Bioterrorism and the threat of Microbial Disease: Dealing Rationally with “The Rationality of That Which Threatens Life”

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The rationality of life is identical to the rationality of that which threatens life.
— Michel Foucault, Birth of the Clinic.

To understand how best to prepare for Bioterrorism, it is necessary to understand the nature of microbial life as distinct from our own. Toward that end I have prepared this brief introduction to the immune system, the biology of infection, the notion of domesticating microbes by vaccination, the futility of any drug-war against microbes, and the policy implications of these biological facts.

The Immune System

Though our minds work as if each of us were a single, autonomous entity, the body is permeated with other, invisible lives. Most of these intimate neighbors respect the skin as a boundary between themselves and our cells, but some do not. Dry on the outside and moist within, the continuous coat of dead skin cells that separates the body from the world is constantly breached by microbes, some of whose lives depend on getting inside one of the live cells beneath it. They usually do not get very far beneath the skin before they are met by cells from the body’s immune system. As a tissue, the immune system is as big as the brain and spinal cord combined. It is less noticeable than the brain only because it is not in one place but spread under the skin, the better to find and kill invading microbes before they can establish a beachhead. If the brain is the center of the neural networks, the gut comes closest to being the center of the immune system: more than half

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of the immune system's cells lie just beneath the moist skin lining the tube that runs from lips to anus.

The immune system is similar to the nervous system in many ways: it is about as large, it is about as complicated, and membrane-bound receptors on some of its cells give the system as a whole a comparable capacity to sense and respond to changes in the body's situation. The main differences are that the immune system is designed to sense changes in the body, while the nervous system senses changes outside it, and that the immune system is not linked to the brain's cortical processes we call consciousness, so its operations are for the most part odorless, tasteless, and invisible — in a word, insensible. Because the brain is not directly wired to the immune system, we cannot notice whether or not a microbe has gotten past the skin. We sense an invading microbe only when the ensuing interaction between microbe and immune cell generates the symptoms of an infectious disease.

**Infection**

The smallest and simplest of infectious microbes are the viruses. A virus can cause the symptoms of a disease only after it has found its way into one of the cells that make up a person's body and begun to reproduce. Viruses with fewer than a dozen genes or more than a hundred are rare. Bacteria are many times more complicated and larger than viruses, though still far smaller than any of our cells. With thousands of genes on their chromosomes, they are complex enough to live on their own. Most kinds of bacteria are finicky, growing only under narrowly defined conditions. For thousands of bacterial species, these conditions are best met somewhere in our bodies; for the most fastidious, nothing less than the inside of one of our cells will do. The most complex microbes are the protists: single large cells with the same architecture as one of our own cells, complete with a nucleus holding chromosomes that contain tens of thousands of genes. Like the bacteria that find our bodies hospitable, many protists grow best — or only — inside one of our cells.

Regardless of the particular symptoms, each case of an infectious disease is a Darwinian struggle for survival between microbes and the cells of our immune system. Each infection can have only one of three outcomes: the microbe dies, the person dies, or the microbes and the immune system reach a truce. Microbes and immune system cells bring the same weapons to this struggle for survival: evanescence and genetic malleability. Just as every brain changes its synaptic connections in response to life's experiences, every immune system is constantly retuning itself. When a person recovers from an infection, it is because the infecting microbe has selectively stimulated the growth of cells from the immune system with the capacity to recognize it, neutralize it, and then remember to do so if it reappears. The persistence of a very low dose of the infectious microbe is a goad; in cases where there is complete microbial obliteration, there is also a loss of immune memory and the risk of serious disease the second time around.

Microbes have different ways to get past our defenses as they move in and out but only one way to grow: simple division. One microbe can become two, and two four, in an explosive chain reaction of growth that can overwhelm an infected cell in a
few minutes and an infected body overnight. Like our own germ cells, most microbial offspring are destined to die without leaving any trace. Just a few need to survive and infect another person in order to keep the microbial species going. All microbial strategies for survival in the body are built on the same basic plan of infection and reinfection: seed one body, multiply in it, seed the next.

Interludes of reinfection are as essential to microbial survival as children are to the survival of our species. All successful microbes have found ways to negotiate the leap from one person to the next, that is, to be contagious. Contagion makes even the most dangerous microbes depend on our behavior, putting them in an unavoidably precarious ecological situation. In the few weeks of a flu infection, for instance, hundreds of generations and billions of viruses will be born inside the cells lining a person's bronchial tubes and nasal passages. All but a few of the virus particles will die in the body or be sneezed out to dry to death in an inhospitable Kleenex. But so long as a single virus makes it from one of the victim's cells into another human cell — the victim's or anyone else's — before dying, the population of viruses will survive and persist through time.

