Evolutionary Biology

a basic science for medicine in the 21st century

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ABSTRACT Evolutionary biology was a poorly developed discipline at the time of the Flexner Report and was not included in Flexner's recommendations for premedical or medical education. Since that time, however, the value of an evolutionary approach to medicine has become increasingly recognized. There are several ways in which an evolutionary perspective can enrich medical education and improve medical practice. Evolutionary considerations rationalize our continued susceptibility or vulnerability to disease; they call attention to the idea that the signs and symptoms of disease may be adaptations that prevent or limit the severity of disease; they help us understand the ways in which our interventions may affect the evolution of microbial pathogens and of cancer cells; and they provide a framework for thinking about population variation and risk factors for disease. Evolutionary biology should become a foundational science for the medical education of the future.

"There can be no doubt," said [Thomas] Huxley, "that the future of pathology and of therapeutics, and therefore of practical medicine*, depends upon the extent to which those who occupy themselves with these subjects are trained in the methods and impregnated with the fundamental truths of biology."*

— A. Flexner (1910, p. 25 [citing Lewis 1909]; original emphasis)

Although Huxley did not mention evolution in "The Connection of the Biological Sciences with Medicine" (1881), the essay from which Flexner quotes, he certainly believed that evolution was one of "the fundamental truths

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Perspectives in Biology and Medicine, volume 54, number 1 (winter 2011):75–88

of biology." In that essay, Huxley traced the history of medicine from its empirical origins to the (then) present time and argued that while the biological sciences—specifically, anatomy and physiology—were essential for the advancement of medicine, they could not be incorporated into medical education or practice until they themselves had been sufficiently well developed; his essay provides "a brief sketch of the steps by which a philosophical necessity has become an historical reality" (Huxley 1881, p. 350).

In Huxley's day—and in Flexner's—evolutionary biology was not yet developed to the point that it could be usefully applied to medicine. Evolutionary biology was still more of a popular science than an academic science (Ruse 2009). There were no university departments, professional societies, or scholarly journals devoted to evolution. Evolutionary theory was in disarray; scientists who did study evolution disagreed about the roles of natural selection and of mutation, and the importance of gradual versus saltatory change in evolution. It was only after the "modern synthesis" of evolutionary biology with genetics in the 1930s and 1940s that evolutionary biology became a mature science (Huxley 1942). Even then, evolutionary biology and medicine developed as separate disciplines, with little interaction (Zampieri 2009). Evolutionary biologists were concerned with systematics, with enriching the fossil record, and with refining and using the tools of population genetics. Except for paleontological studies of human evolution, they shied away from studying humans, perhaps because these biologists were mainly housed in museums and field stations, isolated from medical centers, and because they did not wish to be associated with the eugenics programs that had been carried out in the name of evolution. Moreover, the focus of evolutionary biology on populations seemed incommensurable with the concerns of physicians for their individual patients. There were sporadic attempts to integrate evolutionary ideas into medicine; by far the most important was J. B. S. Haldane's (1949) insight that selection for resistance to disease must have played a major role in evolution, which led to the recognition that the alleles that cause sickle-cell anemia, thalassemia, and other hemoglobinopathies have spread in the human population because they confer resistance to falciparum malaria (Allison 2004; Weatherall 2008). Nonetheless, evolutionary biology still had not progressed in ways that made this integration flourish.

Ongoing, productive application of evolutionary concepts to medicine dates to the early 1990s (Nesse and Williams 1994; Williams and Nesse 1991). Since that time, there has been increasing awareness that, to paraphrase Dobzhansky, "nothing in medicine makes sense except in the light of evolution" (Swynghe-dauw 2008). Evolutionary biology has now developed to the point that its "fundamental truths" provide a necessary foundation for the education of physicians (Nesse et al. 2010). This essay will highlight some of the ways in which an evolutionary perspective can help medical students and physicians understand health and disease and also can benefit "practical medicine." It is time to recognize evolutionary biology as one of the foundations for medical education in the 21st century.

