achieve this success if its increased replication led to a level of transmission into new hosts that exceeded the loss of transmission resulting from the host's illness or death. In this scenario, the extinction of the host may eventually cause the demise of any pathogen that relies exclusively on one host. But the possibility of extinction does not inhibit the spread of the more virulent genes within the population of pathogens.

This perspective suggests that a parasite's virulence may reflect its mode of transmission. If the illness of a host impairs transmission, evolutionary biologists would predict that parasites would evolve to have milder effects. In contrast, if the host's disability does not inhibit transmission, pathogens could gain a competitive advantage by reproducing more rapidly.

Consider, for instance, a pathogen that relies on the mobility of its host. Rhinoviruses, causes of the common cold, reproduce in the cells that line the nasal passages. The viruses are shed in nasal secretions that trickle out as a runny nose or blast out during a sneeze. A person's finger may wipe away the mucus and may then touch the fingers of another person in the course of a handshake or by way of a borrowed pencil. The exposed individual may later touch fingers to nose or inhale the contaminated air, planting rhinoviruses on fertile ground.

Whichever route is taken, the ability of the host to move is critical. If the pathogen reproduces so extensively that the host is too unwell to leave home, thousands of rhinoviruses shed that day will die of exposure. A few might squeak by if they infect a family member, but such transmission could hardly be considered a great accomplishment, especially if the new host also becomes bedridden. For rhinoviruses, a person's movement improves prospects for transmission. Accordingly, rhinovirus replication is restricted to cells scattered in a sea of uninfected nasal mucosa, and virulence remains slight.

**UNPROTECTED WATERS, including wells (above) and rivers, such as the Yamuna in India (right), have been infamous disseminators of disease. Purification limits the spread of infection. It also may provide an unrecognized benefit: it may force pathogens to evolve into mild forms.**

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The opposite can occur when pathogens are transported by a vector, an organism that transmits an infectious agent. If a mosquito-borne pathogen reproduces so extensively that the host becomes immobilized, the pathogen can still pass along its genes. The vector transports pathogens from the incapacitated host to susceptible individuals. Transmission can even be facilitated

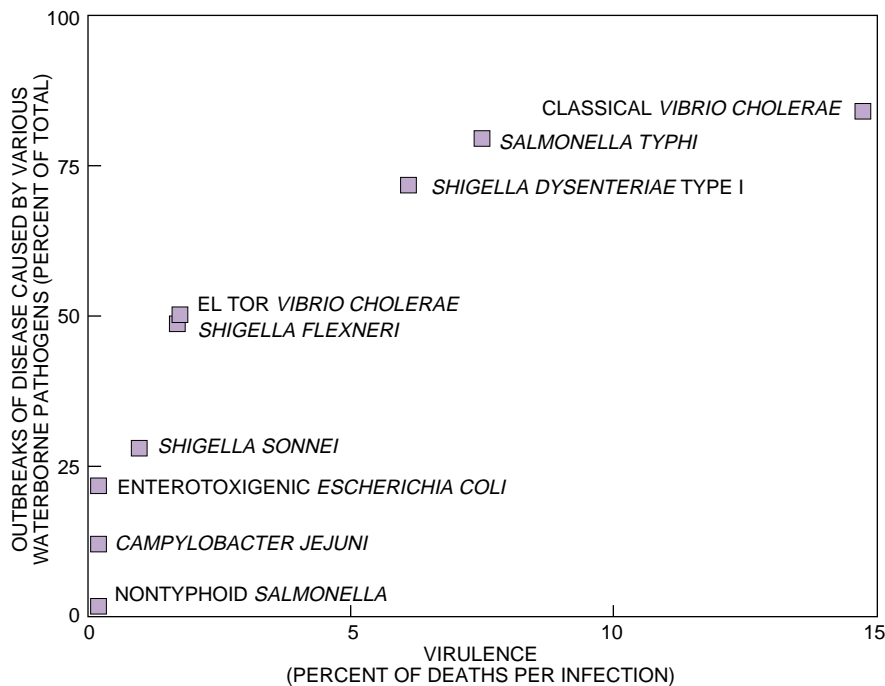
when hosts are sick because they are then less able to prevent mosquitoes from biting. (Pathogens tend to treat their vectors kindly: a delirious mosquito could not effectively shuttle malaria-causing organisms to new hosts.)

