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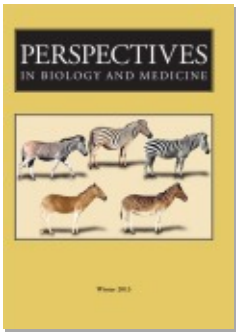

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ABSTRACT Evolutionary medicine is a new field whose goal is to incorporate an evolutionary perspective into medical education, research, and practice. Evolutionary biologists and physicians have traditionally been concerned with different problems and have developed different ways of approaching and understanding biological phenomena. Evolutionary biologists analyze the properties of populations and the ways in which populations change over time, while physicians focus on the care of their individual patients. Evolutionists are concerned with the ultimate causes of biological phenomena, causes that operated during the phylogenetic history of a species, while physicians and biomedical scientists have been more interested in proximate causes, causes that operate during the ontogeny and life of an individual. Evolutionary medicine is based on the belief that an integration of these complementary views of biological phenomena will improve our understanding of health and disease. This essay reviews the theory of evolution by natural selection, as it was developed by Darwin and as it is now understood by evolutionary biologists. It emphasizes the importance of variation and selection, points out the differences between evolutionary fitness and health, and discusses some of the reasons why our evolutionary heritage has left us vulnerable to disease.

Charles Darwin "had medicine in his blood" (Bynum 1983). His father and grandfather were physicians, and he himself studied medicine. Although Darwin left medical school after two years and did not become a physician, he retained a strong interest in medicine and regularly used examples drawn from human biology and medicine in his writings. Clearly, he believed that medicine fell within the purview of his theory of evolution, and he recog-

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nized the ways in which the study of evolution and of medicine could be mutually enriching. In *The Descent of Man* (1871), Darwin argued that humans, like other species, have evolved from earlier, ancestral species. "Descent with modification," Darwin's term for evolution, accounts for the many anatomic and physiologic similarities between humans and other animals. Rudimentary organs played an important role in Darwin's argument. These organs have no function in humans and, as with the appendix, they may increase the risk of disease and death. They can only be understood as relics of structures that had a function in our evolutionary ancestors and that have decreased in size but have not been eliminated during human evolution. Darwin was especially interested in heritable variation, which plays a central role in his theory of evolution by natural selection. In *The Variation of Animals and Plants under Domestication* (1883), Darwin discussed heritable variation in humans. After mentioning a number of trivial or unimportant variations, such as families in which several members had one lock of hair that was differently colored from the rest, he noted that there are also inherited variations in predispositions to various diseases, and he discussed heritable diseases of the eye in detail (1:452–54).

As the theory of evolution became more widely known and accepted in the late 19th century, some physicians began to apply evolutionary concepts to medicine (Bynum 1983; Zampieri 2009). For the most part, however, these efforts had little lasting impact. Perhaps the most important contribution of evolutionary thinking to medicine in the 19th century was the work of the neurologist John Hughlings Jackson. Jackson (1884) viewed both the development of the nervous system and the loss of function in neurological diseases from an evolutionary perspective. He saw the evolution of the nervous system as progressive, beginning with the automatic or involuntary regulation of respiration and circulation, and culminating in the "highest centres" of consciousness and mind, which controlled the lower centers. Jackson noted that these highest, and evolutionarily most recent, portions of the brain were most susceptible to damage by neurotoxins (alcohol, for example) or disease (epilepsy), and thus many neurological diseases resulted in what he called "dissolutions," or reversals of evolution. Jackson's views on the hierarchical, evolutionary organization of the nervous system continue to influence thinking in neurology. For example, Paul MacLean's (1990) concept of the triune brain proposes that the human brain comprises a reptilian brainstem, an early mammalian limbic system, and a more recent neocortex. But Jackson's ideas have had relatively limited impact on other branches of medicine.