Like songbirds in a suburb, infectious microbes are a metapopulation, living on islands — backyards on the one hand, sick people on the other — separated by hostile territories in which they cannot survive for long. Microbial metapopulations no more demand the suffering or death of an infected person than avian ones demand the loss of woodland. Birds maintain metapopulations by migratory flights before nesting, and microbes do the same. Just as songbirds may disappear from one neighborhood as they migrate to another, microbes die off when a person either gets well or succumbs to the disease. The symptoms of illness induced by a microbe often occur simply because they help it to reach another host. For example, cholera bacteria do not benefit because the diarrhea they cause leads to the death of their host but because the diarrhea spreads the bacteria around so quickly and widely that some have a good chance of reaching a new intestinal environment, even if the infected person dies in only a few days. Other microbes follow a waiting strategy, walling themselves off from a hostile world as spores until they can get inside a susceptible body; for example, anthrax spores can remain viable for decades in dry soil and then germinate to cause a serious lung disease when a few are finally inhaled.

Flying creatures — birds and insects — establish the most wide-ranging metapopulations, passing over large inhospitable areas to establish small, temporary pockets of fertile growth. Some microbes have adapted to a flying host's tissues as well as our own in order to expand their capacity to establish their own metapopulations in people. A bird or an insect can bring a microbe from one person to another, when by themselves few pairs of people would make sufficiently intimate contact to accomplish the microbial handoff. Insect-borne microbes can create great misery over a wide area because their insect host can transport them miles away to their next human host even as their current victim lies immobilized by illness.

The malaria parasite, for example, grows so well in red blood cells that even a mosquito bite's worth of blood from an infected person will be loaded with parasites ready to be transferred to the mosquito's next victim. But without the mosquito, these parasites are all marooned in the sick person's body, unable to reach a fresh supply
of red blood cells. The two-host strategy works for bacteria and viruses as well as protists: epidemics of mosquito-borne yellow fever, louse-borne typhus, and flea-borne plague are examples of microbial metapopulations moving very rapidly from person to person inside their second hosts.

**Survival by domestication: vaccines**

Whatever their strategies for contagion, all successful microbes must also elude the immune system. Immune cells called macrophages will ingest any microbes they find, informing other immune cells of the invader so that they can zero in on infected tissues, killing any cells already harboring a nest of growing microbes and marking the infected area with chemicals called cytokines for later rescreening. The power of the immune system is unleashed by microbial growth; it cannot be exerted if a microbe gets into a cell and simply sits there. Recovery from microbial infection is rarely a total victory of the immune system over a microbe. More commonly, it is the cold peace of mutual coexistence between an armed immune system and a genetically unstable, ever-shifting population of temporarily domesticated microbes.

In establishing this compromise with infectious agents — grow and I'll kill you, sit around and I'll leave you alone — the human immune system has encouraged the differential survival of the slow-growing, well-hidden variants of many contagious microbes. Sometimes the compromise leads to true domestication, but if a microbe comes out of hiding and begins to grow, it can do a lot of damage. The microbe responsible for tuberculosis, for instance, audaciously sets up house inside the very immune cell that catches it as it enters the lining of the lung. There it lives in suspended animation, surviving for decades without causing symptoms, just in case it has the chance to flower into rapid growth — causing the immediately devastating, acute symptoms of tuberculosis — should the host's immune system for any reason begin to fail.

Microbial genetic variation coupled to changes in human behavior can lead to entirely new means of contagion. A few centuries ago the plague bacterium mutated into a form that could live well in a person's lungs, moving from a sick person to a well one by a cough, as if it were tuberculosis or the flu. This variant, called pneumonic plague, no longer needed to pass through a flea to get from one person to the next. In the new, unsanitary cities of medieval Europe, pneumonic plague killed about one person in three before it died out for want of new, immunologically vulnerable hosts.

Microbes continue to adapt themselves to our changing habits. Each new infectious disease is a new perturbation in the equilibrium between our species and the microbial world. Our behavior can shift the equilibrium, for better or worse. Travel, for instance, shifts the equilibrium in favor of a new microbe by giving it new chances of finding its way into a body with a naive immune system; every new way we invent for traveling about the planet makes us more vulnerable to emergent diseases. When plague emerged in Europe about seven hundred years ago and killed about a third of the population, it had traveled at about three miles a day from Asia, and the trip took about a thousand years. When European explorers brought smallpox and measles to the New World five hundred years ago, the trip took a year by ship. Cholera went by boat from Asia to Peru in a few weeks. Two decades ago, an emergent virus called Ebola flew from
Africa to a laboratory in Virginia in a few hours in an inadvertently infected monkey being shipped to a research laboratory. Insect vectors travel with us as well: a survey of sixty-seven airlines arriving at Heathrow Airport in London a few years ago found healthy insects — including mosquitoes — in the wheel wells of about one airplane in twelve.

