Living with Microbes

Human beings have long used antibiotics and other weapons to wage war on microbes. But microbes seem to evolve almost as quickly as scientists devise new means to destroy them. It is time to abandon the war paradigm, the authors argue, and embrace new methods that will allow us a greater measure of peaceful coexistence with microbial life.

by Joel L. Swerdlow and Ari D. Johnson

In January 2000, nearly two years before terrorists destroyed the World Trade Center and attacked the Pentagon, before anthrax-laden letters spread fear and death through the postal system and the country, the National Intelligence Council warned that naturally occurring infectious diseases were a serious threat to national security and international stability.*

This threat is growing worse. In the past 20 years, nearly three dozen deadly microbes have been identified for the first time. These include the viruses that cause hepatitis C, D, and E; the Ebola virus; hantaviruses, which attack the respiratory system; and, most pervasive, the Human Immunodeficiency Virus (HIV). Epidemics of dengue fever, meningitis, influenza, cholera, and other diseases have become increasingly common. One in every 12 people on earth is infected with malaria, in part because the anopheline mosquito has grown increasingly resistant to insecticides and, as an effect of global warming, is now found in areas where it was never seen before. With the emergence of multidrug-resistant bacteria and the AIDS pandemic, the tuberculosis mortality rate is rising for the first time in 40 years.

The first new class of antibiotics to be discovered in 30 years has already encountered resistance even though it has not yet been widely used. The same is true for the new antiviral drugs. By 2005, half of all AIDS patients in San Francisco will not respond to any treatment currently available. Mounting evidence implicates bacteria, viruses, and protozoa in an array of conditions and diseases previously thought unrelated to infection: heart disease, rheumatoid arthritis, diabetes, multiple sclerosis, autism, chronic lung diseases, and at least one-quarter of the known varieties of human cancer.

*The unclassified version of the report is available at *www.cia.gov/cia/publications/nie/report/nie99-17d.html*.

A worker at the U.S. Centers for Disease Control in Atlanta can safely conduct research on deadly biological agents—both natural and manmade—in the High Containment Laboratory.

Nonetheless, there is reason for optimism. During the past two decades, evolutionary biologists, microbiologists, and other researchers have begun to learn how and why microbes evolve. In the process, they have found a more effective way of dealing with infectious disease than the old state-of-war, them-or-us approach. This new understanding focuses on our evolutionary relationships with microbes. It tells us that virulence, the harmfulness of a microbial infection, is a product of the evolutionary interplay between microbes and humans. And it shows how we can direct microbial evolution away from infectious disease and toward a more mutually beneficial relationship. In an essay nearly 20 years after his seminal *Structure of Scientific Revolutions* (1962), Thomas Kuhn wrote that in certain periods "the pieces suddenly [begin] sorting themselves out and coming together in a new way." That is exactly what is going on now.

The evolution of any species requires a population with a diverse gene pool that gives each individual in the species unique characteristics. As Charles Darwin pointed out in *Origin of Species* (1859), environmental forces favor the survival and reproduction of individuals with certain specific characteristics. Take the human thumb. For our hominid ancestors to develop opposable thumbs, individuals must have appeared whose genes governing the thumb happened to be different, giving them the new ability to hold weapons and tools. This proved a great advantage in surviving in their environment and therefore passing those genes to the next generation. Over time, those without these particular genes evolved in another direction, or died out.

Now turn to the surprising mechanics of microbial evolution. Darwin had no idea of the importance of microbes when he published *Origin of Species*, but

microbes follow Darwinian evolutionary theory very efficiently. Some bacteria can create three generations in an hour. Such brief life spans together with high mutation rates facilitate the rapid development and transmission of minute variations. But there is a twist. Microbes have been devising survival strategies for billions of years and they have developed some remarkable qualities. Bacteria and viruses, for example, can capture and incorporate DNA from *other* microbes, plants, and animals, and pass this DNA on to their progeny.

Humans live on extraordinarily intimate terms with these highly adaptive organisms. Indeed, we cannot live without them. Recent studies have shown that we owe at least three percent of our genetic material to viruses, and that many of our genes have bacterial origins. Mitochondria—the very small, rodlike structures found in most cells that help break down glucose into usable energy—evolved from bacteria and are vestiges of a mutually beneficial relationship so intimate that their individual bacterial identities became subsumed by animal cells long before humans appeared.

The figures are astounding. Microbes living inside each human being outnumber the human population of Earth. The microbes that live in our bodies and on our skin outnumber our body's cells 9 to 1. Microbes flow through our veins, lie on our eyes, and colonize our digestive and respiratory systems. Among other benefits, they aid digestion, make possible the production of vitamin K and other essential elements, and stimulate development of the immune system—all without our being conscious that living things are constantly at work inside us. Some neuroscientists believe that the presence of bacteria might even be necessary to normal growth of the human brain.

So important are microbes to human identity that Joshua Lederberg, who won the 1958 Nobel Prize in medicine for his discoveries concerning genetic recombination and the organization of genetic material in bacteria, has suggested the term "microbiome" to describe the single biological unit of humans and the microbes that dwell within them. Within that microbiome, however, humans can direct the forces that favor the propagation of certain microbes over others. Even the most minute changes inside our bodies can determine which microbes die and which survive and reproduce. Thus do we define the path of the microbes' evolution.

