

# Evolution and the Origins of Disease

by Randolph M. Nesse and George C. Williams

Thoughtful contemplation of the human body elicits awe--in equal measure with perplexity. The eye, for instance, has long been an object of wonder, with the clear, living tissue of the cornea curving just the right amount, the iris adjusting to brightness and the lens to distance, so that the optimal quantity of light focuses exactly on the surface of the retina. Admiration of such apparent perfection soon gives way, however, to consternation. Contrary to any sensible design, blood vessels and nerves traverse the inside of the retina, creating a blind spot at their point of exit.

The body is a bundle of such jarring contradictions. For each exquisite heart valve, we have a wisdom tooth. Strands of DNA direct the development of the 10 trillion cells that make up a human adult but then permit his or her steady deterioration and eventual death. Our immune system can identify and destroy a million kinds of foreign matter, yet many bacteria can still kill us. These contradictions make it appear as if the body was designed by a team of superb engineers with occasional interventions by Rube Goldberg.

In fact, such seeming incongruities make sense but only when we investigate the origins of the body's vulnerabilities while keeping in mind the wise words of distinguished geneticist Theodosius Dobzhansky: "Nothing in biology makes sense except in the light of evolution." Evolutionary biology is, of course, the scientific foundation for all biology, and biology is the foundation for all medicine. To a surprising degree, however, evolutionary biology is just now being recognized as a basic medical science. The enterprise of studying medical problems in an evolutionary context has been termed Darwinian medicine. Most medical research tries to explain the causes of an individual's disease and seeks therapies to cure or relieve deleterious conditions. These efforts are traditionally based on consideration of proximate issues, the straightforward study of the body's anatomic and physiological mechanisms as they currently exist. In contrast, Darwinian medicine asks why the body is designed in a way that makes us all vulnerable to problems like cancer, atherosclerosis, depression and choking, thus offering a broader context in which to conduct research.

The evolutionary explanations for the body's flaws fall into surprisingly few categories. First, some discomforting conditions, such as pain, fever, cough, vomiting and anxiety, are actually neither diseases nor design defects but rather are

evolved defenses. Second, conflicts with other organisms--Escherichia coli or crocodiles, for instance--are a fact of life. Third, some circumstances, such as the ready availability of dietary fats, are so recent that natural selection has not yet had a chance to deal with them. Fourth, the body may fall victim to trade-offs between a trait's benefits and its costs; a textbook example is the sickle cell gene, which also protects against malaria. Finally, the process of natural selection is constrained in ways that leave us with suboptimal design features, as in the case of the mammalian eye.

### **Evolved Defenses**

Perhaps the most obviously useful defense mechanism is coughing; people who cannot clear foreign matter from their lungs are likely to die from pneumonia. The capacity for pain is also certainly beneficial. The rare individuals who cannot feel pain fail even to experience discomfort from staying in the same position for long periods. Their unnatural stillness impairs the blood supply to their joints, which then deteriorate. Such pain-free people usually die by early adulthood from tissue damage and infections. Cough or pain is usually interpreted as disease or trauma but is actually part of the solution rather than the problem. These defensive capabilities, shaped by natural selection, are kept in reserve until needed.

Less widely recognized as defenses are fever, nausea, vomiting, diarrhea, anxiety, fatigue, sneezing and inflammation. Even some physicians remain unaware of fever's utility. No mere increase in metabolic rate, fever is a carefully regulated rise in the set point of the body's thermostat. The higher body temperature facilitates the destruction of pathogens. Work by Matthew J. Kluger of the Lovelace Institute in Albuquerque, N.M., has shown that even cold-blooded lizards, when infected, move to warmer places until their bodies are several degrees above their usual temperature. If prevented from moving to the warm part of their cage, they are at increased risk of death from the infection. In a similar study by Evelyn Satinoff of the University of Delaware, elderly rats, who can no longer achieve the high fevers of their younger lab companions, also instinctively sought hotter environments when challenged by infection.

A reduced level of iron in the blood is another misunderstood defense mechanism. People suffering from chronic infection often have decreased levels of blood iron. Although such low iron is sometimes blamed for the illness, it actually is a protective response: during infection, iron is sequestered in the liver, which prevents invading bacteria from getting adequate supplies of this vital element.