In the mid-20th century, the British biologist J. B. S. Haldane (1949a) suggested that "the struggle against disease, and particularly infectious disease, has been a very important evolutionary agent" (p. 68). Haldane and Anthony Allison, a physician interested in parasitology and tropical medicine, independently proposed what became known as the "malaria hypothesis." Specifically, they proposed that the alleles which cause the diseases thalassemia and sickle-cell anemia

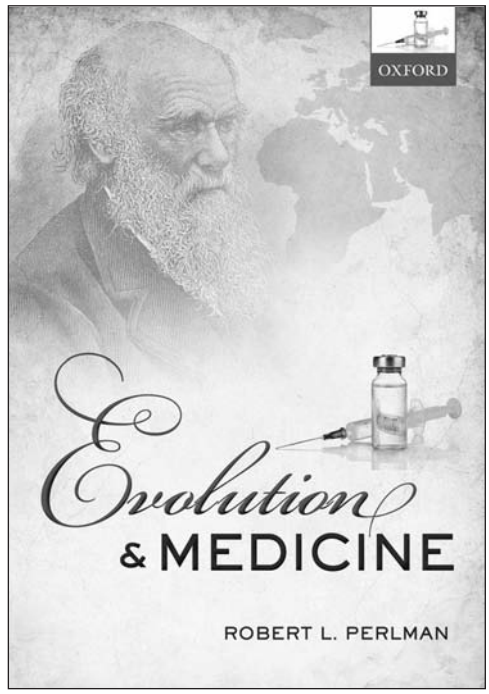

FIGURE 1

Cover of Evolution and Medicine *(Oxford: Oxford University Press, 2013).*

spread in human populations because when these alleles were present in heterozygous individuals, they conferred resistance to malaria (Allison 1954; Haldane 1949b). Allison went on to demonstrate that people who were heterozygous for sickle-cell hemoglobin were in fact resistant to malaria, and that the selective advantage of malaria resistance could account for the frequency and geographic distribution of the sickle-cell trait (Allison 1964). Although Haldane's insight and Allison's research stimulated a search for other genetic variants that were maintained because they conferred resistance to malaria, such as glucose-6-phosphate dehydrogenase deficiency (Luzzatto, Usanga, and Reddy 1969), they too did not lead to a broader incorporation of evolutionary thinking into medicine.

The emergence of antibiotic-resistant bacteria shortly after the introduction of antibiotics into clinical medicine is the most striking example of the medical relevance of evolution (Dubos 1942). Concerns about antibiotic resistance led to important studies on the mechanisms of resistance and to the development of new antibiotics that overcame this resistance. Recognition that the spread of antibiotic-resistant bacteria was due to selection for antibiotic resistance led to calls for the more responsible use of these drugs. Unfortunately, these calls largely went unheeded. Moreover, little attention was given to understanding the dynamics of selection or the ways in which regimens of antibiotic usage might modulate the strength of selection for antibiotic resistance.

Until recently, the hierarchical organization of the nervous system, the prevalence of disease-associated alleles, and the spread of antibiotic resistance were simply isolated instances of the application of evolutionary concepts to medicine. Stimulated by the pioneering publications of Randolph Nesse and George Williams in the 1990s, however, physicians and other scientists have now begun to integrate evolutionary biology and medicine into a coherent discipline (Nesse and Williams 1994; Williams and Nesse 1991). This is the new field of Darwinian, or evolutionary, medicine (Gluckman, Beedle, and Hanson 2009; Stearns and Koella 2008; Trevathan, Smith, and McKenna 2008).

Given that the theory of evolution by natural selection is the central, unifying theory in biology and that our understanding of disease is heavily based on our knowledge of human biology, it may seem surprising that evolutionary medicine is such a new field. Yet there are many reasons why evolutionary biology and medicine developed as separate disciplines and have until recently remained isolated from one another. When Darwin proposed his theory of evolution by natural selection, medicine was already a well-established profession, with a history in the West going back at least 2,500 years to Hippocrates. In the 19th century, medical practice stressed careful physical examination of patients, description of the natural histories of diseases, and correlation of the signs and symptoms of disease with autopsy findings. Later, with the rise of the germ theory of disease, medicine became increasingly focused on laboratory diagnoses and on identifying the etiologies or causes of disease (Porter 1998). Medicine was taught in its own institutions, which were typically based in hospitals, and the medical curriculum was already crowded. There was no room and no apparent need to bring the theory of evolution into medical education, research, or practice.