Our Evolved Vulnerabilities to Disease: The Limits of Natural Selection

The body is a machine of the nature of an army, not of that of a watch or of a hydraulic apparatus.

—T. H. Huxley (1881, p. 369)

Huxley used this military metaphor to stress the idea that our bodies comprise individual units (cells) that are organized into larger and larger functional units (tissues, organs) whose activities are coordinated and regulated, and to capture the important concept that our bodies are not machine-like because they have been designed by an engineer. Instead, our bodies are machines that have been shaped by our evolutionary history. We have evolved machine-like properties because these properties enhanced the reproductive fitness—the ability to survive until reproductive maturity and then to bear and raise offspring—of our evolutionary ancestors. Natural selection enhances reproductive fitness; it does not eliminate disease, suffering, or death. Understanding the limits to natural selection provides a framework for understanding our evolved vulnerabilities or susceptibilities to disease (Nesse 2007; Perlman 2005). Several of these limits—the decline in the efficacy of natural selection with age, the coevolution of humans with our pathogens, and the rapid pace of environmental change—are especially important in contributing to the burden of human disease.

Aging

The evolutionary theory of aging is based on the recognition that, in nature, most organisms die of "extrinsic" causes—predation, starvation, catastrophes, accidents—causes that cannot be prevented by natural selection. (The survivors of a tsunami or an earthquake survive because they have good luck, not because they have disaster-resistance genes, and so these catastrophes do not lead to selection for such genes.) As a population cohort ages, its size will inevitably decrease. A gene that is expressed late in life will affect fewer individuals and so will have a smaller effect on the population than will a gene that is expressed earlier (Charlesworth 1994). Moreover, as a population cohort ages and becomes smaller, its future reproductive capacity (including raising as well as bearing offspring) will diminish. Therefore, the effect of a lethal gene on reproductive fitness will decrease as a function of the age at which it causes death. In other words, the force of natural selection—its ability to decrease mortality (or to increase fertility) at a given age—also declines with age (Hamilton 1966).

Humans, like other organisms, must allocate our resources of energy and time among a variety of tasks—growth and development, reproduction (including the development of secondary sexual characteristics, finding mating partners, and raising children), the work involved in daily living, and bodily maintenance and repair. Because these resources are limited, their allocation necessarily entails tradeoffs; energy that is used for growth and development cannot then be used

for bodily maintenance. Natural selection has shaped our "life history strategies," our allocation of resources to these various needs over the life course, in ways that optimize our reproductive fitness.

Genes that affect energy usage are necessarily pleiotropic. For example, genes that direct the use of metabolic energy towards reproduction will divert this energy away from bodily repair. These genes may spread in populations because the fitness benefits of early reproduction outweigh the risk of diseases of aging later in life. In genetic terms, aging appears to result primarily from this antagonistic pleiotropy (Williams 1957). Antagonistic pleiotropy exemplifies the trade-offs that are common in evolution.

Our bodies are constantly being subjected to damage. Mutations occur, proteins unfold, and a variety of cellular constituents become oxidized or undergo other chemical changes. If the damaged molecules are not replaced or repaired, cells malfunction and die; if the dead cells are not replaced, organ function will be impaired. Not surprisingly, we have evolved elaborate mechanisms to minimize somatic damage and to repair it when it does occur. But natural selection has shaped the uses of metabolic energy in ways that enhance our reproductive fitness, and maximal reproductive fitness is evidently accompanied by incomplete bodily maintenance. Because our repair mechanisms are not perfect, over time damage accumulates, cells die, organs malfunction, and we suffer from cancer, cardiovascular diseases, neurodegenerative diseases, and other diseases of aging. Tom Kirkwood (1999, 2005), one of the architects of the evolutionary theory of aging, has dubbed this the "disposable soma" theory; in today's idiom, it might be thought of as the "recyclable soma" theory (Perlman 2008). Natural selection has optimized our ability to transmit our genes to our offspring, but as a consequence, our bodies are disposable and their components are recycled.