Extensive multiplication and distribution in the vertebrate host are beneficial to those pathogens traveling by vector. Such agents tend to reach higher

densities than less noxious pathogens do, increasing the probability that a biting insect will obtain an infective dose. Without systemic spread, a mosquito or another carrier would pick up the pathogen only if it bit near the site of the bite that originally infected the host.

Medical literature provides ample evidence of these trends. Pathogens that are transmitted by biting arthropods





**PATHOGENS that are most frequently transported by water systems, such as classical *Vibrio cholerae*, are more virulent than those that are not, such as nontyphoid *Salmonella*. A waterway contaminated by wash or sewage can serve as a cultural vector, a transporter of pathogens that is created by human behavior.**

are especially damaging to humans: they tend to cause death more frequently than do pathogens that are transmitted directly [see illustration on page 90]. The severity of diseases such as malaria, yellow fever, typhus and sleeping sickness can thus be explained as an evolutionary consequence of vector-borne transmission.

But there are exceptions to this rule. Some directly transmitted pathogens—including the smallpox virus and the tuberculosis bacterium—can often be lethal. One possible explanation for their virulence is the sit-and-wait hypothesis. A pathogen can be passed from an incapacitated host to a susceptible host in two ways. As already described, it can be transported by something that travels, such as an insect. Alternatively, if the pathogen is able to survive in the external environment for an extended time, it can just sit and wait for a host to happen along. Like their vector-borne counterparts, such enduring pathogens benefit from extensive multiplication inside their hosts, while losing little from the ensuing immobilization of their hosts. According to this argument, sit-and-wait pathogens would be particularly virulent.

Indeed, pathogens that are able to survive for long periods in the external environment are often more injurious. This trend was recently documented in a study of human respiratory pathogens I conducted with one of my students,

Bruno Walther. Infectious agents that survive for weeks or years in the environment tend to cause death most frequently: for example, smallpox kills one in 10 people, and the virus that causes it can persist for more than a decade outside a host. The pathogens giving rise to tuberculosis and diphtheria can also live externally for weeks to months and are correspondingly noxious. Most other pathogens tend to survive for only hours or days without hosts; they tend to be less destructive, causing death in fewer than one in 10,000 infected people.

**H**uman behavior may also affect virulence. As the emergence of antibiotic resistance shows, pathogens can evolve quickly in response to human interference. But modification of pathogens by people is not limited to the introduction of medical treatments. Some activities create cultural vectors—amalgams of culture, human behavior and the physical environment that allow pathogens to be transmitted from immobilized, infectious hosts to susceptible individuals.

For instance, the virulence of diarrheal pathogens should reflect their tendency to be effectively transmitted through drinking-water systems. Like pathogens transmitted by insects, those spread by water may have little to lose from the immobility of their hosts. A sick person can release infectious agents onto bed sheets or clothing that will be

washed. If the contaminated washing water can reach unprotected drinking water, even an immobilized person with diarrhea can infect many others. I conducted a review of the literature on bacterial diarrheal diseases and found just such a correlation between waterborne transmission and mortality. The evidence supports the idea that such transmission leads to an increase in virulence. The severity of typhoid fever, cholera and the most dangerous forms of dysentery can therefore be explained as the evolutionary result of waterborne transmission.

It follows, then, that if transmission by water confers an advantage to highly virulent bacteria, the introduction of uncontaminated drinking supplies should reduce virulence, because pathogens would not gain much benefit by reproducing rapidly. In fact, this trend has been documented. As water supplies were purified in cholera-endemic regions in India during the 1950s and 1960s, the milder agent of cholera, the El Tor type of *Vibrio cholerae*, displaced the more dangerous form, classical *V. cholerae*. In Bangladesh, however, where the war of independence and extensive socioeconomic difficulties have delayed water purification, classical *V. cholerae* persists.

The three causes of bacillary dysentery have experienced similar transitions. In all countries with detailed records, the most virulent bacteria, *Shigella dysenteriae*, virtually disappeared as major improvements in water purification were regionally enacted, while the moderately virulent *S. flexneri* predominated. As these improvements progressed toward complete purification, *S. flexneri* was replaced by the mildest species, *S. sonnei*. In the same regions the agent of typhoid fever, *Salmonella typhi*, has also been replaced by the less debilitating species of *Salmonella*.

