
CHAPTER 23

The Importance of Evolution for Medicine

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As one of the “fathers” of evolutionary medicine, Nesse’s sense of confidence can be seen as he assesses from the perspective of a more mature discipline the potential sticking points and inherent differences between clinical practice and basic medical research, medical culture, theories, and practice. His analysis of the “state of the field” helps to establish in this chapter a realistic and critical perspective on the early years of evolutionary thinking and moves to offering advice on what can be done better and, more generally, what can be done to assure expansion, integration, and growth toward the future of the field. He provides some advice about how to assure that research itself will continue and directs his comments to what in the future, from the framing of an evolutionary medicine curriculum to pedagogy to a teaching point of view, needs yet to be done. That he ends his chapter and, not coincidentally, this volume with a concrete curriculum for the teaching of Darwinian medicine is one significant indicator that, as this volume hopes also to assure, the next wave of this new application of evolutionary principles to sustaining and improving human health is not just around the corner but is already here.

INTRODUCTION

The importance of evolutionary biology for medicine should be obvious. Medicine is based on biology and biology is based on evolution, so you would think that medicine would long ago have applied evolutionary principles in every possible way. Would that it were so! Instead, nearly a century and a half after publication of *The Origin of Species* (Darwin, 1859), medicine is just beginning to make full use of evolutionary biology. The chapters in this book illustrate the rapid progress and substantial promise of evolutionary medicine. Each examines a particular problem or bodily system and shows how an evolutionary perspective can deepen understanding. In conjunction with other recent and forthcoming publications, they document the many specific ways that evolution is important for medicine.

This chapter does not attempt to review these specific contributions, but instead steps back to address several more general questions. What is evolutionary medicine? Should it be a distinct field? What is its history? How can it be useful? How can evolutionary hypotheses about disease be tested? And, what is needed to move work forward faster at the intersection of evolution and medicine? The theme throughout is that quickly trying to meet demands for direct clinical applications now may limit the scope of the field in the long run. While evolutionary medicine has some useful applications, its greater promise arises from its ability to pose new research questions and to offer a solid framework for integrating much medical knowledge about why our bodies are so vulnerable to disease.

WHAT IS EVOLUTIONARY MEDICINE?

Evolutionary medicine is the enterprise of using evolutionary biology to address the problems of medicine. Some areas of medicine, such as infectious disease and genetics, have long been grounded in evolutionary biology. For them, the main question is how they can best incorporate and contribute to new advances in evolutionary biology. Many of the more recent applications of evolution in medicine address somewhat different questions about the adaptive significance of aspects of the body that make it vulnerable to diseases. This emphasis on adaptive functions has long been at the center of physiology, where such questions are so intrinsic to the discipline that they sometimes are not even recognized as evolutionary. Anatomy is also inherently based on evolution, although time pressures in the medical curriculum have greatly reduced its ability to provide a comparative perspective. Other topics, however, such as nutrition, pharmacology, and even developmental biology, are often still researched and taught with little attention to evolutionary principles. Opportunities for progress are plentiful.

It is easy to offer a few specific examples of how evolution can help in the clinic today, such as how a deeper understanding of host–pathogen co-evolution can assist in managing antibiotic resistance, or the need to consider the utility of defenses such as fever and cough before prescribing medication. However, the great benefits of evolution in medicine will emerge from new research and from the framework evolution provides for understanding why organisms are vulnerable to disease.

Why We Get Sick (Nesse & Williams, 1994) ends with the famous Dobzhansky quotation, “Nothing in biology makes sense except in the light of evolution” (1973). The quotation is not, however, entirely correct. While evolution is essential to make complete sense of any trait, much biology proceeds without much attention to evolution. Examples include studies of drug outcomes, endocrine mechanisms, epidemiology, and research that identifies new genetic variations. Most work in biology is, however, connected to evolution; in medicine, most is not. This should not be surprising. Medicine is not a science, it is a profession. To prevent and treat disease it uses tradition and empirical studies along with basic science. Setting a bone, doing a colonoscopy, treating acne, or treating diabetes, depression, or hypertension is mostly a matter of technical knowledge and routine. Doctors do not need to know why the appendix persists in order to treat appendicitis or why modern humans are prone to atherosclerosis to treat heart failure.