Humans also direct the evolution of microbes through our impact on the external environment. We have radically increased our numbers on Earth, domesticated plants and animals, contributed to global warming, drawn our food supplies from around the world, crowded into cities, and fought a continuum of wars—and all of these activities constitute intense, unforgiving, *selective* forces

> Joel L. Swerdlow *(e-mail: joel@jswerdlow.com), a former Wilson Center guest scholar, has been writing about medical topics for* National Geographic *for the past decade. He has written as well for the* Atlantic Monthly, Harper's, *and many other publications, and is the author of more than a half-dozen books of nonfiction, including* Nature's Medicine: Plants That Heal *(2000).* Ari D. Johnson *is an undergraduate concentrating in neuroscience at Brown University where he is a Writing and Rhetoric fellow and an editor of the* College Hill Independent. *The authors wish to thank Paul Ewald, a professor of biology at Amherst College, and Jennifer Hughes, an assistant professor of ecology and evolutionary biology at Brown University, for reviewing this essay.*

that guide the evolution of microbes striving to survive in our shared environment. Moreover, deforestation and the spread of industrialized society into previously isolated areas have facilitated contact among microbes that had formerly lived in separate ecosystems. A study in *Global Change & Human Health* (July 2000) concluded that "logging activities, hunting of non-human primates, and international travel are likely to increase the frequency at which novel microbes successfully enter the global human population." The rise of HIV and AIDS is an example of this phenomenon.

How and why some microbes began to make us sick remains a secret still locked inside the human and microbial genomes, but civilization itself is the leading suspect. Jean Jacques Rousseau took the improbable view that his "Noble Savage" lived with "almost no illness." It is probable, however, that by domesticating animals very early in the history of human development we came in close contact with microbes that became virulent once inside us. In his book *The Origins of Human Disease* (1988), Thomas McKeown states flatly: "We owe the origin of most serious infectious diseases to the conditions which led to our cultural heritage, the city-states made possible by the planting of crops in the flood plains of Mesopotamia, Egypt, and the Indus Valley." Civilization has its price.

HOW AND WHY SOME MICROBES BEGAN TO MAKE US SICK REMAINS A SECRET STILL LOCKED INSIDE THE HUMAN AND MICROBIAL GENOMES.

HIV, the virus that causes AIDS, comes from Africa's equatorial rain forest, as does the Ebola virus, which in Gabon seems to be marching slowly toward more populated areas. "We cannot abruptly move into entirely new environments without peril," health policy expert Marc Lappe writes. "The history of malaria, plague, Lyme disease, and exotic viral diseases such as Lassa fever and hemorrhagic fever [has] shown us that when we disturb the environment, we often imperil ourselves."

This history deserves emphasis because it runs so contrary to modern attitudes, which regard infectious diseases as calamities of nature, inflicted on us like a tornado or earthquake, rather than something we ourselves have helped to create by changing the environment around us. The new selective forces that the altered environment creates direct the microbes' evolution, sometimes encouraging an evolutionary path that leads to the emergence of new diseases or to changes in diseases that already exist. These processes have been going on for a long time. When the Spanish explored the Amazon River basin in 1562, for example, they reported nothing resembling malaria, which was soon to be—and still is today—one of the region's greatest killers. How does our disease-stimulating activity compare with that of other eras? It's "operating in high gear now," historian William H. McNeill wrote recently in a new preface to *Plagues and Peoples*, his classic 1976 study of epidemics from ancient Egypt to the present.

Associating disease with other forms of life is a relatively recent idea. Ancient

Greek writers attributed illness to spontaneously generated "putrefactive effluvia" in the air. Chinese healers believed that smallpox came from "womb poison" generated at the time of sexual intercourse. The first conceptual breakthrough came when 16th-century Italian poet and physician Girolamo Fracastoro argued that living seeds of disease traveled through the air. In the late 17th century, lens grinder Anton van Leeuwenhoek (1632–1723) observed that "animalcules" appeared under the lens of the microscope he had invented. But it wasn't until more than 300 years after Fracastoro that French chemist Louis Pasteur (1822–95) provided the framework for understanding these living things the naked eye could not see. Pasteur discovered that milk spoiled only when microscopic organisms were allowed to enter, and that, conversely, beer and wine needed such organisms to ferment properly. He demonstrated that microbes could be benign and useful tools as well as our deadly enemies. Pasteur's subsequent work on vaccines for anthrax and rabies proved conclusively that microbes cause disease in humans, replacing the theory, which had dominated Western thought for more than 2,000 years, that disease derives from imbalances within the body.

French chemist Louis Pasteur demonstrated that microbes could have useful purposes, but his work chiefly gave weight to the view of microbes as the enemy.

"Pasteur single-handedly spawned the antibacterial age," biologist Tom Wakeford writes in *Liaisons of Life* (2001). Darwin, who had lost a daughter to scarlet fever while writing *Origin of Species*, hailed the microbe-disease connection as the "greatest triumph" science had ever achieved. By the end of the 19th century, demonization of germs fueled sales of products such as Microbe Killer, a concoction that included red wine, hydrochloric acid, and sulfuric acid. By 1890, it had become so popular in the United States that 17 factories were needed to produce it. (The phobia continues to thrive today, as witnessed by the increasing number of antibacterial products found in supermarkets.) More significantly, scientists soon provided support for the germ assassin perspective by identifying the infective microbes associated with specific diseases, including tuberculosis, diphtheria, typhoid, cholera, plague, and malaria.

The solution to the problem of disease suddenly seemed straightforward: Identify the guilty microbe, then destroy it. In 1910 Paul Ehrlich, a physician and pharmaceutical researcher, discovered that a synthetic compound derived from

arsenic killed the microbe responsible for syphilis. "We must learn to shoot microbes with magic bullets," Ehrlich told colleagues.