Hospitals may generate another form of cultural vector. Attendants inadvertently carry pathogens on their hands from patient to patient. They do so by direct contact or indirectly through the use of equipment. As with transmission by arthropods or water, attendant-borne transmission could promote virulent genotypes of pathogens—again because extensive replication in the infected host would enhance the infection of new hosts.

In such settings, newborn infants would be at risk of being infected by attendants. From the pathogen's point of view, a neonate is very different from a nurse. Neonates are highly vulnerable because they lack the acquired immunity of adults. A nurse typically touches each baby about 20 times a day and at-

tends very ill babies more frequently. Intense diarrhea should facilitate transmission by attendants given that it is easier to avoid a well-formed stool than a diffuse fecal film. In addition, hospital strains of diarrhea-causing pathogens may persist and sometimes multiply, even after standard washing with disinfectants. Contaminated hands may accidentally touch objects before hand washing; these contaminated items can then recontaminate hands after washing.

Reports describing outbreaks of a common inhabitant of the human intestine, *Escherichia coli*, support this argument. When outbreaks of pathogenic *E. coli* were over in a week or so, few infected babies died. But in places where the incidents continued for weeks to months, about one of every

10 infected babies died [see illustration on opposite page]. At first glance, the association between lethality and the duration of outbreak may appear to be the result of poor hygiene, not of evolutionary forces. Hospitals that put less effort into curbing outbreaks might put less effort into cleanliness and therefore might have had more severe infections because patients received larger doses of the pathogen.

The details of the outbreaks, however, are inconsistent with such an interpretation. To quell the attacks of *E. coli* and other bacteria, hospital staff usually extensively disinfected the facility and the hands of attendants. During these campaigns, it stands to reason that the doses of *E. coli* must have been drastically reduced. Yet damaging infections per-

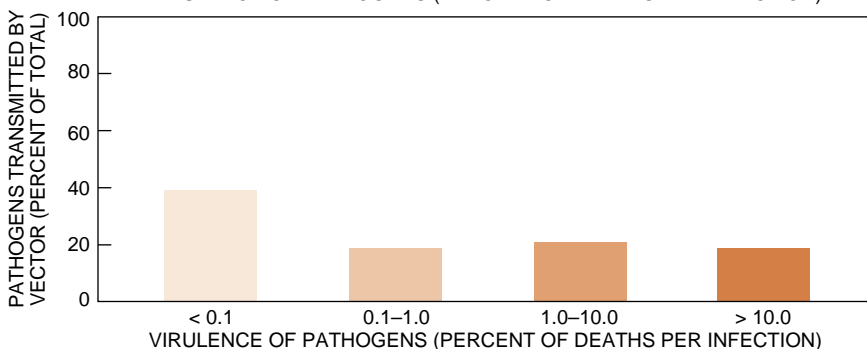
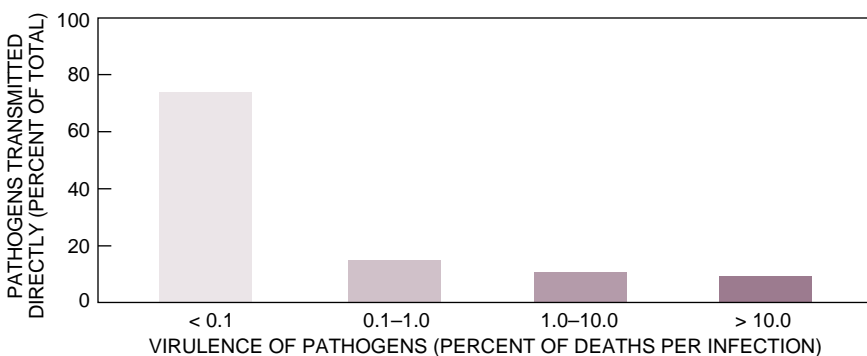
sisted. The ability of pathogens to cause severe illness in the presence of such improvements in sanitation suggests that their virulence, rather than increased contamination, was to blame. To extinguish such ongoing outbreaks, the staff frequently closed the affected wards and doused them with disinfectants.