Evolutionary biology did not develop into an academic discipline until long after Darwin. At the time of the Flexner Report (Flexner 1910), which laid the foundations for today's science-based medical education, there were still no university departments, professional societies, or scholarly journals devoted to evolution. Only after the integration of evolutionary biology with genetics in the 1930s and 1940s did evolutionary biology become a mature science (Ruse 2009). Even then, evolutionary biology and medicine continued to develop as separate disciplines, with little interaction. Evolutionary biologists were concerned with classification of species, with enriching and analyzing the fossil record, and with finding evidence of natural selection in the wild. Except for paleontological studies of human origins, most evolutionists shied away from human biology. Many of these biologists worked in museums and field stations, isolated from medical centers, and they may not have wanted to be associated with the eugenics programs of the early 20th century that had been embraced by some evolutionists (Kevles 1995). Perhaps most importantly, as the following brief review of the theory of evolution by natural selection will make clear, evolutionary biology and medicine have different and seemingly incompatible ways

of understanding biological phenomena. Evolutionary biologists and physicians have been concerned with different problems, they speak different specialized languages, and they see the natural world in different ways. These differences have helped to keep these fields apart and continue to hinder their integration.

The Theory of Evolution by Natural Selection

Although our understanding of evolution has increased greatly since Darwin's time, biologists still use essentially the same arguments to support the theory of evolution by natural selection as Darwin did when he proposed it.

Darwin began by pointing out the abundant variation that exists among individual organisms in a population. The first two chapters of *On the Origin of Species* (1859) are devoted to a discussion of variation, first in domesticated species and then in nature. Darwin focused on small, often barely discernible, variations; he regarded the greatly deviant organisms that occasionally arise in nature as "monstrosities" that had no role in evolution. Of course, people had long been aware of variations among organisms within populations or species. As Ernst Mayr (1964) has emphasized, however, before Darwin species were understood in typological or essentialist terms. In this view, each species was thought to be characterized by a unique, unchanging essence. Variation was seen as an irrelevant distraction, due to imperfections in the material realization of the ideal form of the species. Darwin introduced what Mayr called "population thinking" into biology. Biologists no longer think of species as having ideal or essential forms: instead, they commonly think about species (at least extant, sexually reproducing species) in terms of Mayr's biological species concept. According to this concept, species comprise populations of organisms that can interbreed and produce viable offspring in nature but that otherwise exhibit a wealth of variation and change over time—in other words, species evolve (Mayr 1988a). Variation remains a critical aspect of evolutionary thinking because it provides the raw material for evolution by natural selection.

Next, Darwin pointed out that, while the number of organisms in a population might potentially increase without limit, the resources needed to support these populations are finite. In other words, the reproductive capacity of the organisms in a population must greatly exceed what we now call the carrying capacity of the environment, the population that the local habitat can sustain. This inequality between reproductive potential and environmental resources means that individual organisms in a population must compete for survival and reproduction. Darwin called this competition the "struggle for existence," a concept based on Thomas Malthus's *Essay on the Principle of Population* (1798); in *The Origin*, he refers to the struggle for existence as "the doctrine of Malthus applied with manifold force to the whole animal and vegetable kingdoms" (Darwin 1859, p. 63). Malthus was concerned with the disparity between human population growth and the availability of food. Darwin expanded Malthus's ideas from

humans to all species and from food to all of the environmental resources that organisms need to survive and reproduce. Evolutionists understand the struggle for existence in what Darwin called "a large and metaphorical sense" (p. 62): it refers to all of the difficulties that organisms must overcome in order to survive and reproduce in the complex and challenging environments in which they live. Organisms struggle to secure food and other resources they need to grow and develop, to avoid being eaten by predators, to attract mating partners and reproduce, and to promote the survival of their offspring. Although the term may conjure visions of hand-to-hand combat, the struggle for existence is primarily a struggle between organisms and their environments. Only occasionally does the struggle for existence involve a direct physical confrontation between two individuals of the same species, as in two dogs fighting over a scarce piece of meat or two males fighting to mate with a female.

The environment in which the struggle for existence takes place includes both the physical or nonliving environment (air, water, sunlight, climate, etc.) and the living or biotic environment. The biotic environment comprises all of the other species with which organisms interact or on which they depend (directly or indirectly), as well as other members of their own species. Organisms of other species constitute especially important components of an organism's environment. For this reason, evolution is closely connected to ecology and to the ecological relationships among species. Many of us in developed countries live in environments in which our interactions with organisms of other species are largely hidden. Our direct experience is limited to our pets, to the plants and animals in our gardens and parks, to the insects and other pests that annoy or plague us, to infectious microorganisms, and to the food we eat, much of which we purchase prepackaged in grocery stores. We should remember, however, that our lives and our health are intimately related to and affected by the innumerable species that form part of our environment—those that contribute to our health, as well as those that cause disease.