Morning sickness has long been considered an unfortunate side effect of

pregnancy. The nausea, however, coincides with the period of rapid tissue differentiation of the fetus, when development is most vulnerable to interference by toxins. And nauseated women tend to restrict their intake of strong-tasting, potentially harmful substances. These observations led independent researcher Margie Profet to hypothesize that the nausea of pregnancy is an adaptation whereby the mother protects the fetus from exposure to toxins. Profet tested this idea by examining pregnancy outcomes. Sure enough, women with more nausea were less likely to suffer miscarriages. (This evidence supports the hypothesis but is hardly conclusive. If Profet is correct, further research should discover that pregnant females of many species show changes in food preferences. Her theory also predicts an increase in birth defects among offspring of women who have little or no morning sickness and thus eat a wider variety of foods during pregnancy.)

Another common condition, anxiety, obviously originated as a defense in dangerous situations by promoting escape and avoidance. A 1992 study by Lee A. Dugatkin of the University of Louisville evaluated the benefits of fear in guppies. He grouped them as timid, ordinary or bold, depending on their reaction to the presence of smallmouth bass. The timid hid, the ordinary simply swam away, and the bold maintained their ground and eyed the bass. Each guppy group was then left alone in a tank with a bass. After 60 hours, 40 percent of the timid guppies had survived, as had only 15 percent of the ordinary fish. The entire complement of bold guppies, on the other hand, wound up aiding the transmission of bass genes rather than their own.

Selection for genes promoting anxious behaviors implies that there should be people who experience too much anxiety, and indeed there are. There should also be hypophobic individuals who have insufficient anxiety, either because of genetic tendencies or antianxiety drugs. The exact nature and frequency of such a syndrome is an open question, as few people come to psychiatrists complaining of insufficient apprehension. But if sought, the pathologically nonanxious may be found in emergency rooms, jails and unemployment lines.

The utility of common and unpleasant conditions such as diarrhea, fever and anxiety is not intuitive. If natural selection shapes the mechanisms that regulate defensive responses, how can people get away with using drugs to block these defenses without doing their bodies obvious harm? Part of the answer is that we do, in fact, sometimes do ourselves a disservice by disrupting defenses.

Herbert L. DuPont of the University of Texas at Houston and Richard B. Hornick of Orlando Regional Medical Center studied the diarrhea caused by *Shigella* infection and found that people who took antidiarrhea drugs

stayed sick longer and were more likely to have complications than those who took a placebo. In another example, Eugene D. Weinberg of Indiana University has documented that well-intentioned attempts to correct perceived iron deficiencies have led to increases in infectious disease, especially amebiasis, in parts of Africa. Although the iron in most oral supplements is unlikely to make much difference in otherwise healthy people with everyday infections, it can severely harm those who are infected and malnourished. Such people cannot make enough protein to bind the iron, leaving it free for use by infectious agents.

On the morning-sickness front, an anti-nausea drug was recently blamed for birth defects. It appears that no consideration was given to the possibility that the drug itself might be harmless to the fetus but could still be associated with birth defects, by interfering with the mother's defensive nausea.

Another obstacle to perceiving the benefits of defenses arises from the observation that many individuals regularly experience seemingly worthless reactions of anxiety, pain, fever, diarrhea or nausea. The explanation requires an analysis of the regulation of defensive responses in terms of signal-detection theory. A circulating toxin may come from something in the stomach. An organism can expel it by vomiting, but only at a price. The cost of a false alarm--vomiting when no toxin is truly present--is only a few calories. But the penalty for a single missed authentic alarm--failure to vomit when confronted with a toxin--may be death.

Natural selection therefore tends to shape regulation mechanisms with hair triggers, following what we call the smoke-detector principle. A smoke alarm that will reliably wake a sleeping family in the event of any fire will necessarily give a false alarm every time the toast burns. The price of the human body's numerous "smoke alarms" is much suffering that is completely normal but in most instances unnecessary. This principle also explains why blocking defenses is so often free of tragic consequences. Because most defensive reactions occur in response to insignificant threats, interference is usually harmless; the vast majority of alarms that are stopped by removing the battery from the smoke alarm are false ones, so this strategy may seem reasonable. Until, that is, a real fire occurs.