Natural selection adjusts the rate of aging, and of death from "intrinsic" causes, in relation to the rate at which populations die from extrinsic causes, the causes it cannot prevent. This relationship makes sense intuitively. If most organisms in a species die young, the species must have life history strategies that promote rapid development and early reproduction; they do not invest large amounts of energy in bodily maintenance. If, on the other hand, species have evolved mechanisms that reduce the rate of extrinsic death, they can evolve life histories that include prolonged growth, delayed reproduction, and long life spans—and that must, then, include greater investment in somatic repair. Humans, fortunately, fall into this latter group.

An economic metaphor may help to clarify the evolutionary view of aging. During development, we accumulate excess physiological capacity; for example, we produce many more nephrons than we need for normal renal function. This excess capacity can be thought of as "physiological capital" (Fogel 2003). Because our maintenance and repair processes are not perfect, we spend this capital over our lives. When our supply of physiological capital becomes low or is exhausted, we develop diseases of aging and eventually we die. This metaphor may also sug-

gest strategies for slowing the aging process. Good prenatal and neonatal nutrition and hygiene may increase our supply of physiological capital, and good nutrition (especially micronutrients that are essential for repair processes; Ames 2006) and reduction of exposure to agents that increase somatic damage (e.g., tobacco smoke) may slow the rate at which we deplete our physiological capital. Increases in physiological capital and reductions in rates of somatic damage are presumably responsible for the large increase in life expectancy over the past century. Even though human aging seems to be inevitable, its time course is evidently not immutable.

Host-Pathogen Coevolution

Our bodies provide environments in which a myriad of microorganisms can live and reproduce. Some of these organisms may be beneficial to us or have little effect on our health or well-being, but some are pathogenic. Natural selection enhances the reproductive fitness of all of these organisms. The action of natural selection on hosts (in our case, humans) and on our pathogens leads to a process of "host-pathogen coevolution," in which we evolve to be resistant to our pathogens (i.e., to minimize the fitness cost of pathogen infections) and pathogens evolve to escape or overcome our resistance (i.e., to maximize their fitness in the face of our defenses). Pathogens have a number of advantages in this coevolutionary process: they typically have large populations, high mutation rates, and short generation times. Our survival is dependent upon our adaptive immune systems and on public health practices that minimize our exposure to virulent organisms. Nonetheless, old pathogens evolve mechanisms that enable them to persist, and new pathogens are constantly arising (Lederberg 2000).

The theory of host-pathogen coevolution provides a coherent way of understanding the natural histories and virulence of infectious diseases (Perlman 2009). People used to believe that pathogens would inevitably evolve to be benign, because those pathogens that killed their hosts would also die. We now understand that this is not correct; pathogens evolve a level of virulence that optimizes their own fitness. The evolution of virulence is complex, because it depends on the biology of the pathogen, the ecology of host-pathogen interactions, and the age structure, population density, and resistance of the host population. In general, however, a useful measure of pathogen fitness is their transmissibility, the number of new infections that result from a single infected host. Pathogens that are most efficiently transmitted from healthy people (e.g., rhinoviruses) will evolve to be benign, whereas pathogens that are most efficiently transmitted from sick people (e.g., *P. falciparum*) will evolve to be virulent (Ewald 1994). This understanding of the evolution of virulence suggests strategies that may select for less virulent organisms. For example, the use of mosquito nets to prevent the most seriously ill malaria patients from being bitten and transmitting their disease might select for less virulent malaria parasites.

The Rapid Pace of Environmental Change

Microorganisms, including pathogens, comprise an important part of our environment. But the human environment is shaped not only by our pathogens, but also by our cultural practices and artifacts. And cultural practices, like microorganisms, can evolve very quickly. Genetic evolution is much slower than cultural change, and so in a sense we are always playing catch-up to a changing environment. The environment in which we now live differs in many important respects from the environments in which our evolutionary ancestors lived, and to which they were more-or-less well adapted. We live in large communities made up of genetically unrelated individuals; we eat different foods and have different patterns of physical exercise than did our ancestors; we are exposed to numerous pathogens that we acquired from our domesticated animals and that can only survive in large populations ("crowd diseases"), as well as to novel toxins; and we are shielded from parasites that were probably common during most of human evolution. Many of what Thomas McKeown (1988) called "diseases of affluence"—heart disease, diabetes, etc.—seem to be due to "mismatches" between our current environment and the genetic endowment we inherited from our evolutionary ancestors (Gluckman and Hanson 2006).