A romantic aura began to shape the public image of the warrior-scientists fighting to protect us. "It is as sure as the sun following the dawn of tomorrow," proclaimed Paul de Kruif in his immensely popular *The Microbe Hunters* (1926), "that there will be other microbe hunters to mold other magic bullets, surer, safer bullets to wipe out for always the most malignant microbes."

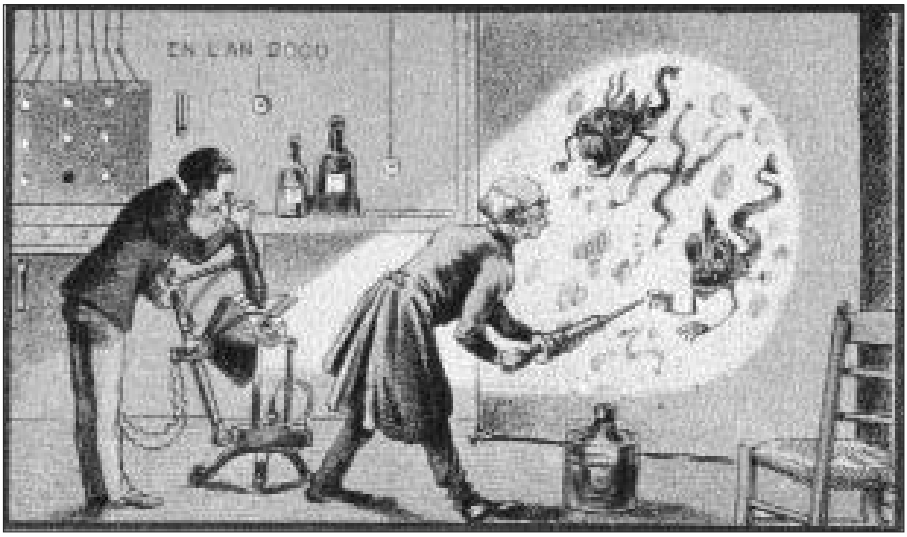
Penicillin, identified in 1928 by Alexander Fleming and first used on a patient in 1940, solidified the faith in magic bullets. Microbes were the enemy, and the human body was the battleground. To begin to sense just how welcome these magic bullets were, one need only remember 16-year-old Calvin Coolidge, Jr., son of the 30th president. In 1924, young Calvin developed a blister on his big toe while playing tennis at the White House. It became infected. As his fever rose, surgeons decided that it was too late to amputate his foot. They cut his leg open to the bone and drained the spreading infection. An anxious nation hung on the news bulletins. After a week of extraordinary pain, the boy died.

The generation that remembers the Coolidge story, and what it felt like to be so helpless, is past or passing. Their children and grandchildren, the baby boomers, came of age with antibiotics and experienced the sexual revolution with an if-you-get-it, penicillin-will-cure-it attitude. These antibiotics, together with vaccinations, prompted post-World War II experts to predict an end to infectious disease. The U.S. surgeon general proclaimed in 1969 that it was "time to close the book" on the problem. Macfarlane Burnet, who won the 1960 Nobel Prize in medicine for his work on the human immune system, said in 1972, "The future of infectious diseases will be very dull." Lewis Thomas, dean of the Yale Medical School, told students in 1976 that there were "no new diseases to be discovered." Five years later, when the U.S. Centers for Disease Control (CDC) reported the first deaths from what became known as AIDS, 250,000 people were already infected in the United States alone.

THE SOLUTION TO THE PROBLEM OF DISEASES SUDDENLY SEEMED STRAIGHTFORWARD: IDENTIFY THE GUILTY MICROBE AND DESTROY IT.

Today's young people have only known a world in which HIV makes sexual intercourse far more risk filled than it was in the years before Ehrlich found a treatment for syphilis. They also face the threat of drug resistance, which is taking a lot of the magic out of the magic bullets, sometimes rendering them useless.

Using antibiotics and other drugs to carpet-bomb our bacterial populations and kill them en masse creates enormous selective pressure that favors the survival, propagation, and evolution of microbes that can resist these attacks. Some abuses from the 1950s and 1960s—such as penicillin throat lozenges and adding antimalaria drugs to table salt in high-risk areas—seem incredible to us now. But abuses continue. According to the World Health Organization, two-thirds of all



In 1912, a French cartoonist envisioned "Germ Hunting in the Year 2000": find and kill.

oral antibiotics used worldwide are purchased without proper medical advice, diagnosis, or care. Moreover, people do not use them properly. One-third of U.S. pediatricians admit to overprescribing antibiotics to ease the concerns of parents and their young patients—even though resistance has been observed and well documented beginning with the first patient to receive penicillin.

At least one-quarter of all antibiotics used in the United States are employed in the food industry. The drugs prevent infection in animals and fish that are raised in crowded conditions, and, through mechanisms no one understands, they also stimulate growth. Apples and other fruit crops are commonly sprayed with antibiotics in an effort to combat microbial attacks. The result—not surprising in terms of human influence over microbial evolution—is that people acquire serious infections resistant to antibiotics they have never ingested *except in food they've eaten*.

As resistance to every known antibiotic increases, we continue to see ourselves in a war. "The enemy is invisible, furtive and gaining in strength and numbers," the CDC warned last year in "Plans for the New Millennium."* Just as in traditional warfare, new technologies promise to make killing easier and more effective. Like laser-directed "smart bombs," drugs based on the microbial genome will target biochemical processes with increasing precision. (Of course, smart bombs sometimes turn out to be not so smart.)