Those individuals that are successful in the struggle for existence will survive, reproduce, and leave offspring; in evolutionary terms, producing offspring who themselves survive and reproduce is the definition of success. Biologists commonly use the term *fitness*, sometimes modified as *reproductive* or *evolutionary fitness* to avoid confusion, to denote this reproductive success. The term "survival of the fittest," introduced by the English philosopher Herbert Spencer (1864), has become a widely used metaphor to describe the evolutionary process. This metaphor may be misleading, however, because it is easy for people who are concerned with "fitness" today to think that evolutionary fitness refers to something akin to physical fitness. In evolutionary terms, fitness does not simply refer to strength or endurance, but to all of the traits that enable organisms to function—to survive and produce offspring—in their environments. A more appropriate meaning of *fitness* might be "suitability." Successful organisms are well

suited to their environments. They fit into and may shape their environments the way hands fit into and shape gloves.

"Survival of the fittest" may also be misleading because it seems to imply that fitness is an attribute of individual organisms. Although we often talk loosely about the fitness of organisms, fitness is best understood in terms of alleles or genotypes. In this respect, fitness is the expected average reproductive success of organisms of a given genotype, relative to the average reproductive success of other organisms in the population. Alleles that enhance fitness survive in the sense that they are preferentially transmitted from parents to offspring. Thus, in genetic terms, fitness may be thought of as the ability of organisms of a specific genotype to contribute genes to the gene pools of their populations. Organisms can pass on their genes directly, by their own reproduction, or indirectly, by enhancing the reproductive success of their genetic relatives. A broader concept of fitness, which is especially relevant to social species such as humans, is *inclusive fitness*, which comprises both the direct and indirect components of fitness (Hamilton 1964).

Although Darwin did not understand the molecular basis of heredity, he recognized that many traits are heritable. By and large, offspring tend to resemble their parents. As a result, traits that increase survival and reproduction—traits that make organisms well suited to their environments and thus enable them to succeed in the struggle for existence—will in general spread in the population. In contrast, traits that decrease survival and reproduction, and the alleles that underlie these traits, will, over time, be eliminated. This is natural selection, which Darwin defined as "This preservation of favourable variations and the rejection of injurious variations" (Darwin 1859, p. 81). Favorable variations—traits associated with increased fitness—that are preserved by natural selection are known as adaptations. Darwin adopted the term *natural selection* by analogy with artificial selection, which he called "selection by man." Natural selection may also be a misleading term, since it implies that nature, like humans, is actively selecting the traits that spread in populations. It may be more appropriately understood as a process of nonrandom elimination of organisms, along with their traits and their genes. Darwin rarely used the word *evolution*, which originally meant unrolling or unfolding. In the 19th century, evolution was commonly used to describe development, which was thought to result from the unfolding of a pre-existing developmental plan. Instead, as mentioned earlier, Darwin referred to evolution as "descent with modification."

All that is needed for Darwinian evolution, or evolution by selection, is a population of entities that exhibit heritable variation in traits that affect their reproductive success, their success in leaving progeny who themselves survive and reproduce. Since populations of living organisms have these properties, evolution by natural selection is inevitable (Lewontin 1970). Other entities that have these properties, including computer viruses, cultural traits, and artificial organisms,

may evolve by selective mechanisms that are analogous to natural selection. Artificial selection, or selection by humans, continues to shape the evolution of domesticated species of plants and animals, as well as the evolution of antibiotic resistance in bacteria and other pathogens. Natural selection may be thought of as a natural law of biology; it is a necessary consequence of the nature of living organisms.

Evolution, however, is a historical process, which depends on chance events and historical contingencies as well as on natural selection. For this reason, the course of evolution is not predictive in the way that some physical laws are. As the French biologist Jacques Monod (1971) has written, biological processes result from "chance and necessity." Natural selection plays a special role in evolution because it is the process that gives rise to adaptations, to traits that enhance reproductive fitness. Despite the attention that is understandably given to natural selection, however, we should not forget or minimize the importance of chance in evolution.