All people are potential vectors, carrying new pathogens in and on their bodies as well as in their luggage. Because the environments and the immune memories of people from different places are different, each is likely to carry a different spectrum of pathogens. As people from different parts of the planet mingle in airports and cities, microbes that live on the skin and all variety of intestinal flora get a chance to jump around and to test a range of human environments they would never see in the natural course of events. In 1800 fewer than two percent of the world's population lived in cities; by the year 2000 — the population as a whole having increased by more than a hundredfold in two centuries — more than half of all people were living in cities, and five hundred or more of those cities each house more than a million people. Besides accelerated growth, the other hallmark of the twentieth century — total, mechanized war — has provided particularly attractive opportunities for microbial variation. The more people, the more habitat islands for any human pathogen; the more complete a war, the less medical interference to their spread.

In peacetime, the growth of cities and the widespread conversion of forest edge to suburb bring many people into contact for the first time with insects and birds bearing novel microbes: Lyme disease is an example of deer, mice, ticks, a bacterium, and people all meeting together for the first time. At the same time, one major large-scale consequence of our numbers and our reliance on fossil fuels for transportation and industry — a global increase in average annual temperature — has brought tropical insect vectors into temperate climates, allowing mosquitoes to bring malaria to large numbers of new, uninfected people.

Our own chromosomes are the most elegant hiding place of all for the genes of any microbe clever enough to insert its DNA into one of them. If even a piece of a microbe's DNA can find its way into a chromosome in one cell of the body, it can then piggyback its own copying onto the copying of the cell's DNA and so always be present in all the descendants of that cell. HIV — the small virus responsible for the symptoms of AIDS — does this quite well: it tricks an immune cell into seeing viral genes as its own by inserting itself into chromosomal DNA. From then on the virus has no need to do anything; every time the cell divides, it makes new copies of the virus's genome. The most clever of all hiding places is the DNA of a cell that makes sperm or egg cells: from such an eyrie, microbial genes can be assured of survival for as many human generations as the human family of their choice continues to propagate successfully. They never have to spring out and confront any descendant's immune system. Once in the germ line, a microbial sequence need never function at all in order to survive indefinitely. The result of such luxury is degeneracy: the human genome is riddled with nonfunctional sequences that had once been potentially virulent microbial genomes until random mutation destroyed their meaning.
Example 1: smallpox and the original vaccination

Vaccination — the intentional, preemptive infection of a healthy person with a benign, domesticated version of an infective agent — prepares the immune system for later, more dangerous infection. Vaccines were developed more than two centuries ago in response to the smallpox virus, well before the discovery of the virus itself or of the immune system. Before vaccination, a runaway smallpox infection was a miserable experience, with disfiguring scars on the skin as the mildest outcome and death as a serious possibility.

The smallpox virus grows so rapidly beneath the skin that the cells it kills merge into blisters filled with clear, viral soup. The fragility of the blisters makes them excellent vehicles of contagion, delivering an infectious dose of virus to any breach in the skin of a person touching one of them. The blisters defined the disease: smallpox survivors would always have deep pits — eponymous pocks — at the sites of their blisters. Experiments carried out in the late 1600s — the sort of experiments we now consider to be acts of criminal irresponsibility — showed that a relatively mild case of smallpox would result from putting a tiny bit of the fluid from a victim's sore onto a scratch made in an uninfected child's skin.

The intentional administration of a potentially lethal infection — called variolation, after variola, the name of the disease at the time — did in fact work, at least some of the time. A variolated child usually would get a mild case of smallpox, with a big pock at the site of the inoculation, but then be immune to further infection, surviving any number of subsequent epidemics that might swirl through a city like London or Berlin. There were problems with the technique. Sometimes the variolation would simply kill the child; more often variolated children would themselves get well but be sufficiently infectious for a time to trail a wake of lethal infections as they recovered from their own illness. The first recorded variolation in the United States was performed by the Reverend Zebdiel Boylston on his son and two of his slaves; there is no record of the good reverend trying it out on his own body.

By making a single, subtle change in the accepted procedure of variolation, the British physician William Jenner created the first vaccine. “Vaccine” is taken from the French for “cow,” because the first viral domestication was the unexpected consequence of people and cows living in close quarters. Farmers and milkmaids who drew milk from a cow often survived their first smallpox epidemic without any disease at all. Jenner knew that protection depended on their having been exposed earlier to cowpox. Cows infected by the cowpox virus would have pocks on their udders that quite resembled smallpox lesions, and as they were milked, these pocks would spread the virus to the milkers' hands. Exposed milkers would experience a cowpox infection as a mild fever and rash and thereafter bear a few, small pocks. It is one thing to notice that milkmaids are protected from smallpox by their cowpox scars; it is quite another to propose to infect someone with cowpox to see if it would protect them against smallpox as well. Oddly, the idea of infecting a person with a cow's virus bothered the very doctors who were happily infecting people with smallpox by
variolation. Experimenting on people with live viruses seemed not to be a problem, but the notion of mixing living material from different species was.