The best doctors are wary of grand theories, and for good reason. Consider homeopathy. This long-standing alternative medicine recommends infinitesimal doses of drugs

that cause symptoms similar to the patient's complaints, using the rationale of Samuel Hahnemann's principle *Similia Similibus Curentur* (like cures like) (Hahnemann, 1916). Dozens of similarly simple theories entrance patients and physicians alike. Many attribute most diseases to one cause, whether sugar, imbalances in energy flow, misalignment of the spine, or stress. Such factors do contribute to disease; the problem is the human tendency to simplify by overemphasizing one cause. Likewise, it is attractive to think that one treatment can work for the vast majority of diseases. Practitioners understandably recommend the kind of treatment they provide. Surgeons recommend surgery, internists recommend medications, nutritionists recommend dietary change, and psychotherapists recommend whatever kind of psychotherapy they offer. Theories tend to be too simple, and patients are often shortchanged.

In short, good doctors are justifiably wary of theories in general. They will embrace evolutionary biology as a foundation for medicine only after they recognize evolutionary biology as a basic science for medicine. In contrast to other theories, evolutionary medicine does not overemphasize one cause or one treatment. Most important of all, it does not make direct clinical recommendations and should not be the basis for a special kind of medical practice. Instead, it suggests new research questions whose answers, carefully validated, will improve clinical care. It also provides a framework for deeper understanding of every disease and every patient. The importance of these two benefits is addressed below at length.

Concerns that evolutionary medicine will distort clinical practice are premature at best. The growth of the field has been almost entirely in research institutes and basic science classrooms. While many undergraduates now get an introduction to evolution as a basic science for medicine, no medical school has a systematic course on the applications of evolutionary biology in medicine. Only a handful of medical schools have any evolutionary biologists on the faculty (Nesse & Schiffman, 2003). Every month several well-qualified physicians and researchers contact me to ask where they can get specialized training to pursue research in Darwinian medicine; so far no such program exists. While it would be wonderful if evolution was already recognized as the foundation for medicine, we are far from that goal; the idea of evolutionary or Darwinian medicine remains essential in order to develop work in the field.

The above paragraphs emphasize some difficulties encountered in bringing evolutionary biology to bear more fully on the problems of medicine. Why not just focus on the many positive recent developments? Because the above difficulties and related obstacles are keeping medicine from making full use of evolutionary biology. Recognizing and overcoming them will speed progress. Another important principle is to promise only what we can deliver, taking care not to overstate the practical benefits that evolutionary medicine offers now. Evolutionary medicine is not focused on a specific clinical problem or one aspect of the body's mechanisms; its contributions are more like those of embryology, biochemistry, and other basic sciences.

NOMENCLATURE

What should we call work at the interface of medicine and evolutionary biology? A brief historical review may help minimize the distraction about the matter. This volume and its

predecessor use the phrase “evolutionary medicine” (Trevathan, McKenna, & Smith, 1999). The other major overview edited volume, also published by Oxford University Press, is titled *Evolution in Health and Disease* (Stearns, 1998). In our 1991 article and 1994 book, Williams and I used the phrase “Darwinian medicine” (Nesse & Williams, 1994; Williams & Nesse, 1991). A brief note is in order to explain why we chose “Darwinian medicine” instead of “evolutionary medicine.”

I argued for calling the field “evolutionary medicine,” on the belief that this would speed acceptance by staying away from any “ism,” by dissociating the field from the negative connotations that Darwin has for many people, and by not associating the field too closely with one scientist. George Williams argued for a more exacting approach, noting that “evolution” refers to any gradual change over time and does not necessarily refer to natural selection or even biology. He noted that “Darwinism” signals close attention to natural selection, and that we should not shy away from crediting the great man whose work inspired us. He convinced me. While “Darwinian medicine” is more exact, on practical grounds it has disadvantages because so many people associate the term “Darwinism” with ruthless competition. The designation “evolutionary medicine” reduces these concerns, but only modestly. The search term “Darwinian medicine” yields more specific results than “evolutionary medicine,” but neither locates all relevant research. After talking with many people about the alternatives, my main conclusion is that debate about nomenclature is not especially useful. In order to provide a designation as general and inclusive as possible, I now call the field “evolution and medicine.” This avoids any possible misunderstanding about the field being excessively circumscribed and emphasizes the intersection between the basic science of evolutionary biology and the applied profession of medicine. The web site EvolutionAndMedicine.org strives for the broadest possible coverage of work in the field.