Among the possible new weapons are bacteriophages, viruses that can kill bacteria. Use of bacteriophages began in the early 20th century, but research stopped—except in the Soviet Union—with the advent of antibiotics. In Sinclair Lewis's 1925 novel *Arrowsmith*, researchers gasp at this "supreme way to kill pathogenic bacteria." Bacteriophages offer exciting prospects, but far from reason enough to think we'll win the war. We are instead merely escalating a race that lacks

*This is a chapter from the CDC's report *Emerging Infectious Diseases: A Strategy for the 21st Century*. The entire report is available at *www.cdc.gov/ncidod/emergplan/summary/index.htm#home*.

what military planners call an "exit strategy." Julian Davies, president of the American Society of Microbiology, strongly believes that "as competitors the microbes are unbeatable."

Nor will vaccines provide victory. "The evolution of vaccine resistance is almost as inevitable as the evolution of antibiotic resistance," biologist Paul Ewald writes in *Plague Time* (2000). Two examples: Rapidly evolving HIV has so far defied the efforts of our best brains and huge amounts of money; and influenza viruses evolve ahead of vaccines that are redesigned every year. Neglecting the impact of our efforts on such rapidly evolving microbes may make things even worse. Using mathematical modeling, researchers have demonstrated that partially effective vaccines—those that temporarily limit toxicity but do not prevent transmission to new hosts—can force the evolution of microbes toward increased virulence.

In 1973, biologist Leigh van Valen proposed "a new evolutionary law" which he called the "Red Queen Principle." Acknowledging that the principle simplifies reality, he cited the Red Queen's proclamation in Lewis Carroll's *Through the Looking Glass*: In Wonderland, everyone must run as fast as possible just to stay in the same place. Van Valen concluded that the evolution of multiple organisms is a race that "no species can ever win, and new adversaries grinningly replace the losers"—only to be replaced in turn. To think otherwise, van Valen wrote, is "wishful thinking, the imposition of human values on nonhuman processes."

What we are in fact doing may be worse than what van Valen imagined. By devising weapons of increasing technological sophistication just to stay in place, we escalate a race that soon weakens or renders useless even the most potent new drugs. This escalation is not inevitable. If we think and act in accordance with evolutionary principles, recognizing our role as the chief director for microbes in and around us, we can shut off the escalator.

But to do so, discipline is crucial. "A call for prudence and control has often been made during the past 25 years," microbiologist John Davison writes, "but has been largely ignored." The record does not give great cause for optimism, but there are ways to de-escalate. Possible strategies include:

- Choosing drugs that are less susceptible to resistance. All antibiotics do not work in the same way on the same types of microbes. For some drugs, resistance might develop within weeks, while other drugs might stay effective for decades.
- Ending abuse by the food production industries. The European Union, for example, has banned the agricultural use of antibiotics to promote livestock growth, if those antibiotics are also used in human medicine.
- Monitoring patient use of antibiotics. Programs that observe tuberculosis patients to ensure that they take all the necessary drugs throughout their six-month treatment regimen have significantly stemmed epidemics of drug-resistant bacilli.
- Screening for resistance. Genotype screening and genome mapping, though costly and time consuming, can identify those drugs that will be most effective against microbe strains that infect a given patient. These

Understanding Microbes

Microbes are often divided into four major categories—bacteria, viruses, protozoa, and fungi—each with its own characteristics. This article focuses on the first three.

Bacteria reproduce by splitting, and can pass through 30 generations, which would span considerably more than 1,000 years in humans, in as little as a single day. This ability alone gives bacteria the capacity to generate vast genetic variation by mutations of single base-pairs, the building blocks of DNA, with every generation.

Viruses and protozoa exhibit similarly short life spans, and to similar effect. Retroviruses are especially volatile because they carry their genes not in the stable double-stranded form of DNA, but rather in a more volatile single-stranded form that must be copied and integrated into host-cell DNA in order to reproduce.

The retrovirus HIV is the foremost example of rapid viral evolution in action. This volatility is amplified by the tendency of reverse transcriptase, the enzyme tool that HIV uses to copy and integrate itself into the DNA of its host, to make errors without the normal built-in capacity to correct them, thus creating a high frequency of random base-pair mutations in the virus. The frequency of such mutations is so high that if it were increased, the virus would not be able to function properly and propagate. Its rapid mutation rate causes so many different forms of HIV to develop quickly within each host that in each patient certain mutant forms of the virus are able to evade every attack by synthetic drugs and by the immune system. These forms, or strains, multiply and change in turn. Thus, once the HIV virus enters a human and begins to replicate, multiple different strains start evolving in response to selective pressure from immune responses and synthetic treatments. Much like Keanu Reeves stopping time in *The Matrix* to dance between bullets, rapid evolution allows HIV to escape any magic bullet drug shot at it.

Unlike bacteria and viruses, protozoa can replicate sexually, reshuffling their genes with every successive generation in a process called recombination. Compare the last 300 or so human generations spanning many thousands of years, with the 300 generations a bacterium, virus, or protozoan might run through in a week or two. Through this rapid succession of generations, microbes generate immense genetic variability.

But the awesome evolutionary capacity of bacteria and viruses extends far beyond the mutations of generational replication. In fact, much of the ability of viruses and bacteria to adapt rapidly to new environments stems from their ability to transfer genes laterally. Bacteria and viruses can acquire advantageous genes during their life span and pass them on—not only to their progeny but to vast populations of microbes of varying degrees of relatedness. Bacteria can acquire and spread genes

tests are particularly useful in determining treatments for such rapidly evolving infections as HIV.

- Using multidrug cocktails. These treatments reduce the chances of developing resistance because microbes are less likely to adapt to numerous drugs simultaneously.

Late in his career Darwin concluded, "The more I look at plants, the higher they rise in my mind." *Arabidopsis*, a common weed and the only plant whose genome has been completely mapped, teaches us one way to

not only from divergent species of bacteria but from viruses, protozoa, fungi, plants, and animals, and the environment.