In the late eighteenth century, a doctor could still do pretty much what he wanted as long as he was a British gentleman, so Jenner was free to intentionally infect his children and servants with cowpox by scratching some of the fluid from an infected udder into their arms. The uncontrolled, unethical “experiment” worked. His cowpox-infected children and servants first developed a mild set of symptoms, then one small pock at the site of the infection — the first vaccination mark. Thereafter they could go through epidemic after epidemic of smallpox without any ill effects while their unvaccinated friends and relations sickened and even died.

Jenner's vaccinations depended on a sick cow, a pharmacopoeia too fraught with uncontrolled variables even for that time. His solution for maintaining the vaccination material was as novel and as radically inconsiderate as his initial decision to try the cowpox on his children: he always made sure to have a freshly vaccinated person on hand so that he could vaccinate new people with the material from the recovering person's vaccination sore. To bring his technique to the United States and India, he used relays of immigrant children, vaccinated from one another on the journey. The pox-virus odyssey ended in the mid-1800s, when someone infected the udder of a cow with fluid from a newly vaccinated person's sore and thereafter used the cow's sores as a source of vaccination material. That trip — from cow to human and back to cow — created the vaccinia virus. In its travels, vaccinia has accumulated a very large set of genetic differences from both smallpox and cowpox viruses, but it was never a wholly safe agent to administer. Preparations differed in potency, and the intentional infection sometimes raged into a fairly good imitation of smallpox itself.

Despite this checkered past, vaccination using stable, standardized preparations of vaccinia eradicated smallpox by the early 1980s. Killing smallpox took a hundred million free vaccinations as well as twenty years of unprecedented and subsequently unmatched international cooperation. In 1967 there were a million deaths from smallpox worldwide; in 1980 there were no deaths and no cases were reported. The very last recorded death from smallpox in the West did not involve infection: in 1978, after a technician at a virus-stockpiling laboratory in England died of inadvertent infection from an archival strain being handled in the next room, the laboratory director committed suicide in his disgrace.

Vaccinia remains alive and well, and it is the subject of intensive research aimed at using it as a vehicle for the introduction of single microbial genes that would convert it into a benign Trojan horse, useful for “vaccinating” a person against any number of other infectious agents. Smallpox remains in suspended animation in a few laboratories, preserved by scientists curious to know the relationship of its virulence to its DNA sequences; although the move to destroy the last stocks gains force every year, the argument that its sequence should be obtained first has so far held sway. Smallpox was conquered by the cooperation of hundreds of millions of people acting in their own interest, not by any particularly elegant basic medical science. Even with our immune systems at work inside us, we needed mass education, a willingness to come clean about the presence of the disease, and a gift from the industrial world to its poorer parts of
hundreds of millions of doses of an effective if poorly understood vaccine to eliminate smallpox completely.

Example 2: Tuberculosis

Medical science has not eliminated any other infectious agent. Some, like the bacterium that causes tuberculosis, the parasite that causes malaria, and the virus that causes AIDS, are currently killing vast numbers of people each year. Tuberculosis and malaria are the most prevalent microbial diseases we face today, and neither has yet been domesticated into an effective, live vaccine. Until a decade ago, antibiotic chemicals that kill microbes even as they hide inside a cell seemed to be the perfect complement to the immune system and its boosters in dealing with such bacterial diseases. By getting inside a microbe or an infected cell of the body and specifically blocking a step in the growth of a virus, bacterium, or parasite, an antibiotic can deliver a clean and complete cure, removing an offending microbial population down to its last evanescent individual. But antibiotics are also agents of natural selection, and the microbial strategy of survival through mutability and evanescence thrives on the challenge of a simple chemical. In their initial success, antibiotics destabilize the equilibrium between an immune system and a microbe, first in a favorable direction, but then sometimes tipping the balance against us. The rare microbe born at random with a mutation freeing it from the grip of an antibiotic will overgrow its dying cousins, producing no recovery but rather a new, antibiotic-resistant infection.