### **Conflicts with Other Organisms**

Natural selection is unable to provide us with perfect protection against all pathogens, because they tend to evolve much faster than humans do. *E. coli*, for example, with its rapid rates of reproduction, has as much opportunity for mutation and selection in one day as humanity gets in a millennium. And our defenses, whether natural or artificial, make for potent selection

forces. Pathogens either quickly evolve a counterdefense or become extinct. Amherst College biologist Paul W. Ewald has suggested classifying phenomena associated with infection according to whether they benefit the host, the pathogen, both or neither. Consider the runny nose associated with a cold. Nasal mucous secretion could expel intruders, speed the pathogen's transmission to new hosts or both [see "The Evolution of Virulence," by Paul W. Ewald; *Scientific American*, April 1993]. Answers could come from studies examining whether blocking nasal secretions shortens or prolongs illness, but few such studies have been done.

Humanity won huge battles in the war against pathogens with the development of antibiotics and vaccines. Our victories were so rapid and seemingly complete that in 1969 U.S. Surgeon General William H. Stewart said that it was "time to close the book on infectious disease." But the enemy, and the power of natural selection, had been underestimated. The sober reality is that pathogens apparently can adapt to every chemical researchers develop. ("The war has been won," one scientist more recently quipped. "By the other side.")

Antibiotic resistance is a classic demonstration of natural selection. Bacteria that happen to have genes that allow them to prosper despite the presence of an antibiotic reproduce faster than others, and so the genes that confer resistance spread quickly. As shown by Nobel laureate Joshua Lederberg of the Rockefeller University, they can even jump to different species of bacteria, borne on bits of infectious DNA. Today some strains of tuberculosis in New York City are resistant to all three main antibiotic treatments; patients with those strains have no better chance of surviving than did TB patients a century ago. Stephen S. Morse of Columbia University notes that the multidrug-resistant strain that has spread throughout the East Coast may have originated in a homeless shelter across the street from Columbia-Presbyterian Medical Center. Such a phenomenon would indeed be predicted in an environment where fierce selection pressure quickly weeds out less hardy strains. The surviving bacilli have been bred for resistance.

Many people, including some physicians and scientists, still believe the outdated theory that pathogens necessarily become benign after long association with hosts. Superficially, this makes sense. An organism that kills rapidly may never get to a new host, so natural selection would seem to favor lower virulence. Syphilis, for instance, was a highly virulent disease when it first arrived in Europe, but as the centuries passed it became steadily more mild. The virulence of a pathogen is, however, a life

history trait that can increase as well as decrease, depending on which option is more advantageous to its genes.

For agents of disease that are spread directly from person to person, low virulence tends to be beneficial, as it allows the host to remain active and in contact with other potential hosts. But some diseases, like malaria, are transmitted just as well-or better-by the incapacitated. For such pathogens, which usually rely on intermediate vectors like mosquitoes, high virulence can give a selective advantage. This principle has direct implications for infection control in hospitals, where health care workers' hands can be vectors that lead to selection for more virulent strains.

In the case of cholera, public water supplies play the mosquitoes' role. When water for drinking and bathing is contaminated by waste from immobilized patients, selection tends to increase virulence, because more diarrhea enhances the spread of the organism even if individual hosts quickly die. But, as Ewald has shown, when sanitation improves, selection acts against classical *Vibrio cholerae* bacteria in favor of the more benign El Tor biotype. Under these conditions, a dead host is a dead end. But a less ill and more mobile host, able to infect many others over a much longer time, is an effective vehicle for a pathogen of lower virulence. In another example, better sanitation leads to displacement of the aggressive *Shigella flexneri* by the more benign *S. sonnei*.

Such considerations may be relevant for public policy. Evolutionary theory predicts that clean needles and the encouragement of safe sex will do more than save numerous individuals from HIV infection. If humanity's behavior itself slows HIV transmission rates, strains that do not soon kill their hosts have the long-term survival advantage over the more virulent viruses that then die with their hosts, denied the opportunity to spread. Our collective choices can change the very nature of HIV.