Through unique processes, bacteria can pick up and incorporate naked DNA they encounter in the environment (transformation). They can also contact cells of other organisms directly. For example, a bacterium and a plant, or a bacterium and a yeast cell, could transfer genes in the form of highly mobile genetic elements—plasmids and "transposable elements," or transposons (conjugation). Finally, they can acquire new genes from other organisms through infection by bateriophages—viruses whose name means "bacteria eaters"—that can package microbial DNA and transfer it to bacteria, or to whole populations of bacteria (transduction).

Through these processes, virtually any gene sequence of any origin can be transferred to and between bacteria, blowing away the generational and species boundaries that limit the evolutionary rates of sexually reproducing animals. Imagine being able to acquire and exchange new genes through a handshake, or by picking them up off the street. All these capacities allow bacteria to generate and share immense genetic variation that, under selective pressure, can drive evolution at an unparalleled rate. Mechanisms of lateral transfer, such as plasmids and transposons, lie behind the rapid evolution of antibiotic resistance as well as the evolution of virulence characteristics in bacteria such as *Vibrio cholerae* and subspecies of *Salmonella*.

Viruses exhibit similarly dramatic adaptive abilities of genetic variance, as they are capable of capturing genes from any of the range of hosts they infect. A 1999 study published in the *Proceedings of the National Academy of Science* demonstrated that a plant virus infected an animal host and then recombined with an animal virus, to form an entirely new viral strain with a new combination of genes. In almost comic-book superhero fashion, microbes acquire special powers from one another, and even gain new powers, by combining or collaborating.

Scientists have recently discovered an extraordinary process that allows bacteria to use complex cooperation techniques to enhance their adaptive capabilities. Some species of bacteria have also evolved the ability to form single-species or multiple-species communities, in which they can build communal defenses and regulate communal expression of different genes based on population size or changing environmental pressures. These communities, called *biofilms*, now account for a high percentage of infectious diseases, and are virtually unaffected by all conventional drug therapies.

Underlying the vast diversity of the microbial world is unparalleled genetic variation. Such awesome evolutionary capacity reveals the extent to which the magic-bullet strategy for disease eradication underestimates the complexity and the power of microbes.

use natural evolutionary forces for our own ends. Plants, like humans, face constant assault by microbes, and respond, in part, by producing defensive chemicals. Researchers were surprised to discover that *Arabidopsis* rotates its antimicrobial chemicals instead of unleashing them all at once. When it changes chemical defenses, microbes that are expending extra effort to maintain genes resistant to the now-irrelevant chemical are suddenly at an evolutionary disadvantage and are far more likely to disappear—losing in the evolutionary competition to more efficient, nonre-

sistant microbes. Plant and human defensive systems have much in common, and many plants generate compounds that stimulate the human immune system—something achieved by only a small number of recently developed synthetic drugs. As more plant genomes are studied, more immunity-stimulating drugs are likely to emerge.

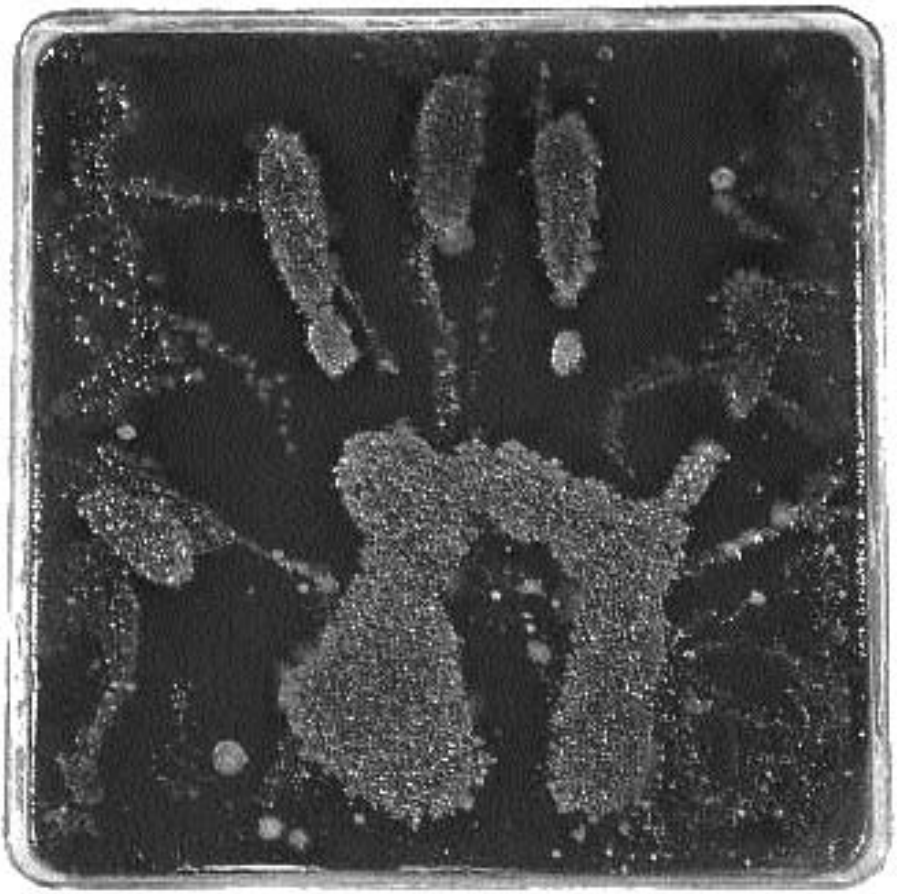
In the meantime, we can borrow techniques from *Arabidopsis*. Bacteria that are resistant to tetracycline, a widely used antibiotic, produce certain essential proteins more slowly than nonresistant bacteria do. Substitute another antibiotic for tetracycline, and the resistant bacteria suddenly find themselves at an evolutionary disadvantage. Eventually they disappear. The result, which can seem miraculous to both physicians and patients, is that resistance is reversed. When the patient takes tetracycline again, it works. Using similar procedures, doctors have also reversed resistance to the commonly used antimalaria drug chloroquine. Researchers are now working on ways to apply rotational techniques to the mounting challenge of multidrug-resistant infections that are spreading rapidly through intensive care units.