About one of every 20 hospitalized patients in the U.S. acquires an infection before leaving the hospital. The annual total approaches four million infections and thousands of deaths. Despite the magnitude of this problem, the possibility that attendant-borne transmission heightens virulence remains untested—except in the case of *E. coli*. Long-term studies that monitor frequencies of infection as attendant-borne transmission is suppressed need to be broadened to determine whether this intervention reduces virulence.

If an evolutionary understanding of virulence could help resolve vexing medical problems, its application to HIV would be extremely timely. Some 10 million people are infected with HIV, and one million have symptoms of AIDS or have already succumbed to it. By examining the conditions that influence the competitive success of sexually transmitted pathogens, we can begin to clarify the influences determining the virulence of HIV.

Consider a sexually transmitted pathogen in a population of relatively monogamous individuals. After it infects a couple, the pathogen would have to remain viable until one member engaged in sexual activity outside the pair. If such activity took place only, say, once every three years, the typical duration of infectiousness of directly transmitted pathogens would not allow the agent to survive—as the example of rhinoviruses suggests. Only the variants that had some way of extending their infectiousness would be transmitted venereally.

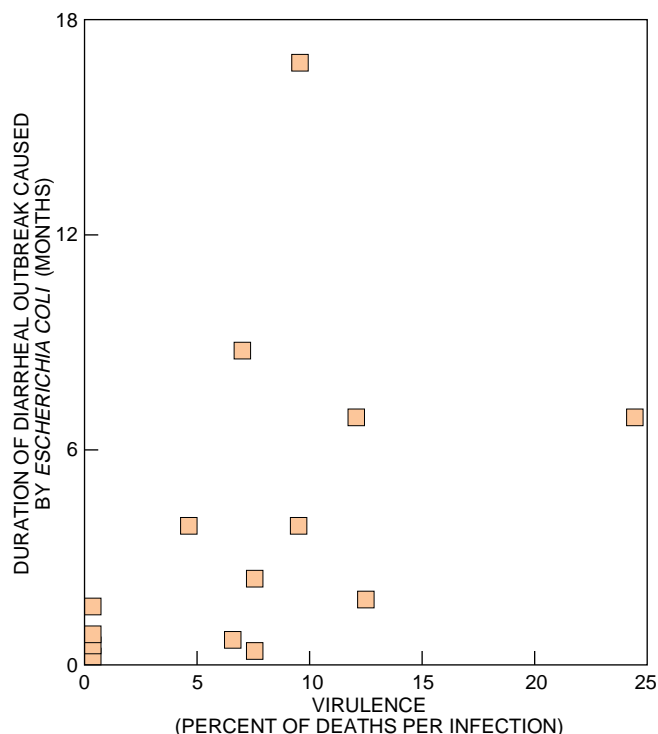
To extend infectiousness, pathogens must avoid being destroyed by the host's immune system. At the same time, however, they must maintain access to new hosts. One option is to remain latent inside long-lived cells. By merging with a chromosome in a host cell and by suppressing the creation of products that would trigger an immune response, a latent virus can wait out the time between new sexual partners. Indeed, retroviruses such as HIV can hide in long-lived white blood cells and be transmitted years after the initial infection. (Retroviruses operate by inserting their RNA into host cells; the RNA is then transcribed into DNA, which is incorporated into the host's genome.)



**MODE OF TRANSMISSION** reflects a pathogen's virulence. If the pathogen moves directly from host to host (*top*), its effects must be mild enough that they do not disable the host: if the host cannot move, the pathogen cannot be transmitted. But pathogens carried by a vector, such as a mosquito (*bottom*), need not spare the host: the vector can transmit the pathogen regardless of the host's state. Thus, vector-borne pathogens tend to be quite virulent (*middle*).



**HOSPITAL ATTENDANTS**, who may touch many babies (left), can inadvertently serve as vectors. As the chart shows, *Esche-*



*richia coli*, a diarrhea-causing organism, is particularly lethal when it is repeatedly transmitted in a hospital (right).

Of course, the benefit of latency would have to be weighed against the higher rate of reproduction that would occur in the absence of latency. HIV has the raw material for both strategies. It remains latent in most of the cells that are infected at any given time, but throughout each infection some actively reproducing viruses tend to be present. The rapid rate at which HIV mutates results in a great potential for quick changes in replication rates. In fact, nonlatent HIV regularly evolves an increased replication rate in the interval between the onset of infection and death.

