WHY WE GET SICK

by

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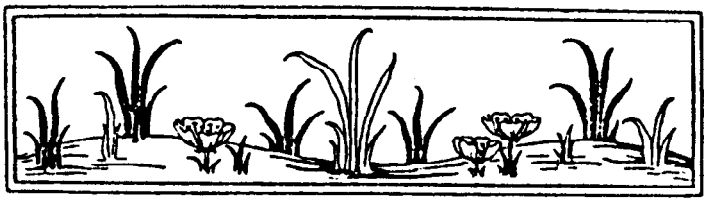

Why We Get Sick

First, I want to thank you for selecting me as this year's Arthur Baer Fellow. I am both pleased and honored to be a member of this interesting club. I have spent most of my career in academic medicine, carrying out traditional biomedical research. About ten years ago, I began teaching biology in the College at the University of Chicago. Because the theory of evolution by natural selection is the unifying concept of biology and is, in my view, the most important biological concept that all of our students need to understand, my College teaching has led me to become an amateur evolutionary biologist. This in turn has led me to become interested in a new discipline, Darwinian or evolutionary medicine, whose goal is to understand the evolutionary origins of health and disease. Darwinian medicine seeks to understand why diseases occur and why they have the symptoms and natural course that they do. This is what I want to talk about this evening.

The title of this paper was taken from that of the first book on Darwinian medicine, *Why We Get Sick: The New Science of Darwinian Medicine* (New York: Times Books, 1994) by Randolph M. Nesse and George C. Williams.

To begin, though, I'd like briefly to review Darwin's theory of evolution by natural selection, since this forms the basis for thinking about Darwinian medicine. Darwin's argument comprised the following elements:

First, Darwin noted that there is abundant variation in virtually all traits between members of a population.

Second, Darwin realized that although the ability of a population to reproduce is potentially boundless, the resources available to support that population are finite and limited. Thus, there will be a competition between individuals for survival and reproduction. Darwin got this idea of competition from reading Malthus's *Essay on the Principle of Population*; he called it the "struggle for existence." Those individuals that are successful in this competition will leave more offspring and so will contribute more heavily to the growth of the population; in evolutionary terms, leaving offspring is the definition of success. The ability of organisms to survive and reproduce is known as their evolutionary fitness.

Finally, Darwin pointed out that, because many traits are heritable, offspring tend to resemble their parents. As a result of the struggle for existence, traits that increase survival and reproduction—that is, traits that increase fitness—will spread in the population, while traits that decrease survival and reproduction will be eliminated. Darwin defined natural selection as "This preservation of favourable variations and the rejection of injurious variations."[1] Darwin

1. Charles Darwin, *On the Origin of Species* (1859; reprint, Cambridge: Harvard University Press, 1964), 81.

rarely used the word evolution, which originally meant unrolling or unfolding. In the nineteenth century, evolution was commonly used to describe development, which was thought to result from the unfolding of a pre-existing developmental plan. Instead, Darwin said that natural selection led to "descent with modification."

All that is needed for Darwinian evolution, or evolution by selection, is a population of entities in which there is heritable variation of traits that affect reproductive success. Given that living organisms manifest these properties, evolution by natural selection is inevitable.

Darwin knew that many traits were heritable—that children tend to resemble their parents—but when he wrote people didn't yet understand the mechanisms of inheritance, that inheritance involves the transmission of genes from parents to children. We now know that the human genome comprises some thirty thousand to forty thousand genes, each of which specifies the structure of a specific protein. Proteins do all the work in the body—enzymes, hemoglobin, antibodies, and so on are all proteins. Our growth, development, and function depend on the activities of the proteins encoded by our genes. Most of the genes in the human genome exist in multiple alternate forms, known technically as alleles. These alleles encode slightly different proteins that have slightly different biological activities. For example, normal hemoglobin and sickle cell hemoglobin are encoded by different alleles of the hemoglobin gene. New alleles arise as a result of mutation. If these new alleles enhance the fitness of the people who have them, they will

spread in the population; if they decrease fitness, they won't. Evolutionary biologists commonly think about evolution in terms of changes in allele frequencies in a population over time. Although several processes can lead to changes in allele frequencies, most evolutionary biologists believe that natural selection is the most important evolutionary mechanism.