Understanding the pathogenic consequences of these mismatches may lead to strategies to prevent or treat disease. Our immune systems evolved in environments in which our ancestors were commonly infected by helminths and other parasites. As a result, normal development of our immune systems may depend on exposure to these pathogens. Modern worm-free environments may contribute to the high incidence of allergic and autoimmune diseases in developed countries. Studies are currently underway to treat patients with inflammatory bowel disease and other immunological diseases with immunomodulatory compounds isolated from helminths (Weinstock and Elliott 2009).

As this brief sketch illustrates, understanding our evolved vulnerabilities to disease is not just of academic interest but can lead to testable hypotheses of interventions to prevent or ameliorate disease.

MANIFESTATIONS OF DISEASE MAY BE ADAPTATIONS

Nature and disease may be compared to two men fighting, the doctor to a blind man with a club, who strikes into the mêlée*, sometimes hitting the disease, and sometimes hitting nature.*

—T. H. Huxley (1881, p. 355)

Patients typically come to physicians because they are aware of, or suffering from, the symptoms of disease. These symptoms may be distressing and if nothing else indicate a departure from health. In the course of physical and laboratory examination, physicians may find other manifestations of disease that, again, represent deviations from health. Understandably, both patients and physicians are predisposed to view the signs and symptoms of disease as part of the disease

process. Understandably, too, many forms of therapy are directed at these manifestations of disease. As Huxley suggests, however, these interventions sometimes may be beneficial and sometimes harmful. Thymus irradiation, which was carried out to "treat" enlarged thymus glands that were thought to be signs of "status thymicolymphaticus," is just one example of interventions directed at what appeared to be signs of disease that turned out to be harmful (Silverman 1993).

Paul Ewald (1980) was the first person to develop an evolutionary analysis of the symptoms of disease—in particular, infectious disease. Ewald suggested that "manifestations of infectious diseases can be classified as (1) adaptations of the host to counteract harmful aspects of the disease, (2) adaptations of the pathogen to manipulate the host, or (3) 'side effects' of the disease that do not serve adaptive functions for either the host or the pathogen" (p. 169). He recognized that adaptations frequently involve tradeoffs, and so may have deleterious as well as beneficial effects. For example, fever appears to have evolved as a defense against pathogens, because on balance the benefits of fever in decreasing the virulence of infectious diseases outweighed the dangers of dehydration, febrile convulsions, and tissue damage. Recognition that a sign or symptom of disease is an evolutionary adaptation does not by itself say whether symptomatic treatment will be harmful and is therefore contraindicated. Treatment decisions need to be based on appropriate clinical trials and well-honed clinical judgment. Nonetheless, understanding that manifestations of disease may be adaptations provides a richer understanding of these manifestations, and it may be helpful to patients to learn that their symptoms, though distressing, are part of their healthy coping with their disease.

It has been known since the 1930s that patients with infectious diseases have markedly reduced levels of serum iron. Subsequently, anemia was found to be a common manifestation of chronic diseases, especially of diseases characterized by chronic inflammation. Indeed, the World Health Organization includes anemia in "chronic diseases classified elsewhere" in the International Classification of Diseases. Reduced serum iron and the subsequent anemia in infectious and inflammatory diseases are now recognized to be manifestations of an "iron-withholding defense" that has evolved as part of the host defense against pathogens (Weinberg 1993). Virtually all pathogens require iron for growth; the iron-withholding defense slows the growth of microbial pathogens by limiting the availability of iron. This defense is a complex and highly integrated response to inflammation, involving increased synthesis of iron-binding proteins and decreased release of iron from intestinal cells and macrophages into the blood. These changes are coordinated by cytokines released from immune cells as part of the native immune response to infection (Ganz 2009).