Conflicts with other organisms are not limited to pathogens. In times past, humans were at great risk from predators looking for a meal. Except in a few places, large carnivores now pose no threat to humans. People are in more danger today from smaller organisms' defenses, such as the venoms of spiders and snakes. Ironically, our fears of small creatures, in the form of phobias, probably cause more harm than any interactions with those organisms do. Far more dangerous than predators or poisoners are other members of our own species. We attack each other not to get meat but to get mates, territory and other resources. Violent conflicts between individuals are overwhelmingly between young men in competition and give rise to organizations to advance these aims. Armies, again usually

composed of young men, serve similar objectives, at huge cost.

Even the most intimate human relationships give rise to conflicts having medical implications. The reproductive interests of a mother and her infant, for instance, may seem congruent at first but soon diverge. As noted by biologist Robert L. Trivers in a now classic 1974 paper, when her child is a few years old, the mother's genetic interests may be best served by becoming pregnant again, whereas her offspring benefits from continuing to nurse. Even in the womb there is contention. From the mother's vantage point, the optimal size of a fetus is a bit smaller than that which would best serve the fetus and the father. This discord, according to David Haig of Harvard University, gives rise to an arms race between fetus and mother over her levels of blood pressure and blood sugar, sometimes resulting in hypertension and diabetes during pregnancy.

### **Coping with Novelty**

Making rounds in any modern hospital provides sad testimony to the prevalence of diseases humanity has brought on itself. Heart attacks, for example, result mainly from atherosclerosis, a problem that became widespread only in this century and that remains rare among hunter-gatherers. Epidemiological research furnishes the information that should help us prevent heart attacks: limit fat intake, eat lots of vegetables, and exercise hard each day. But hamburger chains proliferate, diet foods languish on the shelves, and exercise machines serve as expensive clothing hangers throughout the land. The proportion of overweight Americans is one third and rising. We all know what is good for us. Why do so many of us continue to make unhealthy choices?

Our poor decisions about diet and exercise are made by brains shaped to cope with an environment substantially different from the one our species now inhabits. On the African savanna, where the modern human design was fine-tuned, fat, salt and sugar were scarce and precious. Individuals who had a tendency to consume large amounts of fat when given the rare opportunity had a selective advantage. They were more likely to survive famines that killed their thinner companions. And we, their descendants, still carry those urges for foodstuffs that today are anything but scarce. These evolved desires--inflamed by advertisements from competing food corporations that themselves survive by selling us more of whatever we want to buy--easily defeat our intellect and willpower. How ironic that humanity worked for centuries to create environments that are almost literally flowing with milk and honey, only to see our success responsible for much modern disease and untimely death.

Increasingly, people also have easy access to many kinds of drugs, especially alcohol and tobacco, that are responsible for a huge proportion

of disease, health care costs and premature death. Although individuals have always used psychoactive substances, widespread problems materialized only following another environmental novelty: the ready availability of concentrated drugs and new, direct routes of administration, especially injection. Most of these substances, including nicotine, cocaine and opium, are products of natural selection that evolved to protect plants from insects. Because humans share a common evolutionary heritage with insects, many of these substances also affect our nervous system.

This perspective suggests that it is not just defective individuals or disordered societies that are vulnerable to the dangers of psychoactive drugs; all of us are susceptible because drugs and our biochemistry have a long history of interaction. Understanding the details of that interaction, which is the focus of much current research from both a proximate and evolutionary perspective, may well lead to better treatments for addiction.

The relatively recent and rapid increase in breast cancer must be the result in large part of changing environments and ways of life, with only a few cases resulting solely from genetic abnormalities. Boyd Eaton and his colleagues at Emory University reported that the rate of breast cancer in today's "nonmodern" societies is only a tiny fraction of that in the U.S. They hypothesize that the amount of time between menarche and first pregnancy is a crucial risk factor, as is the related issue of total lifetime number of menstrual cycles. In hunter-gatherers, menarche occurs at about age 15 or later, followed within a few years by pregnancy and two or three years of nursing, then by another pregnancy soon after. Only between the end of nursing and the next pregnancy will the woman menstruate and thus experience the high levels of hormones that may adversely affect breast cells.