An important component of natural selection is sexual selection, which results from competition among members of the same sex for access to mating partners and for being chosen by members of the opposite sex (Cronin 1991). The peacock's tail is the classic example of a trait that arose and is maintained by sexual selection. Large, brightly colored tails attract predators and decrease the survival of peacocks. These large tails evolved because peahens preferred to mate with peacocks who had them, thereby increasing the reproductive success of these peacocks. Many human traits, including patterns of death and disability, are thought to have evolved as a result of sexual selection (Kruger and Nesse 2004).

Evolution by natural selection begins with the presence of heritable variations among individual organisms. Organisms that have favorable variations will (relative to organisms without these variations) survive, reproduce, and transmit these traits to their offspring, and so adaptations, traits that increase reproductive success, will spread in a population. Equally importantly, traits that reduce reproductive success—Darwin's "injurious variations"—will decrease in frequency. For the most part, evolution involves the gradual accumulation and summation of many small variations. As a result, the production of adaptations is a slow process, typically taking many, many generations. If two populations of a species evolve in different environments, they will slowly come to differ, both because different traits will enhance fitness and be selected in different environments, and because of chance events that occur in one population but not the other. As these populations diverge to the point that they are recognizably different, they will generally be referred to as different varieties or subspecies. And as they diverge further, organisms from the two populations may no longer mate with one another because of physical, biochemical, or behavioral differences—or, if they do mate, they may not produce viable and fertile offspring. At this point, biologists would say they have evolved into different species. Biologists frequently distinguish between *microevolution*, evolutionary changes within a species

that lead to the spread of adaptations and the production of distinct varieties or subspecies, and *macroevolution*, the formation of new species or higher taxa. As Darwin argued, when microevolutionary processes are continued over long time periods, they can eventually lead to macroevolution. Adaptations to different environments often underlie the origin of species.

The Different Conceptual Bases of Medicine and Evolutionary Biology

Medicine and evolutionary biology bring markedly different perspectives to the study of biological phenomena. Medicine has traditionally focused on individuals. Physicians are concerned with the health and well-being of their individual patients, and their primary goal is to keep their patients healthy. When their patients do get sick, physicians are interested in diagnosing their patients' diseases and in understanding how these diseases cause the symptoms that they do, because they wish to restore their patients to health or at least relieve their discomfort. Only in times of epidemics are physicians concerned with the spread of disease in populations and with ways in which they might help their patients avoid these diseases. In contrast, evolutionary biology focuses on populations or species. Evolutionists are interested in variations within populations and the ways in which populations change over time. Individual survival and reproduction are crucial for evolution. Differences in the survival and fertility of individuals—differences in fitness of organisms with different genotypes—provide the basis for evolutionary change. But individuals are born, develop, progress through a life cycle, and die. Only populations evolve.

Physicians and evolutionists also use different metaphors to describe and understand their work. One of the most common metaphors for medicine is war; we talk about diseases as enemies and our therapeutic armamentarium as weapons. Richard Nixon's "war on cancer" is just one of the wars we have declared against disease. Sometimes we are unaware of these metaphors: as the British physician Paul Hodgkin (1985) pointed out, a "cohort," which is now used to describe a group of subjects in a clinical trial, was originally a group of soldiers in a Roman legion. The popularity of the "medicine is war" metaphor is not surprising, since modern therapeutics developed in the shadow of World War II and the Cold War. But the uncritical adoption of this metaphor, with patients as the battleground rather than the focus of medical attention, may lead physicians to carry out actions that are not in the best interests of their patients.

Evolutionary biologists also use military metaphors. For example, host-pathogen coevolution is often described as an "evolutionary arms race." But evolutionary concepts are more commonly expressed in economic than in military terms, and the parallels between ecology and economy run deeper than etymology. Karl Marx, who had a high regard for Darwin and his work, was perhaps the first person to realize this. As he commented in an 1862 letter to Friedrich

Engels: "It is remarkable how Darwin rediscovers, among the beasts and plants, the society of England with its division of labor, competition, opening up of new markets, 'inventions' and Malthusian 'struggle for existence.'" It is also not surprising that Darwin was influenced by Adam Smith and other British economists, and by the intellectual climate of Victorian England (Lewontin 1990; Schweber 1980). Metaphors such as "struggle for existence" and "survival of the fittest" are essential in helping us understand abstract concepts (Lakoff and Johnson 2003). But the failure to appreciate the ways in which metaphors shape our thinking can be problematic. We have already discussed some of the confusions caused by the metaphors of struggle and fitness. And as several authors have pointed out, the focus on competition in evolutionary thinking has hindered acceptance of the roles of cooperation and symbiosis (Ryan 2001; Sapp 1994; Weiss and Buchanan 2009).