Rotational strategies could be particularly significant in poor countries. In Zambia, for example, where annual spending on health amounts to only $6.54 per capita, they would be invaluable. Tetracycline is one of the cheapest drugs available, while antibiotics to treat tetracycline-resistant infections can be prohibitively expensive. The same is true of chloroquine. Drug rotation, however, must be administered carefully. Studies indicate that if a single antibiotic is used too long, bacteria will evolve to resist it more and more efficiently. Using one drug in isolation for an extended period could thus create resistance that is even more difficult to reverse.

> With all that we are learning about how microbes evolve, why don't we strike at their evolutionary mechanisms?

A more effective way to kill microbes emerges from a question some evolutionary biologists have raised: With all that we're learning about how microbes evolve, why don't we strike at their evolutionary mechanisms? If therapies reduced, manipulated, or eliminated the evolutionary mechanisms of disease-associated microbes, magic bullets could more easily kill them.

"Drugs are evaluated on their potential to kill virus. Fair enough," biologist Stephen Palumbi writes in *The Evolution Explosion* (2000). "But the virus is not the only enemy we face. Another foe is the *evolution* of the virus, and few drugs are evaluated on the basis of their ability to kill this process. Furthermore, if drug resistance is inevitable, then by choosing drugs, we are in effect choosing the evolutionary trajectory of the virus. Why not use this opportunity to channel the virus into an evolutionary cul-de-sac and then let loose the pharmaceutical dogs?"



An agar plate displays the results of a bacterial test done on a person's hand. The human body teems with such microorganisms, which outnumber human cells 9 to 1.

Palumbi cites an HIV drug called 3TC that serendipitously can also reduce the genetic mutation rate caused by HIV's reverse transcriptase. By reducing genetic variability, 3TC slows HIV evolution and makes the virus an easier target. The most successful treatment strategies for HIV thus far, Palumbi notes, have combined drugs aimed at killing the virus with drugs that slow its evolution.

Or consider this: In order to evolve resistance to the newer antiviral drug ddI, HIV must shake off its resistance to the older drug AZT. So AZT and ddI could be administered together to take advantage of the virus's inability to resist both drugs simultaneously.

Some new drugs are able to disrupt bacteria's evolutionary mechanisms. The newest derivatives of quinolone antibiotics were designed to eliminate the prime culprits in the evolution of antibiotic resistance: the gene carriers called plasmids. Plasmids move between bacteria of the same and different species carrying genes that confer antibiotic resistance. Though these quinolone derivatives eliminate plasmids only when administered in dangerously high dosages, failure does not invalidate the strategy.

The growing scientific understanding of microbial evolution is also inspiring new strategies. Researchers have discovered that bacteria

throughout nature form *biofilms*, which are communities of single or multiple species that coordinate defensive strategies by "talking" to one another via chemical signaling. This helps them respond more forcefully and more quickly to threats from antibiotics or the immune system. One of their techniques is to produce chemicals that make the bacteria invisible to attacking forces until bacterial populations are large enough to develop communal protections.

Biofilms cause many intractable chronic infections, especially in the ear and respiratory systems. Antibiotics are designed to combat free-floating bacteria, so "biofilm bacteria are just about 1,000 times more resistant," explains biologist William Costerton, chair of the American Academy of Microbiology's Committee on Microbial Communities. Costerton and his colleagues are exploring how to strike not at bacteria but at their ability to form biofilms. Their tools include ultrasonic waves, as well as weak electrical and magnetic fields. These interrupt the signaling mechanisms and disrupt biofilms, leaving the isolated bacteria more vulnerable to attack.

As directors of microbial evolution, we can recognize that killing microbes is not necessarily the best way to eliminate disease. Rather than cut off their evolutionary legs, we can point those legs in a different direction, and give microbes reasons to evolve into harmless or even mutually beneficial relationships with us. If Pentagon scientists can "weaponize" microbes by making them more likely to cause and spread disease, why can't we turn the evolutionary engine in the opposite direction—in effect, domesticating microbes much as we have domesticated plants and animals?

Microbial domestication will require new ways of thinking, focused primarily on achieving a more balanced relationship with microbes. It runs contrary to the aims of most biomedical research and to the popular imagination, both of which are heavily invested in better bullets. Talk about balance can seem antiquated, even prescientific. "Why do Westerners want so much to always kill the microbe," asks an ayurvedic physician in India, whose system of knowledge dates back to the dawn of recorded history. "Live at peace with it."

Nobel laureate Joshua Lederberg raises much the same question when he notes that focusing so many resources and so much attention on killing the virus that causes AIDS "may have deflected less ambitious, though more pragmatic aims, including learning to live with the virus by nurturing in equal measure the immune system that HIV erodes. After all, natural history points to analogous infections in simians that have long since achieved a mutually tolerable state of equilibrium."