THE HISTORY OF EVOLUTIONARY MEDICINE

The first mention of the potential utility of evolution for medicine is found in Darwin, not Charles, but his grandfather, the physician and poet Erasmus Darwin. The preface to his 1796 philosophical poem, *Zoonomia*, contains a remarkably prescient description of evolution, as well as its potential as a foundation for medicine (Darwin, 1796, pp. vii-viii; italics and capitalization as in original):

The purport of the following pages is an endeavor to reduce the facts belonging to ANIMAL LIFE into classes, orders, genera, and species; and, by comparing them with each other, to unravel the theory of diseases. It happened, perhaps unfortunately for the inquirers into the knowledge of diseases, that other sciences had received improvement previous to their own; whence, instead of comparing the properties belonging to animated nature with each other, they, idly ingenious, busied themselves in attempting to explain the laws of life by those of mechanism and chemistry; they considered the body as an hydraulic machine, and the fluids as passing through a series of chemical changes, forgetting that animation was its essential characteristic.

The great CREATOR of all things has infinitely diversified the works of his hands, but has at the same time stamped a certain similitude on the features of nature, that demonstrates to us, that the whole is one family of one parent. On this similitude is

founded all rational analogy; which, so long as it is concerned in comparing the essential properties of bodies, leads us to many and important discoveries; but when with licentious activity it links together objects, otherwise discordant, by some fanciful similitude; it may indeed collect ornaments for wit and poetry, but philosophy and truth recoil from its combinations.

The want of a theory, deduced from such strict analogy, to conduct the practice of medicine is lamented by its professors; for, as a great number of unconnected facts are difficult to be acquired, and to be reasoned from, the art of medicine is in many instances less efficacious under the direction of its wisest practitioners; and by that busy crowd, who either boldly wade in darkness, or are led into endless error by the glare of false theory, it is daily practiced to the destruction of thousands; add to this the unceasing injury which accrues to the public by the perpetual advertisements of pretended nostrums; the minds of the indolent become superstitiously fearful of diseases, which they do not labour under; and thus become the daily prey of some crafty empyric.

A theory founded upon nature, that should bind together the scattered facts of medical knowledge, and converge into one point of view the laws of organic life, would thus on many accounts contribute to the interest of society. It would capacitate men of moderate abilities to practice the art of healing with real advantage to the public; it would enable every one of literary acquirements to distinguish the genuine disciples of medicine from those of boastful effrontery, or of wily address; and would teach mankind in some important situations the knowledge of themselves.

There are some modern practitioners, who declaim against medical theory in general, not considering that to think is to theorize; and that no one can direct a method of cure to a person labouring under disease without thinking, that is, without theorizing; and happy therefore is the patient, whose physician possesses the best theory.

These lines are remarkable on several counts. In the first paragraph, Erasmus Darwin notes the need for a theoretical foundation for medicine, he chides those who think of the body as only a machine, and he presages the distinction between proximate and evolutionary explanations. In the second paragraph, he anticipates the origin of species, with the phrase, “*the whole is one family of one parent.*” He concludes by arguing in support of my main thesis: that the theory can “bind together the scattered facts of medical knowledge,” providing a framework that “would capacitate men of moderate abilities to practice the art of healing with real advantage.” Unfortunately, little has changed. Many physicians still see the body as a designed machine instead of an evolved organism, and myriads of medical facts remain unconnected, awaiting a scientific framework.

Of course, there was no real theory to justify Erasmus Darwin’s vision until his grandson Charles Darwin and Alfred Wallace discovered natural selection. In the century and a half since the publication of *The Origin of Species* (1859), one would think that these ideas would have been applied to medicine in every possible way, but it now appears that we are still just getting started. Why it has taken so long is a good question for historians; the one available history of Darwinian medicine is not yet available in English (Zampieri, 2006).

While we wait for historians to address the issue, some reasons for the delay seem straightforward. One is the slow acceptance of Darwinism in general. Opposition from religious quarters is part of the picture. Some doctors are creationists, and a remarkable number of physicians think intelligent design is a viable alternative to evolution. They are too few to constitute a major obstacle in themselves, but together with community

sentiment, they make deans and other leaders wary of public commitments to evolution that may arouse controversy.

A more significant impediment has been skepticism among scientists. At the end of the nineteenth century, many scientists thought natural selection was a theory whose time had passed (Richards, 1987). In particular, Darwin's notion of hereditary transmission from generation to generation via "gemmules" was recognized as incorrect. Also, many scientists believed the critique of the leading physicist of the time, Lord Kelvin, who used the laws of heat radiation to calculate that the earth could not possibly be older than 20,000 years or it would be merely a cold rock (Kelvin, Tait, & Darwin, 1883). This bit of physics was, for many scientists, sufficient to outweigh all Darwin's arguments and the accumulating fossil evidence. The rediscovery of genetics in the first years of the twentieth century eventually provided the foundation for new work on evolution, but early on it was more often seen as proof that Darwin's theory of heredity was wrong than as evidence that his theory of natural selection was right.