If sexual activity increases so that people are involved with a different partner every week, the factors contributing to virulence shift. A sexually transmitted virus that actively reproduces in an infected person could soon infect several new hosts, whereas a virus that is latent for three years would propagate less extensively. Thus, increased rates of partner change could favor HIV variants that replicate rapidly. The pressures favoring the evolution of fast viral reproduction when sexual contact is high and of delayed viral reproduction when sexual contact is low provide the basis for a prediction: HIV virulence should be correlated with rates of sexual contact.

Data gathered over the past decade are consistent with this prediction. One form of evidence comes from the two

types of HIV: HIV-1, the more rapidly lethal form, and HIV-2, which is associated with a longer symptom-free period and with lower frequencies of full-blown AIDS. During the early years of the AIDS pandemic, HIV-1 tended to occur in Central and East Africa and HIV-2 in West Africa. Interestingly, these different forms of infection reflect different social patterns. During the 1960s and 1970s, an economic crisis in Central and East Africa caused a migration away from rural areas. Men left to obtain industrial jobs in cities; large populations of men without families created, in turn, a market for sexual commerce and drew women into these urban areas.

In contrast, West African countries generally did not undergo massive movements of people or increases in sexual contact during the same period. According to the evolutionary theory of virulence, the virus endemic to West African countries (HIV-2) should not be as lethal as that in Central and East Africa (HIV-1). And such is, in fact, the case.

Differences in virulence can also be predicted within these two types of HIV. Although data are scarce, one difference seems to be emerging in the two most extensively studied areas of HIV-2 infection: Senegal and Ivory Coast. In Senegal, HIV-2 infections are associated with a low frequency of AIDS. Since 1985, Phyllis J.

Kanki and her colleagues at Harvard University have followed a large group of HIV-2-infected prostitutes in Senegal to determine the speed at which HIV-2 progresses to AIDS. To date, only one of the women has shown symptoms of AIDS. In addition, during early attempts to isolate HIV-2 from infected Senegalese subjects, Lilly Kong, formerly at the University of Alabama, and her colleagues had little success. Apparently the virus entered cells and propagated at a reduced rate. Kong's one isolate had very mild effects.

Studies conducted in the capital of Ivory Coast, Abidjan, reveal a different trend. This city underwent social change when migrations from rural areas brought influxes of single men. The strains of HIV-2 common to Abidjan appear to be more virulent than those found in Senegal.

Although accurate information on rates of sexual interaction is exceptionally difficult to obtain, sociological studies suggest that Senegal did not experience the same kind of social disruptions found in Abidjan. Olga F. Linares of the Smithsonian Tropical Research Institute believes several cultural factors may have favored reduced partner change in Senegal: a family structure that encompasses rural and urban residences; an intact, traditional agricultural infrastructure; and an Islamic heritage that discourages premarital and extramarital sex.

Rates of sexual transmission may partly explain the evolution toward greater virulence, but the argument must be broadened to describe why HIV has become so deadly. HIV does not kill its host directly: it destroys the immune system, permitting lethal secondary infections to occur. The evolution of this characteristic apparently arose from the virus's predilection for cells critical to immunologic defenses against other pathogens, its ability to replicate quickly and its tendency to alter its genetic material at an accelerated pace.

When partner changes are infrequent and viruses are latent for long periods, a predilection for immune system cells need not destroy the host. HIV's retroviral cousin, human *T* cell leukemia/lymphoma virus type 1 (HTLV-1), for example, infects the same class of lymphocytes that HIV infects. But HTLV-1 has a suppressed level of reproduction and a less detrimental effect on the immune system in most people.

If sexual contact increases, selection may favor greater rates of replication even though such evolution may lead to an earlier death for the host and hence to the demise of any form of HIV that the person harbors. In this case, the virus makes the best of a bad situation. For a sexually transmitted virus infecting a host with frequent partner changes, immune cells are not ideal targets, because destroying the host's immune system will ensure quick death. But once a virus's biochemical machinery has become specialized to enter and reproduce in lymphocytes under conditions of low sexual contact, altering its biochemistry to enter some other less critical cell type could pose a major hurdle.

High rates of mutation, another characteristic of HIV, present additional long-term drawbacks for a virus. Frequent mutations are often costly for

organisms because they tend to mangle finely tuned biochemical machinery. For HIV, increased mutation may also lead to the collapse of the host's immune system and to symptoms of AIDS.