Although the outer wrapping of a tuberculosis bacterium is the steel-belted radial tire of microbial membranes, impenetrable by most antibiotics that work against other bacteria, about a dozen specialized drugs have been found to halt or reverse a tuberculosis infection. One, called INH, is capable by itself of stopping full-blown tubercular overgrowth; the others are less effective. INH worked so well in the 1970s — and strains resistant to it were so rare — that it was assumed that tuberculosis had been conquered. The notion that an organism with the capacity to outwit the immune system would not be able to mutate into a state of INH resistance was willfully naive. Like all other microbes, the tuberculosis bacterium turned out to be a minimalist at self-defense: a single mutation rendered it completely resistant to INH. In 1986, just as tuberculosis was beginning to surface in AIDS patients, the United States government's Centers for Disease Control and Prevention — the CDC — took a step that cannot be explained except as an example of deep and pervasive institutional denial: it ceased to require hospitals to report cases of INH-resistant tuberculosis.

The timing could not have been worse. With this decision, INH-resistant tuberculosis was given the time and chance it needed to send forth variants that would be resistant to other drugs as well. Drug-resistant tuberculosis killed many patients in public hospitals in the 1980s, especially the ones who were too sick with AIDS, too confused, or too disorganized to take their tuberculosis medicines long enough after a first bout of the disease. At the end of the 1980s, multiple-drug-resistant tuberculosis was the most common way a person with AIDS died. The CDC caught up with INH resistance by requiring that any person showing symptoms of tuberculosis take a cocktail of four drugs including INH for six to twelve months. If that mix did not make matters better after a
few weeks, it was to be replaced by a second formula using the remaining seven drugs known to work against the microbe.

Given the contagious nature of full-blown tuberculosis, every one of us is at the mercy of a patient taking either of these cocktails, which must be taken for a full year after they clear up the symptoms of tuberculosis. If a patient takes the drug only until the symptoms diminish, the remission will fail: unless the drugs are given in high enough doses and for a long enough time to kill all tuberculosis bacteria, the ones that survive are all but certain to come back when the drugs are stopped and cause a new round of tuberculosis. Worse, any drugs that are stopped prematurely once are more likely to fail should they be tried a second time, because the bacterial population that survives the first round of treatment will be enriched for drug-resistant variants.

Today, doctors and public health officials in many large American cities no longer hand out drugs to tuberculosis victims. Instead, they require that patients be observed taking their medicine every day. Directly Observed Treatment, Short-Course — DOTS — is remarkably effective in assuring that a person infected with tuberculosis will follow the full regimen of drug treatment and not be the incubator for a new drug-resistant strain of the microbe. Even though it offers no further insight into molecular mechanisms of resistance, DOTS seems to protect against the tuberculosis microbe's strategy of adventitious genetic variation. It is a good example of the utility of acknowledging and working with a microbial strategy, instead of waiting for an endless stream of new antibiotics to save the day.

DOTS has not been widely used outside the inner-city tuberculosis clinic. Because such a large percentage of tuberculosis patients are people in poor nations, the wealthy nations of the world would have to spend a large amount of money to stockpile and deliver the drugs needed to carry out DOTS therapy in a complete, orderly way. So far this has not become part of the scientific agenda of the wealthy nations that do fund medical treatment in the world's poorest countries. Consequently, three million people — almost all of them in poor countries — die of DOTS-treatable tuberculosis each year; half a million of them are children.

**Example 3: Malaria**

The malaria parasite lives well in the human body through a different strategy: it is notorious for the ease with which it escapes the immune system, which recognizes the parasites by the proteins on their coat. People usually have no difficulty mounting an initial immune response to a malarial infection, but then their immune systems simply cannot keep pace with the parasite as it picks new combinations from its genes to make altogether new coat proteins. A variant parasite whose new coat allows it to slip past the immune system will always take advantage of its moment of freedom and fill the body with its progeny. This genetic malleability is more than a match for the immune system's own ability to turn on a dime, and so far it has kept us from finding an effective vaccine for malaria. It is so delicate that we cannot yet grow it in a pure culture and still must do experiments in infected animals. Some laboratories have tried purifying some of the outer proteins of the parasite and making vaccines out of synthetic fragments of them, but
neither these, nor any vaccines made from isolated parts of the parasite, have shown more than marginal effects in the field.

Current research on malaria has focused on a search for effective antibiotics. Quinine — drunk in some cultures as an extract of tree bark and in others as a gin-and-tonic — is a prescientific antimalarial drug of some usefulness and the template from which most other antimalaria drugs are built. The quinine family of antibiotics all work the same way: they force the parasites in a red blood cell to choke on their own gluttony. After finishing off the red blood cell's hemoglobin, the parasite has to spit out the molecule's indigestible pit, an iron-rich compound called heme. Quinine and its synthetic derivatives chloroquine and methoquine all prevent the parasite from pushing heme out of itself into the red blood cell; eventually the piled-up heme kills the parasite.