Because of their concern for their individual patients, physicians develop expertise at synthesizing and integrating their patients' medical, personal, and family histories, their symptoms, the findings of physical examination, and the results of laboratory tests. This deep understanding of patients, and the relationships that develop in the process of gaining this understanding, is an integral part of medical care. In some respects, the diagnostic process in medicine is similar to the process of arriving at evolutionary explanations. Both require judgments about the ways that historical events have resulted in present conditions and both depend on abduction, or reasoning to the most likely explanation. But medical therapeutics is guided by controlled trials of a kind that are seldom possible in evolutionary biology. Because evolutionists are concerned about changes in populations over time, their research typically requires the creation of quantitative mathematical models to test hypotheses about the mechanisms and rates of these changes. Thus, the standards of evidence that are relevant to evolutionary experiments are totally different from those of evidence-based medicine. The different subject matters of medicine and evolutionary biology lead their practitioners to develop different intellectual styles.

The most widely cited definition of "health," as developed and promulgated by the World Health Organization, is not merely the absence of disease or infirmity but "a state of complete physical, mental, and social well-being" (WHO 2006). More recent definitions have stressed the abilities of individuals to adapt and self-manage in the face of social, physical, and emotional challenges (Huber et al. 2011). Natural selection, however, acts to maximize the reproductive success of organisms, not their well-being or their ability to self-manage. Selection may result in longevity and health, but these outcomes are byproducts of selection for increased reproductive fitness. Organisms have to live long enough and be healthy enough to reproduce and to promote the survival of their offspring, but that is all. Evolutionary fitness is not the same as health.

Physicians and their patients regularly confront tradeoffs and constraints, when they are forced to weigh the risks, benefits, and costs of treatment options,

but they usually view these tradeoffs as practical problems rather than as inescapable facts of life. The notion of health as a "state of complete . . . well-being" does not carry any acknowledgment that tradeoffs may prevent the attainment of this goal. In contrast, evolutionists recognize that tradeoffs and constraints limit the ability of natural selection to optimize fitness and believe that they play a large role in evolutionary processes.

Individual organisms are the products of two distinct histories—their own life history, or ontogeny, and the evolutionary history of their species, or phylogeny. Biologists often divide the causes of biological phenomena into proximate causes, causes that operate during the lifetime of an individual, and ultimate causes, causes that operated during the evolutionary history of the species (Mayr 1988b). Proximate causes are sometimes said to answer "how" questions—for example, how (by what physiological mechanisms) do we raise our body temperature in response to infection?—while ultimate causes answer "why" questions—why (for what evolutionary reasons) do we have a febrile response to infection? The Dutch ethologist Nikolaas Tinbergen (1963) pointed out that traits have two distinct proximate causes and two ultimate causes. The proximate causes of a trait include its development during an organism's ontogeny and the physiological or molecular mechanisms that produce it; the ultimate causes are its phylogenetic origin and its adaptive significance. Physicians have traditionally been concerned with proximate causes of disease because these are the causal pathways that are amenable to medical intervention. In contrast, evolutionists want to understand ultimate causes of biological phenomena. Recent advances in evolutionary development biology, or "evo-devo," have called attention to the relationship between evolution and development and have led to a blurring of the distinction between proximate and ultimate causes (Laland et al. 2011). As discussed below, there is currently great interest in understanding the ways in which our evolved mechanisms of development may predispose us to disease in adult life.