Progress does not always mean moving forward. To move forward in our relationship with infectious diseases, we must embrace notions of balance that have been eclipsed by Pasteur's germ theory and the quest for magic bullets. Science itself opens the door to balance by demonstrating how virulence evolves and can be manipulated. Public-health reforms that reduce the possibility of microbe transmission—by, say, keep-

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ing sewage out of the water supply or encouraging safer sex practices—are one way of directing the evolution of microbes away from virulence. The fewer transmission opportunities a microbe has, the more evolutionarily advantageous it is for that microbe to preserve the health of the person upon whom it depends.

This transmission-virulence theory, developed over the past two decades by biologist Paul Ewald, rests on the observation that, in many cases, the more opportunities microbes have to move between hosts, the less dependent they are on each host. And the less dependent they are, the more prone they are to exploit and kill the host.

Microbes are not vindictive; they're just using available resources to survive, exploiting us somewhat the way we exploit the land by strip-mining. Because we are not immediately dependent upon preserving a particular terrain for our own survival, ripping it open to obtain resources to further our own survival is appealing. Microbes don't kill us for fun any more than we strip-mine for fun.

Vibrio cholera, a bacterium associated with cholera, demonstrates how this works. This bacterial species spreads easily through water, even when its human hosts are so sick they cannot move from their beds. After infecting a person who drinks contaminated water, the cholera bacteria replicate rapidly. This proliferation inside a human digestive system triggers acute diarrhea, sending large populations of cholera bacteria through the water supply to many new hosts, continuing the cycle. To *Vibrio cholerae*, humans need be no more than an expendable resource to facilitate its replication.

But if drinking water is clean and waste is disposed of hygienically, viru-

lence no longer offers cholera the same evolutionary advantage. Unable to move easily from one person to another, the bacteria must link their own survival more closely to that of their hosts. Thus, the most virulent strains of cholera are found in communities without effective sanitation systems. Areas with better sanitation systems report cases involving much less virulent strains.

Could the virulence of sexually transmitted diseases correlate with ease of transmission? The most serious and widespread type of HIV, HIV-1, emerged from Central Africa, where studies show that sexual practices favoring transmission of the virus are more common than in West Africa, where the relatively rare, less virulent type, HIV-2, emerged. Similar correlations occur even within each HIV type. Supporters of the transmission-virulence theory assert that HIV-2 is less virulent in Senegal than in Ivory Coast because sexual transmission is less likely in Senegal.

BLOOD TESTS INDICATE THAT SOME PEOPLE HAVE HAD THE EBOLA VIRUS IN THEIR BODIES BUT HAVE NEVER SHOWN SYMPTOMS OF THE DEADLY EBOLA HEMORRHAGIC FEVER.

Great mysteries remain. The poliomyelitis virus, for example, usually lives in the gut and spreads to new hosts by leaving the body through feces and entering the mouths of people who come in contact with the fecal matter. The virus causes disease only when it invades the host's nervous system. What would drive the virus to invade the host nervous system, harming its host without increasing its chances of transmission to new hosts? Further study is necessary to test the transmission-virulence theory and address such paradoxical situations.

Understanding the evolution of virulence may ultimately help us identify the source of the chronic infectious diseases that seem to afflict a growing percentage of the world's population. It would be important to know, for example, if acute diseases evolve into chronic diseases because microbes ratchet down their virulence so that they can keep living inside their human hosts.

The transmission-virulence theory ties virulence to a dynamic relationship between humans and microbes. It thus defies the traditional understanding of virulence, which to some extent persists today. *Virulence* derives from the Latin *virulentus*, meaning "full of poison." As the name suggests, virulence since the advent of germ theory has been seen as the product of microbes' ability to deliver disease-causing poisons.

Genomic research demonstrates that microbes evolve what scientists call "virulence characteristics," mechanisms that facilitate the transfer of genes to other microbes. One example is "pathogenicity islands," clusters of genes that increase microbial virulence. These genes can be transferred by a variety of carriers including the previously mentioned plasmids.

But recent studies indicate that virulence cannot be explained by inher-

ent microbial characteristics alone. To cite a few examples: One-third of the world's 6.1 billion people carry the tubercle bacillus, but 90 percent will never develop active tuberculosis. In the United States, studies indicate that bacteria involved in spinal meningitis live harmlessly inside the noses of one-quarter of everyone in the country. Similarly, heliobacter bacteria cause peptic ulcers, yet half the population is estimated to harbor them. Blood tests indicate that some people have had the Ebola virus in their bodies but have never shown symptoms of the deadly Ebola hemorrhagic fever.

As such examples demonstrate, it is impossible to group microbes strictly into "virulent" and "nonvirulent" categories. "Virulence"—the capacity to cause disease and a measure of the seriousness of that disease—is one of many possible results of a dynamic interaction between immune system and microbe. Virulence emerges both from microbial characteristics and human characteristics, and hence from the interaction between the two.

Thus, we cannot properly say microbes are "disease causing" or call microbes "pathogens." Microbes are not pathogens that cause disease. A particular relationship causes microbes to have a pathogenic effect. We must learn a new vocabulary to describe infectious disease. Only then will we be able to explain why most "virulent microbes" seem to cause disease for only a tiny percentage of the people in whom they live.

"We need to consider the big picture," the editors of *Science* noted recently. "People are not infected with one organism alone—we are host to communities of many species, most of which do us little harm. We need to spot the shift in the dynamics between microbe and host that tells us when harm might follow." Joshua Lederberg believes we should also replace "the war metaphor with an ecological one," concentrating on why most microbes don't make us sick.