These drugs all rapidly select for resistant strains, especially when they are not taken in sufficiently high doses for sufficiently long times. Methoquine, a second-generation variant of chloroquine, took about seventeen years to develop, but methoquine-resistant strains appeared only ten years after it was first administered to people suffering from chloroquine-resistant malaria. Malaria can be prevented by killing off the mosquito that transmits the parasite, but using insecticides for this purpose has the same side effect as any other antibiotic: insecticides like DDT once were the scourge of mosquitoes carrying malaria; today malaria is carried almost exclusively in DDT-resistant mosquitoes worldwide.

Our species has had one last, desperate response to malaria: human genetic resistance. A child born in a region where malaria has been common for a long time — or born of ancestors from such a region — has a good chance of inheriting a variant hemoglobin gene that protects against malaria. If she inherits a protective variant from one parent and a more common version of the gene from her other parent, her red blood cells will be inhospitable to the malaria parasite and she will have a life-long resistance to malaria. But a child who inherits the protective variant of the hemoglobin gene from both parents will soon develop sickle-cell anemia, a serious problem resulting from a far greater variation in the structure of red blood cells. It hurts, and in some cases it can be fatal, to have red blood cells form sharp-edged stacks instead of smooth pillows and to have them jam up the tiniest blood vessels of the muscle and lung. The pain and death of sickle-cell disease and other blood disorders is the price our species has paid and will continue to pay to escape from the otherwise unstoppable combination of mosquitoes and malaria.

A parasite that can force the selection of variants from among our own genes is a force to be reckoned with: malaria has pushed the natural equilibrium far in its favor, and to date all our efforts to push it back have failed. Even with human genetic resistance as a firebreak, the malaria parasite holds the prize as the most damaging of the microbes that use the two-species strategy for getting from one person to the next. Today about three hundred million people carry the parasite in their bodies on any given day, and untreated infections are fatal in up to twenty percent of adults and a much higher percentage of young children.

Example 4: HIV/AIDS
HIV, the human immunodeficiency virus that causes AIDS, has been at least as clever as tuberculosis or malaria at evading our best efforts to tame it. Its strategy of infection and contagion combines tuberculosis's capacity to hide within a cell with smallpox's and malaria's capacity to travel from person to person in a small drop of fluid. HIV needs no insect vector; any actions that carry it from one bloodstream to another will allow it to set up a new infection. The speed with which HIV spreads in a human population is determined by the most efficient of such actions: in Zimbabwe, widespread, unprotected sex with many partners has been the main route of transmission, and life expectancy overall has dropped by more than twenty years as a result of HIV mortality. In Ukraine — a new independent country experiencing all the extremes of the West in a great hurry — the percentage of intravenous drug users who are HIV-positive went from two to sixty percent in less than a year.

Once HIV is in the bloodstream, specific proteins on its outer membrane adhere to the immune system's macrophages. These immune cells readily accept the virus because, ironically, they are there to find foreign material, ingest it, digest it, and trigger the rest of the immune system to prepare for more of it. Once inside a macrophage, the virus manages to integrate its genome into the chromosomes of the cell, and from there it releases great clouds of fresh virus into the bloodstream. Other immune cells respond to the free virus as well as to the infected macrophages. The relationship between HIV and the immune system is quite ordinary at this point, as the immune system's response to the outpouring of HIV generates the fever and sweats of an early HIV infection. In time the immune system sweeps the blood clean of most of this virus, but — and here is the big but — because HIV is growing in the macrophages themselves, the immune system can never completely rid itself of HIV. Even one infected macrophage will release enough virus to infect many others, and so long as there are macrophages in an untreated HIV-positive person, there will be more HIV grown and released into the blood.

Genetic variation is very high during the reproduction of fresh HIV, and among the variants are some that can directly infect other cells of the immune system, in particular those called T-cells. The immune system is still active against HIV, and because it uses its T-cells to attack HIV-infected macrophages, there is a strong selective advantage for any viral variant that can grow directly in T-cells. This sort of variant inevitably overtakes any other versions of HIV in the body. T-cells are required for any immune response; when they start dying, the immune system crashes and the person develops full-blown AIDS.

Strategies

The immune system does not attempt to kill every last microbe that it detects; that would only select for increasingly dangerous survivors, as antibiotic drugs do. Instead, the immune system domesticates the microbes it sees, allowing us to live with them, and using them to keep itself primed for future invasions. A vaccine is a domesticated microbe: like a poodle or an ear of corn, it cannot grow in the wild but needs our intervention to survive. In this sense vaccines have the imprimatur of natural selection, and antibiotics do not. The inability of biomedical science to acknowledge this fact is a good example of the consequences of a science in denial.
New, virulent microbial diseases keep showing up, and we keep discovering that one or another chronic disease we thought had other causes hides an infectious microbe. Meanwhile, despite our best attempts to kill them off with drugs, at least two microbes — the agents of tuberculosis and malaria — continue to infect a considerable fraction of all people alive today. Yet the agenda for basic research on infectious diseases is still heavily invested in the dream of beating microbial enemies into total submission, as if they were small nations subject to our rules of military engagement. The dream — and the denial it engenders — keeps biomedical science from focusing on microbial domestication. The magnitude of the microbial threat to our species requires that we wake from the dream of conquest and learn how we might steer the powerful, disinterested force of natural selection toward safer, mutual accommodation.