Support for the hypothesis that the iron-withholding defense is an evolutionary adaptation that has been preserved because it decreases the virulence of infectious diseases is offered by a number of reports, which indicate that iron supplementation to patients with low serum iron or anemia may be associated

with an increased incidence or increased severity of infectious diseases, especially malaria (Weiss 2009). Even though this defense is an adaptation, however, it involves the tradeoff of causing anemia and interfering with other iron-requiring metabolic activities. Whether iron supplementation to patients with the anemia of chronic disease is helpful or harmful is a complex problem, depending on the patient's age, iron status, and specific infection; recognition that iron withholding is an evolved defense does not eliminate the need for clinical studies to determine the circumstances under which iron therapy might be beneficial. But this evolutionary understanding of the iron-withholding defense should inform these clinical studies and temper the rush to treatment. Referring to the fall in serum iron in infection as "hypoferremia" and designing studies to elucidate the "pathogenesis" of iron retention pathologizes an evolved physiological response to infection (Weiss 2009).

The concept that signs and symptoms may be evolutionary adaptations is not limited to infectious diseases. Increases in serum bilirubin in the newborn period are a significant concern, as they may lead to kernicterus, brain damage, and a variety of neurological defecits. Nonetheless, bilirubin synthesis, and the rise in bilirubin that occurs during the neonatal period, are likely to be evolutionary adaptations that help protect cells against oxidative damage (Sedlak et al. 2009). Bilirubin is a lipophilic substance and appears specifically to protect against oxidative damage to membranes. When hemoglobin or other heme proteins are degraded, the released iron may increase the formation of reactive oxygen species. The concurrent formation of bilirubin may provide physiological protection against the oxidative damage that would otherwise be caused by this iron. The observation that breast-fed babies have higher bilirubin levels than do bottle-fed babies is consistent with the idea that a modest rise in bilirubin in the newborn period is an evolutionary adaptation to the red cell destruction that occurs at that time. Like fever and iron withholding, however, elevated bilirubin in the neonatal period is another tradeoff, involving potential harm as well as benefits. Of course, neonates (and especially premature neonates) with high bilirubin levels need to be treated to prevent kernicterus. Clinical studies, not evolutionary considerations, have to establish appropriate criteria for the treatment of neonatal jaundice. But bilirubin should be seen as a protective antioxidant that unfortunately can sometimes cause harm, rather than as a toxin. Bilirubin formation, like iron withholding, is a reminder that many manifestations of disease may be evolutionary adaptations.

Evolution of Pathogens and Cancer Cells

A deep problem is the failure to appreciate the evolutionary change that occurs in disease organisms as a direct consequence of the attempts to deal with them.

—R. C. Lewontin and R. Levins (2007, p. 20)

The discovery of antibiotics was one of the great advances in 20th-century medicine and is also one of the clearest illustrations of the problems that have arisen

from the neglect of evolutionary principles. Although many people were aware that antibiotic usage would lead to the spread of resistant organisms (Rene Dubos wrote about penicillin resistance in 1942, before penicillin was introduced into widespread use and before the birth of bacterial genetics), these "wonder drugs" were used without concern about selection for resistance. Promiscuous use of antibiotics, in agriculture as well as in medicine, has resulted in our current problems of multidrug-resistant organisms (Levy 2002). Fortunately, we are beginning to learn from our mistakes. Current multidrug treatment regimens for cancer and for HIV are designed to minimize selection of drug resistance (Chow et al. 1993). The ecology and evolution of antibiotic resistance is complex, and we still have much to learn about it. Attempts to slow the spread of antibiotic resistance in hospitals by cycling antibiotic use apparently failed because they did not properly take account of the dynamics of this process (Bergstrom and Feldgarden 2008). The effect of antibiotic treatment regimens on selection for resistant bacteria is still not clear; urging patients to complete full courses of antibiotics even after their infections are clinically resolved may increase selection for antibiotic resistance (Rice 2008).