Another reason for delay was the timing of the great curricular reforms in medicine instituted by Flexner (1910). He proposed adding basic science education during the early decades of the twentieth century, just when evolutionary biology was in maximum eclipse (Richards, 1987). Not until the synthesis with population genetics in the 1930s and 1940s was evolutionary theory widely accepted (Mayr, 1982). Even then, however, applications to medicine developed slowly save for a few exceptions. Population genetics quickly became sophisticated; its initial focus on single gene mutations with medical effects emphasized the role of selection in eliminating deleterious mutations and the power of random factors to influence gene prevalence. The study of adaptation became a foundation for physiology (Schmidt-Nielsen, 1990) and inspired the emergence of modern animal behavior from its precursors in ethology (Alcock, 2001). However, an effective attack on excesses of "adaptationism" (Gould & Lewontin, 1979) got such wide attention that even today, despite many rebuttals (Queller, 1995) and reliable methods (Reeve & Sherman, 1993), many medical researchers remain wary about studying evolutionary questions about function.

The increasing use of antibiotics in the mid-twentieth century was followed quickly by recognition of antibiotic resistance (Cohen, 1992). Here, finally, was an example of natural selection in action. This was not, however, "nice" natural selection shaping wonderful adaptations; instead, it adapts bacteria so our antibiotics can no longer kill them. Perhaps this is why antibiotic resistance is often described as "change" or "adaptation" without explicit mention of evolution. Nonetheless, antibiotic resistance demonstrates that selection can take place before our eyes with profound clinical consequences.

As already noted, microbiology and population genetics are the established elders in the evolutionary medicine family. Their progress is increasingly fast as they make use of newly available genetic information. The question is whether they might advance yet faster if they incorporated evolutionary principles more systematically. In infectious disease, fundamental advances (Anderson & May, 1979; May & Anderson, 1979) and the synthesis offered in Ewald's book (Ewald, 1994), as well as more recent advances (Anderson, 2004; Ebert, 1998; Levin & Bull, 1994), suggest that there is much more to come. Genetics is quickly getting past the technical problems of genotyping and on to evolutionary questions about genes that predispose to disease (Lewontin, Singh, & Krimbas, 2000; Maynard Smith, 1998).

Many recent efforts to further develop the field of evolution and medicine have addressed somewhat different questions. Instead of studying the actions of selection on

TABLE 23-1 Tinbergen's Four Questions*Proximate Questions*

1. *Mechanism*—What is structure and composition of the trait and how does it work?
2. *Ontogeny*—How does the trait develop in an individual?

Evolutionary Questions

3. *Phylogeny*—What is the evolutionary history of this trait?
4. *Selective Advantage*—What selection forces shaped this trait?

genes and pathogens directly, this new emphasis begins from the principle that all biological phenomena need evolutionary, as well as separate proximate explanations (Tinbergen, 1963). Proximate explanations are about the body's mechanisms, how they work, and how they develop from a strand of DNA. Evolutionary explanations are about the phylogeny of the body's components and what selection forces shaped them to their present form. Both kinds of explanations are needed for every aspect of the body. Full recognition of the value of this distinction has been slow in medicine. It was advocated effectively by Niko Tinbergen (1963) and Ernst Mayr (1982, 2004), but so far medical research has made full use of only the proximate half of biology; many physicians have not even heard of Tinbergen's "four questions." There is not room here to describe them in detail, but Table 23-1 summarizes them as two kinds of questions (proximate and evolutionary) about two different objects of explanation (a trait at one time and the series of events that create a trait).

Williams and I began by trying to find evolutionary explanations for diseases. We soon recognized that this was a mistake; with a few exceptions, natural selection does not shape diseases. Progress came when we shifted the focus to shared traits that leave all members of a species vulnerable to a disease—traits such as the appendix, the narrow pelvic outlet, and the limitations of the immune response. We began posing questions about vulnerability to disease in the form: "Why has natural selection left this species vulnerable to this disease?" The potential explanations can be sorted into the six categories listed in Table 23-2.

These six categories have been discussed at length elsewhere (Nesse, 2005; Nesse & Williams, 1994, 1998), so they will not be described in detail here. It is important to recognize that multiple factors may contribute to vulnerability to one disease. For instance, vulnerability to atherosclerosis arises from a mismatch with the modern environment and also from trade-offs involving the endothelium's ability to protect against infection. These causes can be subdivided and categorized in other ways. In the definitive review of the growth of evolutionary contributions to medicine, Stearns and Ebert offer a more differentiated list of possible factors (Stearns & Ebert, 2001). Most categories in the first part of their list correspond to one of the six factors in Table 23-2, but they treat genetic variations separately, offering a very useful taxonomy of reasons for the origins and maintenance of variations that may be associated with disease.