Physicians focus on the health of human beings. To a great extent, medicine has tried to separate humans from the rest of nature and protect us from species that might cause disease. Evolutionists, on the other hand, view populations as embedded in ecological communities that comprise a myriad of interrelated and interacting species, all of which are subject to natural selection and are therefore coevolving. Physicians certainly recognize environmental causes of disease, especially infectious diseases and diseases due to environmental toxins. Nonetheless, medical research has focused on the inner workings of human beings, on the physiological and pathophysiological mechanisms that promote health or lead to disease. Medicine is concerned with what Claude Bernard (1957) termed the "internal environment," the blood and extracellular fluids that provide the immediate environment in which our cells and organs function. In this view, health involves the maintenance of constant, or nearly constant, conditions in the internal environment—conditions that enable cells and organs to function prop-

erly—while diseases are manifest by deviations from these "normal" conditions. Evolutionary biologists appreciate that the physiological mechanisms that maintain homeostasis are adaptations that enhance fitness, but they are more interested in studying the interactions of organisms with their external environments, because it is these ecological interactions that shape the struggle for existence and natural selection. Appreciation of the physiological functions and pathophysiological effects of the human microbiome, the communities of microorganisms that inhabit our skin, intestines, and other body cavities, has led to the recognition that humans are ecological communities. Indeed, study of the microbiome is a growing area of research in which the interests of physicians and evolutionists are converging (Turnbaugh et al. 2007).

Finally, medicine and evolutionary biology have different ways of thinking about variation. Medicine focuses on notions of normality and abnormality. Physicians distinguish between "normal" values of traits, values that are associated with good health or that are common in the population, and "abnormal" values, values that are associated with an increased risk of disease. In a medical context, this distinction between normal and abnormal often makes good sense. Many deviations from normal values—elevated blood pressure, blood cholesterol, and body mass index, for example—are risk factors for diseases that may be prevented or postponed by medical interventions. Occasionally, however, extreme values of a trait—short stature, for example—may be labeled abnormal even if they do not have implications for health. Since the rise of the Human Genome Project, physicians are certainly aware of and concerned about genetic variations among their patients. But medicine is still influenced by an essentialist view of biology that tends to view phenotypic variations as deviations from a normal, healthy, or ideal state. This medical understanding of variation differs from that of evolutionary biologists, who view variation as a fundamental property of biological populations. Not only is variation abundant in nature, it provides the substrate for evolution by natural selection; if there weren't heritable variations among individuals, populations couldn't evolve. The values of specific traits among individuals typically exhibit a distribution, frequently a normal or lognormal distribution, that is associated with variations in fitness. Often, but not always, the median or mean value of a trait is maintained by natural selection because it is associated with maximal fitness. Only rarely if ever are there sharp cutoffs that separate health from disease or distinguish different levels of fitness.

Historically, then, medicine and evolutionary biology have been concerned with different biological problems and have developed different approaches to study their areas of interest. It is not surprising that they have developed as separate, unrelated disciplines. But physicians and nonmedical biologists have begun to realize that there is much to be gained by integrating these disciplines. Evolutionary medicine recognizes that these different perspectives are complementary, and that integrating them will give a richer understanding of health and disease. Understanding evolutionary processes helps to explain our evolved vul-

nerabilities or susceptibilities to disease and our current burden of disease. Conversely, since disease has served as an important selection factor in evolution (Haldane 1949a), knowledge of the present patterns of disease gives insights into our evolutionary history. Analysis of the evolutionary causes of diseases may lead to novel strategies to prevent, postpone, or ameliorate them. Understanding both the proximate and ultimate causes of diseases will provide a richer understanding of disease. Finally, evolutionary explanations of disease are important because patients often want to know why they have the diseases they have. In the absence of evolutionary explanations, they may fall back on unhelpful folk beliefs, such as the idea that their diseases are punishment for sinful behavior (Bynum 2008).

Why Our Evolutionary Heritage Has Left Us Vulnerable to Disease

Many diseases cause premature death (death before the end of the reproductive and child-raising periods) or reduced fertility. But most diseases do not affect all members of a population or do not affect everyone to the same degree. Rather, individuals exhibit variation in resistance or response to diseases, just as they exhibit variation in virtually all other traits. At least some of this variation is due to genetic or heritable variation in the population. Heritable variations in resistance to these diseases represent variations in fitness; individuals who survive and remain fertile in the face of a disease will on average produce and raise more children than will people who die from or become infertile as a result of the disease. As a disease spreads through a population, natural selection will increase the frequency of alleles that are associated with resistance to it. The alleles associated with resistance to malaria are classic examples of this process.