In modern societies, in contrast, menarche occurs at age 12 or 13--probably at least in part because of a fat intake sufficient to allow an extremely young woman to nourish a fetus--and the first pregnancy may be decades later or never. A female hunter-gatherer may have a total of 150 menstrual cycles, whereas the average woman in modern societies has 400 or more. Although few would suggest that women should become pregnant in their teens to prevent breast cancer later, early administration of a burst of hormones to simulate pregnancy may reduce the risk. Trials to test this idea are now under way at the University of California at San Diego.

### **Trade-offs and Constraints**

Compromise is inherent in every adaptation. Arm bones three times their current thickness would almost never break, but *Homo sapiens* would be lumbering creatures on a never-ending quest for calcium. More sensitive ears might sometimes be useful, but we would be distracted by the noise of



air molecules banging into our eardrums.

Such trade-offs also exist at the genetic level. If a mutation offers a net reproductive advantage, it will tend to increase in frequency in a population even if it causes vulnerability to disease. People with two copies of the sickle cell gene, for example, suffer terrible pain and die young. People with two copies of the "normal" gene are at high risk of death from malaria. But individuals with one of each are protected from both malaria and sickle cell disease. Where malaria is prevalent, such people are fitter, in the Darwinian sense, than members of either other group. So even though the sickle cell gene causes disease, it is selected for where malaria persists. Which is the "healthy" allele in this environment? The question has no answer. There is no one normal human genome--there are only genes.

Many other genes that cause disease must also have offered benefits, at least in some environments, or they would not be so common. Because cystic fibrosis (CF) kills one out of 2,500 Caucasians, the responsible genes would appear to be at great risk of being eliminated from the gene pool. And yet they endure. For years, researchers mused that the CF gene, like the sickle cell gene, probably conferred some advantage. Recently a study by Gerald B. Pier of Harvard Medical School and his colleagues gave substance to this informed speculation: having one copy of the CF gene appears to decrease the chances of the bearer acquiring a typhoid fever infection, which once had a 15 percent mortality.

Aging may be the ultimate example of a genetic trade-off. In 1957 one of us (Williams) suggested that genes that cause aging and eventual death could nonetheless be selected for if they had other effects that gave an advantage in youth, when the force of selection is stronger. For instance, a hypothetical gene that governs calcium metabolism so that bones heal quickly but that also happens to cause the steady deposition of calcium in arterial walls might well be selected for even though it kills some older people. The influence of such pleiotropic genes (those having multiple effects) has been seen in fruit flies and flour beetles, but no specific example has yet been found in humans. Gout, however, is of particular interest, because it arises when a potent antioxidant, uric acid, forms crystals that precipitate out of fluid in joints. Antioxidants have antiaging effects, and plasma levels of uric acid in different species of primates are closely correlated with average adult life span. Perhaps high levels of uric acid benefit most humans by slowing tissue aging, while a few pay the price with gout.

Other examples are more likely to contribute to more rapid aging. For instance, strong immune defenses protect us from infection but also inflict continuous, low-level tissue damage. It is also possible, of course, that most genes that cause aging have no benefit at any age--they simply never decreased reproductive fitness enough in the natural environment to be selected against. Nevertheless, over the next decade research will surely identify specific genes that accelerate senescence, and researchers will soon thereafter gain the means to interfere with their actions or even change them. Before we tinker, however, we should determine whether these actions have benefits early in life.

Because evolution can take place only in the direction of time's arrow, an organism's design is constrained by structures already in place. As noted, the vertebrate eye is arranged backward. The squid eye, in contrast, is free from this defect, with vessels and nerves running on the outside, penetrating where necessary and pinning down the retina so it cannot detach. The human eye's flaw results from simple bad luck; hundreds of millions of years ago, the layer of cells that happened to become sensitive to light in our ancestors was positioned differently from the corresponding layer in ancestors of squids. The two designs evolved along separate tracks, and there is no going back.

Such path dependence also explains why the simple act of swallowing can be life-threatening. Our respiratory and food passages intersect because in an early lungfish ancestor the air opening for breathing at the surface was understandably located at the top of the snout and led into a common space shared by the food passageway. Because natural selection cannot start from scratch, humans are stuck with the possibility that food will clog the opening to our lungs.