The development of evolutionary medicine was advanced by conferences as well as publications. Several major gatherings in the 1990s brought together scientists working on topics in evolution and medicine, but the most influential was the conference organized by Stephen Stearns. The resulting edited volume, *Evolution in Health and Disease* (Stearns, 1998), was pivotal for connecting work in the field with established lines

TABLE 23-2 Six Categories of Reasons for Vulnerability to Disease*Natural selection is slow*

- 1) **Mismatch:** Our bodies were shaped for environments far different from those we live in, and the mismatch gives rise to much disease. This explanation is emphasized in this volume and its predecessor.
- 2) **Co-evolution with fast-evolving pathogens:** Because their generation times are so much shorter, pathogens evolve much faster than we can, so evolution cannot provide perfect protection against infection.

There are limits to what selection can shape

- 3) **Constraints:** There is much that selection simply cannot do, such as starting a design from scratch to fix a design defect such as the vessels in the eyeball running between the light and the retina, or creating a gene replication method that never makes mistakes.
- 4) **Trade-offs:** Inevitable trade-offs make every trait suboptimal; for instance, if our vision was as acute as that of the eagle, our color vision and field of vision would be worse.

Common difficulties in understanding what selection shapes

- 5) **Reproduction at the expense of health:** Natural selection increases the frequency of genes that yield a net increase in reproduction even if they compromise health and longevity.
- 6) **Defenses:** Defenses such as pain, fever, nausea, vomiting, and fatigue are not problems, but useful responses shaped by natural selection.

of medical research. Published about the same time, the first edition of *Evolutionary Medicine* (Trevathan et al., 1999) instead emphasized connections with anthropology and topics such as child development, reproductive health, diet, and changes in the environment. The limited overlap of the topics covered in these two volumes reflects differences between preexisting disciplines. Whether the disciplinary barriers will lead to speciation or continued exchange and hybrid vigor remains uncertain.

HOW CAN EVOLUTIONARY BIOLOGY BE USEFUL FOR MEDICINE?

On first hearing about the field of Darwinian medicine, every news reporter and most doctors and medical school deans ask, “How can Darwinian medicine help doctors practice better today?” One is tempted to reply, as Benjamin Franklin did upon being asked about the utility of the just-invented hot air balloon, “What good is a newborn baby?” The question of the practical utility of evolutionary biology for medicine is, however, sincere and deep. We should be grateful to those who want to apply every advance as quickly as possible. However, probing questions are an appropriate response to those who demand practical benefits before they will invest in learning, supporting, or teaching an established body of knowledge that has such utility for medicine. Examples of such shortsightedness are legion. To take one, as the Rockefeller Institute was being organized, some argued that a large investment was not justified because biochemistry had not proven its practical utility. Genomic research, by contrast, is now generously funded, probably because so many diseases are caused by specific genes and because many other diseases show large genetic influences. So far, however, the billions of dollars invested in genetic research have provided remarkably little benefit in day-to-day clinical treatment. That will likely soon change. But if 5% of the investment in genetic research was put towards investigating evolutionary questions about disease, the benefits would likely be

TABLE 23-3 Contributions Evolution Can Make to Medicine

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1. Expanding evolution's contribution to existing research enterprises that rely on it (e.g., genetics, infectious disease, and research on aging)
 2. Providing a theoretical foundation for epidemiology and public health
 3. Heuristic value: formulating new questions about disease that motivate new studies
 4. Unifying research from different disciplines
 5. Providing a framework for understanding disease from the perspective of evolutionary as well as proximate biology
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as large as those we have seen so far from the genomic revolution. Among a hundred other valuable projects, it would be relatively inexpensive to find out whether lowering fever slows recovery from influenza, whether uric acid levels are correlated with rates of tissue aging, whether there are benefits to high bilirubin immediately after birth, and whether the capacity for depressed mood is sometimes useful. The results of such investigations would have immediate clinical utility.

Citing examples of how evolution motivates research that will improve clinical care is worthwhile, but it is important to emphasize that finding quick fixes is not the main goal. As in the case of other basic sciences, many benefits will emerge only after years of research. In addition, some of the most profound benefits may arise, not from specific research findings, but from the secure framework evolution provides for synthesizing knowledge from every area of medicine into a more organic understanding of disease.

Lists of contributions evolution can make to medicine tend to jumble very different kinds of things. The categories in Table 23-3 help to differentiate some of the ways in which evolutionary medicine can be useful.