Vaccinations may also affect the evolution of microorganisms. Incompletely effective vaccines create a population of hosts who may remain susceptible to more virulent strains of an organism and so may provide an environment in which these more virulent strains will be selected. This problem appears to have occurred after vaccination of poultry against Marek's disease virus. Fortunately, it has not yet happened with vaccines in humans—but the example of Marek's disease virus provides a cautionary note that we need to be aware of and monitor this possibility (Read and Mackinnon 2008).

Just as microorganisms have evolved resistance to antibiotics, insects have evolved resistance to DDT. Evolutionary considerations might also lead to the development of interventions that decrease the emergence of resistant organisms. One intriguing idea concerns the development of an "evolution-proof" anti-malarial insecticide (Read, Lynch, and Thomas 2009). Because the time required for the maturation of *P. falciparum* in mosquitoes is long in relation to the life expectancy of the mosquito, only older (female) mosquitoes are infectious. An insecticide that targeted these older, post-reproductive females would prevent the transmission of malaria parasites but would not significantly decrease the reproductive fitness of the mosquitoes and so would not lead to selection for insecticide resistance. Whether or not such an insecticide can be developed and used, the proposal illustrates the potential application of evolutionary principles to important medical problems (Billingsley 2010).

VARIATION AND "NORMALITY"

The physician's function is fast becoming social and preventive, rather than individual and curative. Upon him society relies to ascertain, and through measures essentially educational to enforce, the conditions that prevent disease and make positively for physical and moral well-being. It goes without saying that this type of doctor is first of all an educated man.

—A. Flexner (1910, p. 26)

Flexner's prediction is only now being realized. We are becoming increasingly concerned with identifying risk factors for disease and with designing either population-based or individual strategies to prevent or postpone disease. Identifying and responding to risk factors requires an understanding of the causes and significance of biological variation. Human populations, like the populations of other species, exhibit variation in virtually all of our anatomic, physiologic, and behavioral traits. Values for quantitative traits typically cluster around a median value and often display a normal or lognormal distribution. Variation is essential to evolution; without variation, there could be no natural selection. It may seem surprising that natural selection does not eliminate variation—if there were one ideal type, one genotype with maximal fitness, then why wouldn't natural selection eliminate less fit genotypes? But variation is not only essential for evolution; it is produced and maintained by evolutionary processes. Of the many reasons for the generation and preservation of genetic diversity in the human population, two have special medical relevance. The persistence of both the "normal" adult hemoglobin (HbA) and sickle-cell hemoglobin (HbS) alleles at the ß-globin locus exemplifies a "balanced polymorphism," in which genetic diversity is maintained because (in populations who live in malarious regions), AS heterozygotes have greater fitness than either AA or SS homozygotes. Sickle-cell anemia is a tragic but inevitable result of this balanced polymorphism.

Fitness is not simply a property of a given genotype but may also depend on the distribution of genotypes in the population. In a process known as negative frequency-dependent selection, a genotype may confer a fitness advantage when it is rare but lose this advantage as it spreads in a population. Host-pathogen coevolution is an important cause of frequency-dependent selection. As a pathogen spreads in a human population, it will become adapted to grow in and be transmitted between people with the most abundant genotype, who provide the environment it encounters most frequently. As a consequence, it may be less able to grow in people with rare genotypes, and so these people will have increased reproductive fitness. As these formerly rare genotypes become more frequent, however, mutant strains of pathogen that can grow in people with these now common genotypes will spread. Frequency-dependent selection resulting from host-pathogen interactions is thought to be an especially important cause of genetic diversity in host populations. In particular, frequency-dependent selection is thought to be a major reason for the great polymorphism of our MHC loci.