Mutations, however, may provide compensating benefits. If frequent partner changes confer an advantage on variants that have reduced latency, natural selection should favor any viruses that look different to the immune system over viruses that have already reproduced in the person. If a virus does not look different, then the immune system—primed by its previous encounter with that variant—will do it in. (This generalization breaks down during the terminal stages of HIV infection. By then, though, the point is moot because HIV is generally eliminated from evolutionary competition by the behavioral avoidance of unprotected sex with someone who is very ill.)

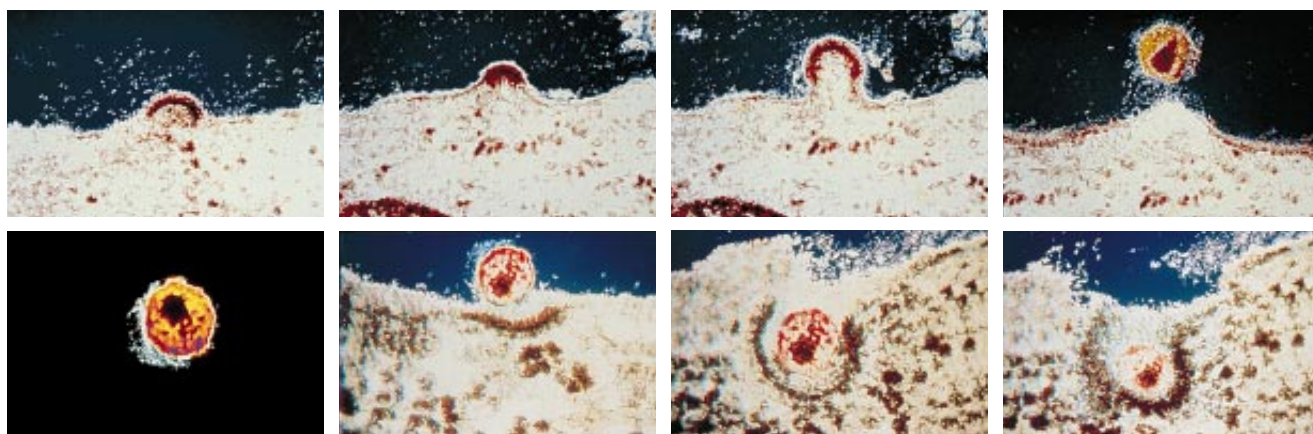
Being different should therefore encourage evolutionary plasticity in the proteins that protrude from the virus and are exposed to the immune system. Indeed, genes that contain the instructions for the production of these envelope proteins are more prone to mutation than is the rest of the HIV genome, and they are among the most mutation prone of any known genes in any organism. This mutability is not common to all retroviruses. Retroviruses show great variations in mutation rates in envelope proteins. HIV-1 lies at one extreme: its genes can diverge by some 5 percent in a few years. At the other end of the spectrum is HTLV-1, which may require centuries to achieve the same degree of change. Ultimately, then, a high incidence of sexual contact may explain why HIV is so dangerous. When the potential for sexual transmission increases, natural selection favors viruses with reduced laten-

cy, more rapid replication among nonlatent viruses and faster mutation rates.

The same kinds of processes should, in theory, be shaping the evolution of HTLV-1. The most detailed studies come from Japan and Jamaica, where data indicate that HTLV-1 is also variable in its virulence and that this variability is associated with rates of unprotected sexual contact with different partners. In Japan, barrier contraceptives, which inhibit retrovirus transmission, are used widely. (Birth-control pills, which do not prevent sexually transmitted disease, are restricted.) Moreover, rates of sexual partner change appear relatively low there. Accordingly, the geographic and age distributions of disease in Japan illustrate that a large proportion of infections arise from transmission from mother to child rather than from sexual contact.

In Jamaica, the analogous distributions indicate that sexual contact is the more common route of transmission. The Japanese-Jamaica comparison suggests that HTLV-1 may be more virulent in areas where rates of sexual transmission are high. Indeed, in Japan, cancers triggered by HTLV-1 occur, on average, at age 60; in Jamaica, they occur at roughly age 45. This comparison, like the geographic comparisons of HIV infection, draws attention to the need for more precise measurements within many geographic regions to determine whether retroviruses are inherently more virulent in areas with greater potential for sexual transmission.