1. Expanding Evolution's Contribution in Research Enterprises That Already Rely on It

Most scientists who study genetics or infectious disease already ground their work in evolutionary biology. Infectious disease and genetic researchers with a background in evolutionary biology tell me, however, that evolutionary theory is by no means fully utilized in their fields and many of their colleagues have outmoded notions about natural selection. The levels at which selection works, for instance, remains a major stumbling block; many otherwise well-educated scientists are unaware of the revolution in biology initiated by recognition that selection rarely acts for the good of the species (Williams, 1966).

Interestingly, many studies of antibiotic resistance do not describe the process as natural selection, and very few systematically analyze the trade-offs between better protection against infection and the risks of damage from protective mechanisms (Anderson, 2004). The notion that pathogens and hosts co-evolve is widespread, but not all scientists recognize the ubiquity of arms races and how selection for defenses and counterdefenses leaves both host and pathogen vulnerable to new problems. Mathematical models of pathogen evolution are becoming more sophisticated, and their conclusions can have immediate applications. For instance, some hospitals have tried to prevent antibiotic resistance by shifting to a different preferred antibiotic every 6 months or so. Evolutionary-based

mathematical modeling demonstrates, however, that such regimes may hasten development of antibiotic resistance; using multiple agents may be a better strategy (Bergstrom, Lo, & Lipsitch, 2004). The implications of influenza evolution for vaccine design are increasingly considered systematically, with models now even making predictions about which strain of influenza is likely to evolve next; the public health implications are obvious and valuable (Ghedin et al., 2005; Smith, 2006).

While all genetics is based on evolutionary biology, simple models of mutation–selection balance and drift predominate in many texts, and there is a tendency, especially in medical research, to presume that genes associated with diseases are defects. For instance, the ApoE4 allele is associated with atherosclerosis and Alzheimer’s disease, but it is not a new mutation but the universal genotype in our primate ancestors (Finch & Sapolsky, 1999). On the other hand, criteria for assessing possible selection advantages associated with such genes remain weak. For instance, it is very difficult to tell if ApoE4 offers benefits that help to maintain its prevalence in the gene pool.

New techniques for measuring the signals of natural selection are identifying genes that have been subject to recent positive selection (Ronald & Akey, 2005; Sabeti et al., 2006). The organizer of a meeting at Cold Spring Harbor, Douglas Wallace, has proposed calling work in this field “evolutionary medicine” (Olson, 2002). Studies of “knockout genes,” whose function has been eliminated in certain lines of mice, rats or fruit flies, are fundamentally evolutionary studies about the adaptive significance of genes, but they are often described with little reference to natural selection. For instance, the finding that as many as 30% of genes can be knocked out with no observable effect is sometimes interpreted to mean that many genes are not necessary; an evolutionary view suggests that many genes are selected for because they provide benefits in the face of certain environmental challenges such as starvation, infection with a certain organism, or mating competition.

2. Providing a Theoretical Foundation for Epidemiology and Public Health

Environmental factors that increase disease vulnerability are the focus of public health and anthropology. This volume emphasizes such factors, especially those that are novel in modern environments. Public health has made remarkable strides without a foundational theory, but work like that reported in this volume suggests that evolutionary biology could provide a unifying framework. For instance, an evolutionary perspective on common chronic diseases of adult life, such as hypertension and atherosclerosis, focuses suspicion on novel aspects of our modern environment, such as the new availability of a wonderful diversity of delicious foods we cannot resist. Novel aspects of the environment are immediate suspects for any common disease that is vastly more prevalent now than it was for hunter gatherers, and for any condition with high heritability that causes early death.

Many genetic contributions to vulnerability are not defects but “quirks”; they cause little harm in the natural environment, but cause disease when they interact with aspects of the modern environment. In contrast, rare genetic diseases are far more likely to arise from mutations. Geographical differences in the prevalence of some diseases appear to arise in part from differences in gene frequencies resulting from natural selection. For

instance, the prevalence of different alleles of the GNB3 gene vary in a latitudinal gradient and strongly predict vulnerability to high blood pressure (Young et al., 2005).

3. *Heuristic Value*

A third way evolution can be useful to medicine is by suggesting new questions. Asking why body is the way it is, and why it is vulnerable to disease, is not new. In fact, it was a theme of William Paley's book *Natural Theology* (Paley, 1970 [1802]). This book originated the analogy of the body with a watch, whose intricacies demonstrated, Paley said, the hand of a designer. Paley was, however, an astute observer who found much in the body that seemed preposterously designed, such as the wandering path of the recurrent laryngeal nerve, descending to below the neck before coming back up to the vocal cords. In a classic example of staying true to the evidence and shifting the theory to fit, he suggested that God placed all manner of such anomalies in the body for scientists to study and wonder at. His examples make good reading today, as they did for Darwin. They also illustrate the seductive appeal of intelligent design.