In retrospect it seems obvious that evolutionary biology might offer important insights into health and disease, and it is surprising that Darwinian medicine is such a young discipline. But the orientation and concerns of most physicians differ from those of evolutionary biologists. Medicine is understandably focused on individuals. Physicians are concerned with the health and well-being of their individual patients and give little consideration to the populations of which their patients are a part; public health has always been a poor stepchild to medicine. In contrast, as I've said, evolutionary biology focuses on populations; it is concerned with genetic variation within populations and with genetic changes in populations over time.

Biomedical research has focused on the properties of what Claude Bernard called the internal environment, the blood and other body fluids, because it is this internal environment that is often altered in disease; medicine has neglected if not ignored the interactions of individuals with the external environment. On the other hand, because evolutionary fitness—survival and reproductive success—depends so heavily on the "fit" between organisms and their external environments, evolutionary biologists have studied

these interactions and have paid less attention to the development and internal workings of organisms.

Finally, physicians have been interested in what have been called proximate causes of disease—the biochemical and physiological mechanisms that act during the lifetime of an individual—because these are the processes that medical interventions can affect, while evolutionary biology is concerned with ultimate causes of biological phenomena, causes that have operated during the evolutionary history of a species. Because of these radically different perspectives, evolutionary biology and medicine developed as separate, unrelated fields. Only recently have evolutionary biologists and physicians begun to realize that there is much to be gained by integrating their disciplines.

Even though evolutionary biologists criticize creationists who cite the Bible as evidence for their beliefs, we like to cite Darwin, not as dogma but because he had such powerful insights about the nature of living organisms. At the end of *On the Origin of Species*, Darwin wrote, "as natural selection works solely by and for the good of each being, all corporeal and mental endowments will tend to progress towards perfection."[2] Darwin probably added this up-beat and optimistic statement to make his theory more palatable to his Victorian readers. But this quote really frames the problem that Darwinian medicine seeks to address. If natural selection tends to perfect "all corporeal and mental endowments," why, after thousands of generations of human evo-

2. Ibid., 489.

lution, and eons of evolution before the origin of human beings, has natural selection not perfected our physical and mental health? Why do we still get sick? What are the limits of natural selection?

Broadly speaking, there are really only a few limits to natural selection, resulting in only a few major categories of disease. I always like to ask my students to estimate how many people die per year. Sometimes their estimates are off the wall but they're usually pretty good. According to the World Health Organization, approximately fifty million people in the world die each year. The major causes of death that the W.H.O. records are infectious diseases—malaria, tuberculosis, and H.I.V. being the most important—cardiovascular diseases, and cancer. The other major cause of death, which doesn't show up in the W.H.O. statistics, is malnutrition. I guess the W.H.O. doesn't report malnutrition as a cause of death because malnourished people usually die of something else—an infectious disease—before they actually die of starvation. Nonetheless, let's think about the evolutionary bases of malnutrition, infectious diseases, cardiovascular diseases, and cancer.

Malnutrition reflects perhaps the most obvious limit to natural selection. Survival and reproduction require some bare minimum of calories and of essential nutrients. As our evolutionary ancestors migrated out of Africa to colonize the planet, the ability to utilize novel food sources must have increased fitness and so must have spread in the human population by natural selection. This is presumably why we have evolved to be omnivores—except for grass and

tree trunks, we can eat almost anything. Natural selection has also led us to have very efficient digestion and metabolism; we get the most we can out of the foods we eat. Nonetheless, there is some minimum food intake that is required for survival, that is required for growing a big brain and for being human. While natural selection can optimize—or, in Darwin's words, perfect—our ability to utilize foodstuffs, there are thermodynamic limits beyond which it can't go.