The path of natural selection can even lead to a potentially fatal cul-de-sac, as in the case of the appendix, that vestige of a cavity that our ancestors employed in digestion. Because it no longer performs that function, and as it can kill when infected, the expectation might be that natural selection would have eliminated it. The reality is more complex. Appendicitis results when inflammation causes swelling, which compresses the artery supplying blood to the appendix. Blood flow protects against bacterial growth, so any reduction aids infection, which creates more swelling. If the blood supply is cut off completely, bacteria have free rein until the appendix bursts. A slender appendix is especially susceptible to this chain of events, so appendicitis may, paradoxically, apply the selective pressure that maintains a large appendix. Far from arguing that everything in the body is perfect, an evolutionary analysis reveals that we live with some very unfortunate legacies and that some vulnerabilities may even be actively maintained by the force of natural selection.

## **Evolution of Darwinian Medicine**

Despite the power of the Darwinian paradigm, evolutionary biology is just now being recognized as a basic science essential for medicine. Most diseases decrease fitness, so it would seem that natural selection could explain only health, not disease. A Darwinian approach makes sense only when the object of explanation is changed from diseases to the traits that make us vulnerable to diseases. The assumption that natural selection maximizes health also is incorrect--selection maximizes the reproductive success of genes. Those genes that make bodies having superior reproductive success will become more common, even if they compromise the individual's health in the end.

Finally, history and misunderstanding have presented obstacles to the acceptance of Darwinian medicine. An evolutionary approach to functional analysis can appear akin to naive teleology or vitalism, errors banished only recently, and with great effort, from medical thinking. And, of course, whenever evolution and medicine are mentioned together, the specter of eugenics arises. Discoveries made through a Darwinian view of how all human bodies are alike in their vulnerability to disease will offer great benefits for individuals, but such insights do not imply that we can or should make any attempt to improve the species. If anything, this approach cautions that apparent genetic defects may have unrecognized adaptive significance, that a single "normal" genome is nonexistent and that notions of "normality" tend to be simplistic.

The systematic application of evolutionary biology to medicine is a new enterprise. Like biochemistry at the beginning of this century, Darwinian medicine very likely will need to develop in several incubators before it can prove its power and utility. If it must progress only from the work of scholars without funding to gather data to test their ideas, it will take decades for the field to mature. Departments of evolutionary biology in medical schools would accelerate the process, but for the most part they do not yet exist. If funding agencies had review panels with evolutionary expertise, research would develop faster, but such panels remain to be created. We expect that they will.

The evolutionary viewpoint provides a deep connection between the states of disease and normal functioning and can integrate disparate avenues of medical research as well as suggest fresh and important areas of inquiry. Its utility and power will ultimately lead to recognition of evolutionary biology as a basic medical science.

### **Evolutionary Biology Resources**

What is Darwinian Medicine?: Randolph Nesse, University of Michigan

Dr. Darwin by Lori Owenstein

#### Further Reading

EVOLUTION OF INFECTIOUS DISEASE. P. W. Ewald. Oxford University Press, 1994.

DARWINIAN PSYCHIATRY. M. T. McGuire and A. Troisi. Harvard University Press, 1998.

EVOLUTION IN HEALTH AND DISEASE. Edited by S. Stearns. Oxford University Press, 1998.

EVOLUTIONARY MEDICINE. W. R. Trevathan et al. Oxford University Press (in press).

#### The Authors

RANDOLPH M. NESSE and GEORGE C. WILLIAMS are the authors of the 1994 book *Why We Get Sick: The New Science of Darwinian Medicine*. Nesse received his medical degree from the University of Michigan Medical School in 1974. He is now professor of psychiatry at that institution and is director of the Evolution and Human Adaptation Program at the university's Institute for Social Research. Williams received his doctorate in 1955 from the University of California, Los Angeles, and quickly became one of the world's foremost evolutionary theorists. A member of the National Academy of Sciences, he is professor emeritus of ecology and evolution at the State University of New York at Stony Brook and edits the *Quarterly Review of Biology*.