Understanding the epidemiology of infectious diseases from an evolutionary point of view permits many assessments—including why virulence evolved in the past, what is currently maintaining it, how it may evolve in the future and, most impor-



**HUMAN IMMUNODEFICIENCY VIRUS** attacks the often long-lived cells of the immune system. These photographs show a newly replicated virus budding from a *T* lymphocyte, wrapping

itself in the cell's membrane (*top row*). The virus travels to another *T* lymphocyte and enters when the membrane surrounding the virus fuses with that of the cell it infects (*bottom row*).

tant, how human activities can influence this evolution. If rates of infecting sexual contact decline, the virulence of HIV and HTLV-1 should drop accordingly.

The rates of unprotected sexual encounters among urban male homosexuals began to decline sharply around 1984, in response to improved knowledge about transmission of HIV. Considering that highly virulent strains of HIV generally require two to three years before they cause AIDS, any evolutionary slowing of progression to AIDS would not be detectable before the late 1980s. In addition, detection of such an effect during the late 1980s is confounded by the effects of zidovudine (AZT) treatment.

Philip S. Rosenberg and his co-workers at the National Cancer Institute have published an analysis that accounts for the life-extending effects of AZT. They have found that the growing lag between HIV infection and AIDS that was observed among male homosexuals before 1988 could be explained entirely by AZT treatment. After mid-1988, however, there was an additional lengthening of time between infection and disease among male homosexuals that could not be so explained. This unexpected delay may be the first sign of a decline in HIV virulence. It is noteworthy that infections in intravenous-drug users did not lead to significant reductions in high-risk behavior during the mid-1980s. This population also did not experience a lengthening of time before the onset of AIDS that was independent of AZT.

The next few years of data should help resolve the alternative explanations for this delay in the onset of disease, because nonevolutionary alternatives do not predict a continued lengthening. In contrast, evolutionary theory postulates a growing period between infection and AIDS in groups whose high-risk behavior has declined. More generally, the evolutionary explanation and the variations in virulence over time and geographic area suggest that an unplanned experiment is now occurring. People reducing their transmission rates fall into the experimental group. The populations in which transmission rates are not being reduced are the controls. HIV in the latter group is expected to remain more virulent than HIV in the former groups.

**T**hese trends potentially provide a basis for changing the course of virulence. By increasing the price that pathogens pay for virulence, we should be able to make pathogens evolve toward a benign state. In the case of HIV and HTLV-1, increased in-



**CONDOM USE, something these demonstrators at an AIDS awareness rally are urging, is associated with less virulent forms of HTLV-1 in Japan. Because the use of condoms reduces opportunities for transmission, the virus must be able to survive for a long time in its host. Thus, it is advantageous for the virus to be mild and long-lived so that it does not impair its host.**

vestment in interventions that reduce the rates of transmission by sexual contact and needle sharing should force HIV and HTLV-1 to become less damaging over time—or at least keep them from becoming increasingly virulent in each subsequent generation. Reducing attendant-borne transmission in hospitals by improving hand-washing practices, by using gloves more effectively and by increasing maternal contact with babies (since mothers tend to touch only their own newborns) should similarly inhibit evolution toward more virulent strains of hospital-acquired organisms. Further improvements in water purification should make the diarrheal pathogens in a region milder. Making houses and hospitals mosquito-proof should make the mosquito-borne diseases evolve toward a more benign state as well.

By identifying the long-term benefits of interventions, an evolutionary approach to disease control adds a novel dimension to policy making. As our knowledge in this area matures, it should provide a clearer view of which interventions are most cost-effective. We have already controlled those pathogens most readily affected by traditional interventions such as vaccination and antibiotic treatment. Pathogens like HIV and the protozoa

that cause malaria remain unconquered.

In the absence of an evolutionary view, the future will repeat the past. When we impede versatile pathogens with a drug, they will evolve resistance. A pathogen's potential for change will undoubtedly lie beyond our ability to anticipate its mutability. It is for such more formidable pathogens that we desperately need a new perspective. Virulent pathogens may be transformed into mild ones not because benign coexistence is the inevitable end point of evolution but because we will have made it the most favorable outcome.

#### FURTHER READING

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