When evolutionary biologists talk about the idea that natural selection causes populations or species to become better fitted or adapted to their environments, it may sound as though environmental niches are inert, stable structures like the niches in churches into which statues are fitted. But nothing could be further from the truth. Natural environments are always changing and, because evolution is a relatively slow process, populations are always playing catch-up to their changing environments; here perfection is illusory, because natural selection is aimed at a moving target. Other organisms comprise an especially important part of our environment, and they too are subject to natural selection. Our bodies provide environments in which other organisms can thrive. Our skin and many of our body cavities—the GI track, the upper respiratory track, and the female reproductive system—are normally colonized by a host of microorganisms—or parasites, as biologists call them—and we are continually coming into contact with new potential parasites. For the most part, these microorganisms don't harm us, and some may in fact be beneficial. And in health, they are restricted to those parts of our bodies that are in contact

with the external world; our insides are normally sterile. But natural selection will always favor the spread of organisms that can overcome our defenses and can enter and grow inside us.

Throughout the course of evolution, parasites must have been a major cause of premature death and infertility, or of decreased fitness, and as a result we have evolved innumerable intricate and effective defenses against parasites. Many of the parasites we know best, including tuberculosis, smallpox, and measles, apparently entered the human population from domesticated animals. These parasites are thought to have become major human diseases at the time of the agricultural revolution, when we came into close contact with domesticated animals, and also began to live in cities with high population densities, which favored the transmission of these parasites.

The coevolution of hosts, such as ourselves, and the parasites that can live in us is sometimes referred to as an evolutionary arms race. Parasites evolve to grow in their hosts; hosts evolve defenses against the parasites; parasites evolve mechanisms to evade these defenses; hosts evolve new defenses, and so on. While we see the failures of natural selection to protect us from parasites, we shouldn't be blinded to its incredible successes in making us as healthy and as parasite-resistant as we are. The problem is that, although, in Darwin's words, "natural selection works solely by and for the good of each being," it works for the good of parasites as much as it works for the good of people. And these parasites have a big evolutionary advantage over us; they out-

number us and they reproduce more rapidly than we do. People who are infected with H.I.V. may have billions of viruses in their bodies. And these viruses reproduce with a generation time of about a day. Since these parasites evolve more rapidly than we do, many of them can stay a step ahead of our defenses, and cause disease. But infectious or parasitic diseases shouldn't simply be thought of as failures of natural selection; rather, they result from the simultaneous action of natural selection on both hosts and parasites. In other words, these diseases result from the coevolution of hosts and parasites.

The idea that we and our parasites have coevolved helps to explain several interesting aspects of parasitic diseases. Evolutionary theory can help us to understand—or at least rationalize—why some parasitic diseases—malaria, for example—are virulent, while others, such as the common cold, are benign. It is sometimes thought that parasites inevitably evolve to be benign, because those that killed their hosts would not survive. But this does not seem to be the case; the coevolution of hosts and parasites can lead to any degree of virulence. To survive, parasites have two challenges. They have to grow in an individual host—you or me—and they have to be transmitted between hosts. Parasites that grow in one of us but can't get transmitted are going to die out when we die; for them, it will be an evolutionary dead end. The parasites that spread in a population are by definition those that are most successful at getting themselves transmitted. Parasites don't care what they do to their hosts. They are selected to have whatever traits they

need to be efficiently transmitted; what they do to their hosts is simply an incidental byproduct of this selection.

One nice way of thinking about how parasitic diseases evolve is that, in general—and I am painting with a broad brush now—parasites that are transmitted most efficiently from sick people will evolve traits that make people sick, while parasites that are transmitted most efficiently from healthy people will evolve to keep their hosts healthy. Think about mosquito-transmitted diseases like malaria. When a mosquito bites, it drinks a tiny, tiny amount of blood—only a few millionths of a liter. In order for malaria to be transmitted from an infected person to a mosquito, there has to be a huge concentration of malaria parasites in the blood; the more, the better. Not surprisingly, malaria parasites have evolved to fill our blood and as a result, they interfere with oxygen transport and make us weak. Moreover, a debilitated malaria-ridden host will probably be less able to brush off or kill mosquitoes and so is likely to be bitten more frequently than a healthy host. In other words, sick people are better at transmitting malaria than are healthy people. So, malaria—and most other diseases that are transmitted by insect bites—are virulent, frequently lethal diseases.