Today's Bug Wars strategy suffers from the same flaw as the defunct Strategic Defense Initiative, the Star Wars defense partially mounted at great cost by the United States in the late 1980s. Even one Soviet missile would cause insupportable damage, and no SDI system could guarantee that every last Soviet missile would be stopped. Similarly, we can be sure that the mutability of microbes will always allow a few to slip through our chemical defenses. Going beyond Bug Wars to a mature approach to infectious disease would require redoubled efforts to develop and distribute new vaccines as well as mobilization on two other fronts: the worldwide reporting of outbreaks of infectious disease and the wide dissemination of what we already know about epidemiology and preventive medicine.

Preventing disease saves not only lives but money. In 1967 smallpox was costing us about a billion dollars a year worldwide. The thirteen-year effort to eradicate it by vaccine and education cost less than a third of a billion dollars, and every year since the economies of the world have saved the equivalent of a billion uninflated dollars by this one act of international cooperation. Despite that precedent, the United States spends less than one thousandth of its annual health care expenditures on international efforts to prevent infectious disease; that is even less than ten percent of the annual increase in overall medical expenses. Medical school education in most countries also reflects this lack of interest in public health, epidemiology, and vaccine-focused, preventive medicine. In the United States, for example, the NIH will pay all medical school tuition for a student deemed bright and motivated enough to enroll in a joint M.D.-Ph.D. program, but there is no parallel track for people qualified and motivated to get both an M.D. and a degree in public health.

The three tools of public health that can keep microbial agents at bay — an enhanced immune response, clean drinking water, and insect control — were developed to a high level of technological sophistication more than a century ago. Vaccines prepared the immune system before infection so that an incoming agent was met and domesticated before it could create a colonizing nest of offspring; clean water cut the oral-fecal path of infection for the many microbes that pass through the body; insect control kept at bay, not just the insects themselves, but any microbes that need to travel in them from one warm-blooded host to another. These tools were very successful. Yet, at the first victories of antibiotics, all three were set aside and forgotten as research strategies. As the twentieth century draws to a close and the great strategy of killing
infectious agents and their vectors continues to breed its own failures, we need to recover the memory of those earlier successes.

The cost worldwide of doing nothing — or, rather, of continuing to do what we do now in the developed West — is millions of deaths each year. Five million babies, for example, died in 1992 of serious childhood diseases like measles, tetanus, diarrhea, whooping cough, and polio because they were not properly vaccinated. That is actually an improvement: in 1983 these diseases killed about nine million babies. The estimated initial cost of a serious effort to produce and distribute the necessary vaccines to protect every newborn from birth is about $25 billion, or about $5,000 per young life saved. After the first few years the cost per saved life would drop precipitously. We already know all we need to know to do this. Surely there will never be a discovery to be made from basic research that would provide so many people with such a great extension of their life expectancy.

Our sort of internal time does not exist for microbes and never has; they must either divide or die. The reward for mindless quickness is robust genetic variation: the smaller the microbe, the simpler its genome; the simpler the genome, the rougher the copying mechanism that replicates it; the rougher the mechanism, the more errors; and the more errors, the more chance for a descendant that will survive any environmental stress. While any individual microbe has its place in the sun — or the gut — for only a few minutes or hours, that very evanescence all but guarantees that among its offspring will be some — or even one — descendant different enough to live and propagate in turn, despite anything we may do to kill them all.

Biomedical science has yet to accept these fundamental differences between the microbes and us; we are still fighting a war that cannot be won. When you fight a war you cannot win, you may still aim to survive by wearing down the enemy until they are willing to accept a compromise.

The invisible, evanescent lives within us will continue to use their ancient weapon of mutational variety to grow inside our bodies, treating people for all their national and cultural differences as if they were interchangeable culture vessels. Their capacity to transcend our differences invites us to consider the harm we do to ourselves by forgetting that we are after all a single species. Planet-wide defenses — vaccines, public health and preventive measures — cannot be set up unless nations and peoples find a way to surrender the dream of victory that has informed our thinking about infectious disease. Short of that, creatures with no internal time at all are likely to make sure that no matter our income, language, religion, or sex, few of us will have as long a run of internal time as we might wish to enjoy our big-bodied intelligence and resources.