While the body's flaws are no longer presented as evidence for design, they remain a staple of conversations in the medical lunchroom. "Why," one doctor will ask another jokingly, "did the good Lord create one passage for both food and air, thus making choking possible?" What is new is not the questions, but the opportunity to take them seriously, formulating alternative hypotheses, and testing them. This was facilitated by increasing recognition of the need for both proximate and evolutionary explanations as suggested by Tinbergen and Mayr and by the work of Williams (1992), Hamilton (1995), Trivers (2002), and others who posed evolutionary questions about traits such as senescence, sexual reproduction, and menopause. While debates about the scientific study of adaptation set back the study of functions in biology (Gould & Lewontin, 1979), they also called much attention to such questions and encouraged greater rigor (Segerstråle, 2000).

The core idea that we should seek reasons for the body's vulnerability to every disease now seems relatively well accepted in evolutionary medicine. A hundred examples are possible, but relatively few are strongly supported and even fewer have major practical implications. For instance, it seems likely that human vulnerability to gout results from the trade-off antioxidant benefits of high levels uric acid, but this by no means proven (Ames, Cathcart, Schwiers, & Hochstein, 1981; Moe, 2006), and I doubt that it has influenced clinical recommendations. Likewise, the antioxidant properties of bilirubin are well documented (Stocker, Yamamoto, McDonagh, Glazer, & Ames, 1987) and the oxidative stress on newborns emerging into the atmosphere is clear, but whether this should influence criteria for putting infants with mild bilirubin increases under lights to reduce bilirubin levels has not been considered as far as I know.

As demonstrated by the chapters in this book, evolutionary thinking encourages asking new research questions. Is menstruation necessary? Why does mountain sickness exist? Do conditions in early life influence later ovarian function in ways that are generally useful even though they increase the risk of cancer? Evolution is not the method for answering these questions, but it is essential to inspire asking them in the first place. An evolutionary perspective also suggests scores of studies that should have been done long ago. Does taking drugs to reduce fever speed or slow recovery from influenza and other common infections? Is menopause explained because taking care of grandchildren increases one's genes in the next generation more than having more children (Hawkes,

2004; Williams, 1957)? Do genes compete with each other within the individual in ways that cause disease (Haig, 1993)? Are negative emotions like anxiety and depression useful (Nesse, 1999)? Is crying by infants useful aside from signaling the need for something (Barr, 1990)? The list of good questions could go on for pages. Without an evolutionary perspective, no one would think to ask them.

4. Unifying Research from Different Disciplines

Evolutionary studies of infection, genetic diseases, novel environmental causes, and reasons for the bodies' vulnerability have proceeded along relatively separate tracks. Each may benefit from closer contact with the others. For instance, it increasingly appears that genetic contributions to disease often arise from otherwise harmless genetic variations interacting with novel environmental factors. A genetic polymorphism may even influence vulnerability to lead toxicity (Kelada, Shelton, Kaufmann, & Khoury, 2001). Some genetic variations that moderate the effects of environmental factors are products of selection. Sickle cell anemia is the exemplar. The allele that causes sickle cell disease was selected for in Africa where it protects against malaria (Livingstone, 1971). A variety of other genetic variations also protect against malaria (Kwiatkowski, 2005), such as absence of the Duffy antigen (Hamblin & Di Rienzo, 2000). At least one genotype, α^+ thalassemia, may offer protection by increasing the risk of getting a mild form of malaria in childhood, which provides immunological protection against severe malaria later (Weatherall, 1997). The mutation that protects against HIV infection is present more frequently in northern Europe (Martinson, Hong, Karanicolas, Moore, & Kostrikis, 2000), although the explanation for this remains elusive.

Will researchers in areas as diverse as genetics, epidemiology, child development, and vaccine development see a benefit to extending their identities to evolution and medicine more generally instead of just their core disciplines? The pressures to keep up in any specialized area are severe, but evolutionary biology offers a simple and secure framework to allow meaningful collaborations across diverse disciplines.