On the other hand, transmission of a cold virus requires that its human hosts be healthy and active, so they can go about their business sneezing on other people. Mutant cold viruses that made their hosts so sick that they stayed home in bed would not spread in a population. Not surprisingly, then, cold viruses have evolved traits that cause their hosts

to remain healthy. Even though we know that sexually transmitted diseases can be lethal, they are typically characterized by relatively long latent periods, during which time their hosts remain healthy and sexually active, and can spread the disease. Even in the absence of treatment, there is now a latent period of about twelve years between the time a person becomes infected with H.I.V. and the onset of AIDS. This latent period can be thought of as an adaptation that enhances transmission of the virus.

I have emphasized that variation is at the heart of the theory of evolution. Variation provides the raw material on which natural selection can work; without variation, there can't be evolution. The coevolution of humans and our parasites is one of the major causes of genetic diversity in the human species. Imagine that you are a parasite that has just entered a human population. As you spread in the population, you will encounter many genetically different individuals. If you can't grow equally well in all of them, you will evolve to grow well in the most common type of person, the type you encounter most frequently. As a result, you may not grow well in people with rare mutations that make them different from the majority.

You've probably read or heard about people who are resistant to H.I.V.—sex workers or other people who have been repeatedly exposed to the virus but who don't become infected. H.I.V. requires a certain protein, known as a receptor, to enter our cells. The vast majority of people have this receptor, and so the virus has no trouble entering our cells and growing in us. A small proportion of people have

an allele that encodes for a mutant receptor that H.I.V. can't recognize. As a result, the virus can't grow in them. As we speak, H.I.V. is killing people who have the normal H.I.V. receptor protein, and the percentage of people with the mutant receptor is increasing; this is human evolution in action, if you will. You can predict that, at some time in the future, if H.I.V. kills enough people, the majority of survivors will now be people with this H.I.V.-resistant receptor. At that point, it wouldn't be surprising if a mutant H.I.V. virus arose that could recognize this mutant receptor and grow in these previously H.I.V.-resistant people, and that there might then be a small number of people who were resistant to this new virus. This is what I referred to as an evolutionary arms race. Because parasites are always adapted to grow in the majority, they are always causing selection for rare mutations, which are beneficial only because they are rare. Not only does it pay to have safe sex—it pays to be different! A large part of the genetic diversity in the human population is thought to have arisen as a result of this kind of natural selection.

Finally, I'd like to talk about the diseases that are the major killers in our society, cardiovascular diseases and cancer. These diseases are sometimes called diseases of civilization because they are so prevalent in our society, but because their incidence increases with age, I think it is more useful to consider them as diseases of aging. From a biological perspective, aging is a progressive generalized loss of function, resulting in an increasing probability of death, and often accompanied by a decline in fertility. Age-specif-

ic mortality rates are high in the newborn period, decline during infancy and childhood, reach a nadir at about age nine or ten, and then increase progressively from then on. I like to tell my twenty-year-old students that they are already aging, and so they should have more empathy for their parents—and their teachers! Many causes of death increase with increasing age—cardiovascular diseases, cancer, and neurodegenerative diseases such as Alzheimer's disease are just the most prominent.

Why, from an evolutionary perspective, do organisms age and die? It's not because of the second law of thermodynamics, some inexorable increase in entropy or disorder. As long as nutrients and energy are available in the environment, there is no thermodynamic reason why organisms couldn't be immortal. And it's not that we have evolved to die in order to make room for our children; evolution doesn't work that way. Evolutionary theories of aging are based on the idea that, in nature, almost all organisms die of extrinsic or environmental causes—starvation, parasites, accidents, etc.—before they exhibit signs of aging. Consequently, aging itself cannot be an evolutionary adaptation; the characteristics of aging must be byproducts of selection for other traits.

Evolutionary fitness entails both survival and reproduction. We have only a limited amount of energy—physical as well as psychic—to devote to these tasks. Bad things are constantly happening to our bodies. All of our bodily constituents, including our proteins and our DNA, undergo spontaneous chemical changes, cells begin to function ab-

normally, and so on. Our survival depends upon repair mechanisms that are continuously degrading and resynthesizing damaged proteins, removing and replacing damaged cells, etc. But these repair mechanisms require energy, energy that might otherwise be devoted to reproduction. We know that reproduction diverts metabolic energy that could otherwise be used for longevity. Of all the treatments that are said to increase life expectancy, the one intervention that is known to work, both in humans and in experimental animals, and in both males and females, is castration. The earlier an animal is castrated, the greater the increase in life expectancy. This of course is a case where the cure is worse than the disease! I mention it only to emphasize that the trade-off between survival and reproduction is real.