Despite selection for disease resistance throughout our evolutionary history, however, natural selection has clearly not eliminated disease. Evolutionary medicine helps us understand the limits as well as the power of natural selection in shaping human biology and the reasons—the ultimate causes—for our continued vulnerability or susceptibility to disease. Broadly speaking, there are several important limits to natural selection that contribute to the persistence of disease (Nesse 2005; Perlman 2005).

First, there are limitations intrinsic to the process of evolution by natural selection itself. Diseases that cause premature death or reduced fertility will select for and increase the frequency of alleles that are associated with disease resistance. But natural selection is not the only mechanism of evolutionary change. New alleles can enter populations either by mutation or by gene flow from other populations of the same species. Once these alleles enter a population, their fate is determined by genetic drift (changes in allele frequency due to random sampling in the transmission of alleles from one generation to the next) as well as by natural selection. These other evolutionary processes may counteract the effects of selection by introducing or increasing the frequency of alleles

associated with susceptibility to disease. For these and other genetic reasons, beneficial alleles—specifically, alleles associated with disease resistance or a decreased risk of disease—may not spread or become fixed in a population.

Natural selection increases the frequency of traits that enhance reproductive fitness. As we have discussed, however, fitness is not the same as health or longevity. If diseases do not decrease reproductive success, there will not be selection for resistance to them. Diseases of aging—diseases that increase in prevalence after the end of our reproductive and child-raising years—are one class of diseases that may not significantly decrease fitness. Evolutionary life history theory and the evolutionary theory of aging provide a framework for understanding and, possibly, postponing these diseases.

Natural selection is a slow process. Even when selection is intense, allele frequencies in populations change only gradually over many generations. Change in a population's environment is typically more rapid than genetic change. The other species with which we interact, and especially the pathogens or parasites that infect us and cause disease, constitute an important and rapidly changing component of our environment. Our pathogens, too, evolve by natural selection. Just as our evolutionary ancestors evolved and we are continuing to evolve increased resistance to our pathogens, these pathogens have evolved and are evolving to overcome this resistance and to grow in and be transmitted among us. This process of host-pathogen coevolution helps to rationalize the natural histories of infectious diseases and to explain why some infections are relatively benign while others are virulent. Understanding pathogen evolution and host-pathogen coevolution may suggest strategies for slowing the spread of antibiotic resistance and for reducing the virulence of infectious diseases.

The human environment is strongly influenced by cultural beliefs, practices, and artifacts, all of which are subject to rapid change. Disease may result from an inability of natural selection to keep pace with a changing cultural environment—in other words, from a mismatch between the environment in which we now live and the genes we have inherited from our evolutionary ancestors, genes that enabled these ancestors to survive and reproduce in the various environments in which they lived. The increasing prevalence of obesity and hypertension exemplifies the principle that genes that enhanced the fitness of our ancestors may now increase our risk of disease.

There are several other constraints on natural selection. In brief, macroevolution constrains microevolution (Stearns, Allal, and Mace 2008). Our macroevolutionary history has left us with complex and highly interdependent developmental pathways. Many of our anatomical peculiarities, such as the placement of our trachea in front of our esophagus, which leaves us vulnerable to choking, can be understood as the result of our evolutionary history—in this case, our history as aquatic organisms whose respiration depended on gills rather than lungs. The development of our respiratory and gastrointestinal systems is now so deeply embed-

ded in the whole of our development that mutations that might have led to a safer anatomic design would almost certainly have been lethal (Held 2009). Moreover, because of our complex internal organization and our complex interactions with the external world, virtually every gene has multiple phenotypic consequences. Evolution frequently involves tradeoffs or compromises, such that natural selection leads to suites of traits that are not perfect or ideal, but work well enough for survival and reproduction, and are better than the available alternatives.

Finally, despite natural selection, survival and reproduction may be constrained by limitations of environmental resources, in the way originally envisioned by Malthus. Availability of nutritional resources is thought to have played a major role in evolution ,and nutritional deficiencies are still important causes of disease and death.

Understanding the evolutionary reasons for our susceptibility to disease complements the traditional biomedical understanding of the etiology and pathogenesis of disease. Together, these two perspectives on health and disease, the ultimate and the proximate causes of disease, can help us understand why we get sick as well as how we get sick, and may provide insights into interventions that might reduce the burden of disease.

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