Development (and disease) depends upon an interaction between genetic and

environmental resources. Even though rapid environmental change is a cause of disease, developmental or phenotypic plasticity may be an adaptation that enables organisms to develop phenotypes that enhance fitness in the environments in which they are living (Gluckman and Hanson 2006). Although variation within populations is often due to genetic diversity, variation between populations may also be due to the different environments in which these populations live. This distinction between within-population variation and between-populations variation is crucial in thinking about risk factors and disease. As Geoffrey Rose (2001) has stressed, the causes of incidence (disease in populations) are different from the causes of cases (disease in individuals): "'Why do some individuals have hypertension?' is a much different question from 'Why do some populations have much hypertension, whilst in others it is rare?'" (p. 428). We have tended to focus on the causes of cases, which has led us to emphasize genetic determinants of disease. As Rose has remarked, however, "If everyone smoked 20 cigarettes a day, then clinical, case-control, and cohort studies alike would lead us to conclude that lung cancer was a genetic disease" (p. 427). Understanding the genetic basis for differences in sensitivity to the toxins in cigarette smoke is fascinating and may lead to clinical benefits; nonetheless, the public health campaigns to reduce smoking (and increased cigarette taxes) are probably the most important reason for the reduction in cancer and heart disease over the last 50 years. Consideration of similar population-level interventions to reduce the burden of other diseases needs to take account of the differences between the causes of cases and the causes of incidence, and of the evolutionary reasons for within-population and between-populations variation.

Although we know that variation is continuous, we are often called upon to make dichotomous classifications: people are either sick or healthy; either they are at significant risk for developing a disease or they are not. Because of the need to make dichotomous classifications, we tend to classify people—or their laboratory values—as "normal" or "abnormal." An evolutionary perspective helps to remind us that these classifications are arbitrary and do not reflect fundamental differences between normal and abnormal, or between health and disease.

Conclusion

> *The so-called "practical" outlook has been and is a great obstacle to the advance of Medicine. The plaintive cry for what is "useful" as against "theoretical knowledge" echoes down the ages. We hear it still. But when and where that cry swells into a chorus, then and there Science dies.*
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> **—C. Singer (1957, p. 37)**

Medicine is a practical subject; physicians must master a vast amount of practical information and must develop *phronesis*, or practical wisdom, about how to apply this knowledge to prevent, cure, or ameliorate diseases in their patients. As Singer reminds us, however, medicine requires theory as well as practical knowl-

edge. Theory helps us organize, evaluate, and "make sense of" factual information, and it provides a guide for decision-making in the all-too-common face of insufficient information as well as for research, for the advancement of medicine. It is easy to become confused and frustrated by the welter of information to be learned and the immediate pressures of medical education and practice. Theory provides "a protection against being overwhelmed by the urgency of need in the momentary and the local" (Lewontin and Levins 2007, p. 10). The theory of evolution by natural selection provides a framework for understanding why people get sick, the manifestations of disease, the effects of our interventions on the evolution of disease, and the relationships between population health and individual health. In short, it provides a firm theoretical foundation for medical education and medical practice.

Given that medical students and physicians should understand the theory of evolution by natural selection and its applications to medicine, when in the education of physicians should this subject be taught? My own view is the earlier, the better. Evolutionary biology should be a central part of premedical education in biology. Indeed, it should be part of a liberal education: I would hope that all citizens—future patients as well as future physicians—would become familiar with the theory of evolution by natural selection. Postponing the teaching of evolution until medical school seems both unnecessary and impractical; the medical curriculum is already too crowded, and making room for yet another basic science seems unrealistic. If students come to medical school with a firm understanding of evolutionary concepts, they should be able to apply these concepts throughout their medical education and into their medical practice.

In the short term, however, we have a "bootstrap" problem. Even if students enter medical school with a strong background in evolutionary biology, they may not be challenged to apply their knowledge of evolution to medicine, because few medical school courses introduce or discuss evolutionary principles. Fortunately, there are now several good books on evolutionary medicine that can help both students and faculty appreciate the relevance of evolution for medicine and help faculty incorporate evolutionary concepts into their teaching (Gluckman, Beedle, and Hanson 2009; Stearns and Koella 2008).

Much has changed since 1910. The scientific basis of medicine as it existed when Flexner wrote is virtually unrecognizable today. Nonetheless, Flexner's vision, that one goal of medical education is to produce physicians who are well educated in the scientific basis of medicine, remains valid. The integration of evolutionary biology into medicine is now a "philosophical necessity"; it is time to make it a reality.

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