Castration aside, organisms must allocate their finite resources either to reproduction or to the repair and maintenance of their somatic tissues. Natural selection has presumably optimized this allocation. The adaptive value of maintaining somatic tissues depends on the expected future reproduction of the organism. Because of deaths from extrinsic causes, older and older individuals will make up a smaller and smaller percentage of the population. Moreover, older individuals have less future reproductive potential than do younger individuals. From an evolutionary perspective, then, what happens to elderly individuals is less important than what happens to the young. In other words, the power of natural selection wanes with increasing chronological age.

In organisms like ourselves, who reproduce over many years and live in family units, the trade-offs between reproduction and somatic repair are complicated. We need to reproduce relatively early in our lives, both because the survival of children depends on the survival of their parents, and because if we put off reproducing until too late, we might die of some extrinsic cause first. Imagine that there was one allele of a gene that caused people to undergo puberty and become fertile at age fifteen, and another that caused puberty to occur at age thirty. Which of these alleles would spread in the population? Obviously, the one associated with early fertility. We must become fertile at the youngest age that is compatible with bearing and raising healthy children. On the other hand, we need to devote sufficient resources to bodily repair to live long enough to reproduce and to promote the survival of our children. Parents contribute to the survival of their children for many years after birth, and may also contribute to the survival of their grandchildren, the so-called "grandmother effect." Nonetheless, the force of natural selection must decrease with age, and there must be some age at which natural selection no longer acts. This evolutionary view of aging is sometimes known as the "disposable soma" theory, because, from an evolutionary perspective, once our reproductive lives are finished, our bodies are disposable. Many diseases of aging must occur simply because of the waning power of natural selection to eliminate them. The average age at which people are diagnosed with cancer, for example, is over sixty. Whatever else may contribute to cancer, one cause is pre-

sumably the fact that cancers in the elderly are not strongly selected against.

One important consequence of the disposable soma hypothesis is the realization that aging is not a specific disease or diseases, but is a generalized loss of function. Although we may die of a specific disease, older people typically have multiple health problems; the longer we live, the more diseases we have. There is an anecdote about Henry Ford that illustrates this aspect of aging.[3] I don't know if the story is true but I think it's instructive. The story goes that Ford wanted to find out why his Model T's stopped running, and so he dispatched one of his employees to visit junkyards in the Detroit area to find out what caused Model T's to be junked. Several weeks later, his employee came back to report that some Model T's stopped running because the engines broke, others were discarded because the clutch wore out, some were irreversibly damaged in accidents, some were junked because their bodies rusted through, and so on. "But," said the employee proudly, "I'm happy to tell you, Mr. Ford, that we make wonderful axles. I couldn't find a single car that was junked because of a broken axle." To which Ford is said to have replied, "That means we're wasting money making our axles too strong," and he then directed that the axles on Model T's be built with a lower grade of steel.

As I said, I don't know if the story is true, but it does capture the essence of the evolution of aging. If most everyone

3. I am indebted to Richard Dawkins for this story. See his "God's Utility Function," *Scientific American,* November 1995, 80-85.

in the population died of one cause or another by age seventy or eighty, the biblical three-score and ten or four-score years, there is no way that natural selection would have led to, say, the evolution of livers or kidneys that would function for 100 or 150 years. Genes that diverted energy from repair of livers or kidneys to reproduction, or to other needs of younger individuals, would certainly have spread through the population.

The allocation of resources between somatic repair and reproduction differs in different species and must depend on the extrinsic mortality of a species. If organisms die at an early age of starvation, or parasites, or predators, natural selection will lead to early reproduction and early aging; these organisms won't waste their scarce resources on bodily maintenance. On the other hand, if organisms have evolved mechanisms that enable them to avoid these other causes of death, then selection will lead to the allocation of more resources to somatic repair, and longevity will increase. When resources are diverted from reproduction to longevity, organisms change; in automotive terms, we now have a Rolls-Royce instead of a Model T.