**Some concrete suggestions**

1

Microbes do not respect national boundaries; the strongest ally infectious agents have is the human notion of national sovereignty. International cooperation was a prerequisite to the elimination of smallpox. If every person on the planet could simply be
vaccinated with the vaccines we already have, hundreds of millions of people, a good fraction of them babies, would be saved from dying.

Only a few agents of infectious disease — yellow fever, an insect-borne virus; Lassa, viral hemorrhagic disease; smallpox; cholera; diphtheria; tuberculosis; and plague — cause illnesses that must be reported to the United States government today. All others, including malaria and all antibiotic-resistant strains of common infectious microbes, come and go unremarked. Many other diseases used to be reported; the shortsighted decision to save a small amount of CDC money guaranteed the fast and distant spread of any outbreak of antibiotic-resistant infection. It also mistakenly presumed that the United States had no need to worry about tropical diseases like malaria, even though the climate of the southeastern United States would suit the insect vector quite well.

To pay for a more rational and comprehensive defense against microbes, we might consider using a version of the military model which is not based on a fantasy of total victory. There is a pleasing symmetry to extending the notion of subsidy for the sake of security from the production and purchase of lethal weapons to the production and distribution of life-saving vaccines. The underlying logic of a military model for mobilization to assist our immune systems through vaccines is the opposite of the SDI notion of perfection. Instead of SDI we need an SVI — a Strategic Vaccine Initiative. SVI would acknowledge that our best hope is a standoff and that our best strategy is to help our immune systems turn microbial mutability to our advantage by domesticating the microbes that get inside us.

In contrast to SDI, SVI could work only if it were the product of total international cooperation. Political, religious, and ideological differences make no difference to tuberculosis or malaria; they have no place in species-wide SVI. National sovereignty may seem an impermeable barrier to the necessary transnational attitudes and actions, but we have a precedent at our fingertips for the permeability of national borders to new technologies. Ideas and information that get onto the Internet travel around the planet, crossing national boundaries with impunity. Organized and run from the beginning on the Internet, an internationally funded SVI would not need to have a single location in any one nation. That would be an appropriate organizational strategy for the kind of international effort it will take to respond — as a species — to the invisible species that will always threaten us. Like the immune system in any of our bodies, the Internet is widely distributed, rapidly adaptable, and quick to learn. A new idea that travels through the Web is quite like a new antigen that stimulates a strong immune response. And like the chemicals and cells in a person's immune system, ideas that move through the Web may be what keep our species going, especially if one or more of the microbes we live among gets going in us in a serious new way.

Oral vaccines available today are prepared from infected, cultured cells. Although it is attenuated, the Sabin live polio vaccine can be taken by mouth because it can still infect the lining of the intestines. It is safe because its genome differs from the pathogenic polio virus in enough places to assure that it will not revert to its ancestral capacity to go
from there into neural cells. An oral vaccine is by definition edible; another way to make an oral vaccine would be to put a few of a pathogen's genes into the germ line of an edible plant, forcing offspring plants to produce antigenic foreign proteins and thereby make them into edible, even nutritious vaccines. Transgenic plants are now being tested for their ability to serve as cheap, stable oral vaccines against hepatitis and cholera. The main limitation so far seems to be tolerance: the intestinal immune cells that see the foreign protein as part of a digested mass of plant material cannot tell that it is foreign unless it comes in as part of a larger, more obviously microbe-like structure.

If the ideal preventive medicine for infectious diseases would be the delivery of an optimal vaccine for all diseases, a solution at hand comes pretty close: mother's milk. A nursing baby winds up with a fiftyfold enrichment of its mother's immune-protective molecules. Milk also carries natural drugs to fight infection, in particular the anti-inflammatory agent lactoferrin and the antibiotic lactoferritin, as well as sugars that trick bacteria into binding to them rather than to the surfaces of a baby's cells. A baby's immune system is set for life by the mother's milk: an organ transplanted from mother to child will take with much greater ease if the child has been breast-fed.

A complete response to microbial disease must begin with the commitment to encourage and assist every mother to nurse her newborn child before it is exposed to any vaccines, let alone any antibiotics. Breast-feeding so enhances the immune system that cultures that do not breast-feed have a tenfold excess of infant mortality over those that do. This difference is due to the absence of similar enhancers of the immune response in any other foods and to the relative contamination of all foods compared to milk from the breast, which is sterilized by the mother's immune system. In a 1994 editorial in the Journal of the American Medical Association, two physicians from the CDC described the worst consequence of our having devalued vaccination in an age of artificial formulas and antibiotics: these three markers of our “progress” have together helped infectious diseases to get back into our children.