In the early 20th century, researchers who were not even thinking in evolutionary terms developed a vaccine for diphtheria whose functioning demonstrates how we can benefit by shifting the dynamics between microbe and host. The principles and mechanisms are straightforward. Diphtheria bacteria infect the respiratory tract and generate a toxin that kills respiratory cells, from which they obtain nutrients. To make this toxin, Ewald explains in *Plague Time*, the bacteria use perhaps five percent of their protein resources. The vaccine contains a mutated toxin that triggers an immune response. Should diphtheria bacteria appear, these antibodies rush into the respiratory tract and sequester the newly appearing toxins before they can kill respiratory cells. The bacteria that continue the production of toxins—now a useless drain on resources—are put at an evolutionary disadvantage. Soon, almost all of the diphtheria bacteria that are left circulating in the vaccinated population are those that do not produce the toxin.

Today, new technologies prepare us to apply this evolutionary model more widely. Although not yet consciously applied to the host-microbe relationship, research in directing evolution has been underway on a molec-

ular level for at least a decade. Chemists, for example, have been placing libraries of different proteins under selective pressure in laboratory environments and developing compounds for industrial and therapeutic purposes. Microbiologists have similarly directed the evolution of RNA—single-stranded DNA—toward novel biological functions.

To improve host-microbe relationships by directing the evolution of microbes, researchers must understand them genetically. New DNA microarray technology can measure the actions of large numbers of genes that carry the code for the human immune system, for microbes related to infectious disease, and for microbes that live normally inside us. Knowledge gained from such measurements could facilitate the development of vaccines like the diphtheria vaccine as well as strategies to stimulate specific elements of the immune system.

Research into the structure and function of particular genes is already producing surprising results. Because of mechanisms not well understood, a genetic mutation that causes the pneumonia-related bacterium *Streptococcus pneumoniae* to resist penicillin also reduces or eliminates the bacterium's virulence. Thus, while penicillin resistance may now limit the drug's use as a microbe *killer*, penicillin could become a tool for directing the evolution of pneumonia bacteria away from virulence.

MODERN SOCIETY HAS GROWN ACCUSTOMED TO ASSUMING THAT WHEN PROBLEMS APPEAR, SCIENCE OR TECHNOLOGY WILL PROVIDE THE NECESSARY FIX.

We can also manipulate the competition *between* microbes that occurs inside the human body. Researchers in northern and western Thailand have observed that the reproduction of HIV is slowed in AIDS patients who also suffer from a disease called acute scrub typhus, a potentially fatal bacterial infection. No one advocates using scrub typhus as a form of treatment for HIV, but clearly there is a mystery here worth probing. As microbiologist and immunologist Cedric Mims puts it, "Successful microbes know more about immunology than do the immunologists!"

"Probiotics"—bacteria administered as medicine—are an increasingly popular means of taking advantage of this ubiquitous competition between microbes. One of the earliest advocates of probiotics was immunologist Elie Metchnikoff (1845–1916), who championed the benefits of sour milk. Metchnikoff drank sour milk in astonishing quantities to chase out intestinal invaders. More than a century later, researchers are finding mounting evidence that lactobacilli, the bacteria found in sour milk, can sensitize the human immune system early in life, preventing allergies by keeping it from attacking harmless or helpful foreign bodies.

To cite another example: Alpha-streptococcus bacteria normally colonize the tonsils, making it difficult for other types of bacteria to enter in ways

that would cause ear or respiratory infections. Antibiotics, however, often knock out alpha-streptococci, making people more susceptible to such infections. Administering alpha-streptococci along with antibiotics is thus one way to protect patients from infections.

Modern society has grown accustomed to assuming that when problems appear, science or technology will provide the necessary fix—even when science and technology themselves have caused or exacerbated the problem. In the case of infectious disease, solutions driven by science and technology do indeed exist. They begin with new concepts: Virulence arises from the relationships between humans and microbes, not from microbes alone. We can direct the evolution of microbes in more benign directions. New discoveries, furthermore, will soon lead to practical applications. As we better understand the selective forces generated by drugs, the immune system, and the body's microbial community on a genetic level, more opportunities will arise to control these forces and direct the human-microbe relationship away from virulence.

The National Intelligence Council report cited in the opening paragraph of this article mentions none of this, even in its "Optimistic Scenario," but we do not need an intelligence report to begin to act. When germ theory emerged in the late 19th and early 20th centuries, people started to wash their hands more often and took other steps to improve sanitary conditions. Hospitals adopted measures to protect patients from infection. Researchers began to look for the guilty microbes and the weapons to kill them. As we recognize that we can direct microbial evolution, we will make the provision of clean water and the disciplined use of antibiotics much more of a priority. These are things we already know we should be doing anyway. And instead of focusing research on killing microbes, more and more scientists will search for ways to improve our relationship with them.

In adopting this approach, we will regain something that has been lost as we've grown more sophisticated. In the *Iliad*, Greek warriors defy instructions from one of Apollo's priests, and the angered god sends an invisible "deadly archer" who kills warriors until "corpse fires burned on, night and day." Only when the priest's instructions are obeyed does the archer leave.

The story may sound primitive to the modern ear, but the ancient Greeks embraced a truth that we too often ignore: Some rules cannot be violated without grave consequences. For them, defying the gods proved disastrous; for us, defying nature's ineluctable laws of evolution will bring us to the same awful end. It is our task to understand these laws and apply them in ways that best serve our interests.

Darwin published his epochal *Origin of Species* 143 years ago. But more than 8,000 years before that, people with only primitive technology and no written system of knowledge saw possibilities in wild jungle fowl. They began to breed them selectively, eventually producing what we now call chickens. As we face challenges with stakes that are immeasurably higher, we must do what they did: make evolution work for us, not against us. ❑