In general, large animals live longer than small ones, presumably because large animals are more successful at avoiding predators. Birds live longer than mammals of the same size, because the ability to fly helps birds escape predators and find food. The longevity of birds is clearly related to flying, since bats live longer than other similar-sized mammals. Closer to home, the human life span is about twice that of chimpanzees, even though the two species are closely relat-

ed and are roughly the same size. Even in captivity, where chimps are given adequate food and medical care, they live only about forty years. The ability of big-brained early humans to reduce the extrinsic causes of death must have contributed to the evolution of our long life span. There is feedback during evolution between extrinsic, environmental or ecological causes of death, and selection for somatic repair and longevity. To use another industrial metaphor, this one by the evolutionary biologist Michael Ghiselin, "What goes on in the marketplace can influence what happens on the factory floor."[4]

What is the value of an evolutionary approach to health and disease? It seems to me that there are several benefits. Physicians have ignored evolution and natural selection at their peril, or at peril to their patients. Both the optimistic predictions that antibiotics would lead to the eradication of infectious diseases and the promiscuous use of these antibiotics over the last fifty years reflect an ignorance or neglect of evolutionary principles.

An evolutionary understanding of disease may yield insights into strategies for disease prevention. Because of the rapidity of cultural change, we now live in an environment that differs greatly from that to which our evolutionary ancestors were adapted; some diseases may be caused by this mismatch. The high incidence of female reproductive cancers in Western societies may be an example of this prob-

4. Michael T. Ghiselin, "The Failure of Morphology to Assimilate Darwinism," in *The Evolutionary Synthesis,* edited by Ernst Mayr and William B. Provine (Cambridge: Harvard University Press, 1980), 191.

lem. These cancers are likely due in part to cultural changes —postponement and limitation of childbirth, together with better nutrition—such that women now have many more menstrual cycles than did our female ancestors, and expose their reproductive tracts to more frequent periods of estrogen stimulation. Contraceptive pills were designed to allow women to have monthly menstrual cycles, because this was thought to be the "normal" female condition. Perhaps these pills should be redesigned to cause cessation of menstrual periods, because that is the hormonal regimen under which women evolved and to which their bodies are adapted.

An evolutionary view of life calls attention to what René Dubos has called the "mirage of health."[5] Our desire for complete and unending health is a mirage. Even if we can overcome the social and economic problems of food production and distribution, and meet the nutritional needs of everyone on the planet, our bodies will continue to provide niches in which parasites can thrive, and we should expect the continued emergence of new parasites that can exploit these niches. Parasitic diseases have always been with us and always will be with us. We shouldn't expect ever to be free of them; we should only be prepared to respond rapidly to prevent their spread when they do arise. Likewise, aging is part of our evolutionary inheritance. Our goal can't be to find the fountain of youth and prevent aging—rather, it has to be the more modest but more realistic one of learning to age well.

5. René J. Dubos, *Mirage of Health* (New York: Harper & Row, 1959).

Perhaps most importantly, evolutionary biology forces us to recognize variation for what it is—an essential part of our biological inheritance and our hope for the future. Our evolution depended on the presence of genetic variation among our ancestors, and the future of the human species—our ability to survive plagues such as H.I.V., for example—may well depend in part on our continued diversity. Genetic diversity is what makes us a biological species rather than a *Brave New World* clone. There is a tendency in medicine to define health and disease in terms of deviation from some norm, or average. We have created a panoply of supposed diseases—hypertension, high cholesterol, and obesity, to name a few—that are defined simply in terms of deviation from some supposed normal or ideal state. Evolutionary biology tells us that there is no such ideal. While deviations from typical values of blood pressure, cholesterol levels, or body weight may be risk factors that increase the probability of disease, they are not themselves diseases and shouldn't be classified as such. It seems to me that the medical obsession with normality and the conflation of deviation with disease contributes to our collective xenophobia, our societal reaction to people who look and act different from us. By helping us to value diversity and individual differences, evolutionary biology has moral as well as medical significance.

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