5. Developing a Framework for Understanding Disease

This section began with the refrain, "How is evolutionary medicine useful in the clinic right now?" Given the many ways evolution can contribute to medicine, such narrow practicality is frustrating. Students learn thousands of important things in medical school that contribute to their overall understanding, even though they do not directly influence clinical care. Many concepts from embryology, biochemistry, physiology, genetics, and histology are in the curriculum not because they tell doctors what to do, but because doctors need a scientific framework that makes sense of what is otherwise a hodgepodge of unconnected facts. From this point of view, evolutionary biology should be at the very center of the medical curriculum. It is the ultimate foundation for all other basic sciences in the curriculum; it is the only one that can unify the rest into a consilient whole (Wilson, 1998).

Those who devote their careers to medical education are all too aware that their curricula cannot present all the knowledge medical students need, much less ensure that students learn it. Their first response to the suggestion of adding a new course on evolution is to describe the impossibility of adding one more hour to the curriculum. Given that

most medical schools do not have even one evolutionary biologist on the faculty, the outlook for getting future doctors up to speed in the basic medical science of evolution would seem dim. However, the very frustration with the current system, and recognition that it consists of thousands of poorly connected facts, provides an opportunity to start from scratch in a way that natural selection never can. Sometime soon, a student who studied evolution and medicine as an undergraduate will be in charge of the curriculum at a major medical school and will have the opportunity to create a learning experience that makes more sense. On a larger scale, medical schools would quickly bolster their teaching of evolution if medical certification examinations included questions on evolutionary biology, as they do for every other basic medical science. How can it be that we do not test students on the basic principles of evolutionary biology?! Many medical students never learn about proximate and evolutionary explanations, kin selection, levels and speed of selection, the importance of drift, pleiotropy, parent–offspring conflict, the evolutionary origins of sexual reproduction, or even the evolution of virulence. We insist that engineers learn physics. We should insist that doctors learn evolution. (Nesse, Stearns, & Omenn, 2006)

A FEELING FOR THE ORGANISM

The above many specific benefits of evolution for medicine may be less important than the ability of an evolutionary perspective to give physicians and researchers a deeper feeling for the organism. At present, many see the body as a machine—a machine that fails and often needs repair. This incorrect analogy gives rise to false beliefs. For instance, many physicians think there is a normal human genome. Exposure to evolutionary thinking helps most to realize that genes increase or decrease in frequency depending on the reproductive success of the phenotypes they make. There is no normal human genome, there are just genes that are less or more successful in gaining representation in the gene pool.

Doctors also find it easy to think of pathogens as evil intruders who threaten us instead of small bits of DNA that replicate themselves at our expense. It seems as if pathogens should become more benign after long-term association with a host, but this is incorrect; selection shapes virulence up as well as down to whatever level maximizes the pathogen's spread (Ewald, 1994; Frank, 1996).

Descartes is widely cited for fostering mischievous mind body dualism (Rozemond, 1998), but in the seventeenth century he was a radical for suggesting that the body could be understood as a machine. The analogy served well to extricate biology from religion and metaphysics. It is, however, fundamentally inaccurate. Machines are created from plans made by designers. Bodies were not designed. Bodies arise from interactions between genetic codes and environments. They exist in an unbroken continuity from the first living cells billions of years ago. We are only now beginning to grasp the severity of constraints imposed because nothing in a body can be redesigned from scratch. The body has to work well in every single generation, so big sudden changes are impossible. There is no way selection can turn the eyeball right side out, or route childbirth through the abdominal wall instead of through the narrow pelvic opening. Some of the body's most marvelous adaptations are compensations for fundamental design flaws; for instance, the

tiny constant eye movements that give us a complete field of vision unobstructed by the blind spot or shadows of blood vessels would be unnecessary if the nerves and vessels ran on the outside of the eyeball instead of the inside.

Machines inevitably wear out and break, and organisms age and die, but the reasons are fundamentally different. Machines cannot replicate their parts, so eventually things break. Bodies can make new parts; lizards grow new tails, and we can replace damaged skin and liver cells. But we cannot regrow a severed finger, nor can we replace heart or brain cells to any extent. The explanations are evolutionary. Rates of aging, abilities to replace damaged cells and organs, rate of growth, age at sexual maturity, and life span are all life history traits that are shaped by natural selection (Stearns, 1992). Why doesn't natural selection do a better job so we can live longer with fewer diseases? Table 23-2 lists six specific reasons. But the global reason is that organisms are not machines shaped for some purpose by a designer. Organisms are, instead, in Dawkins's memorable metaphor, vehicles for genes to maximize the transmission of genetic information regardless of the impact on individuals or society (Dawkins, 1989). Some genes that cause aging are never exposed to selection; others may offer benefits earlier in life when selection is stronger. Evolution's greatest contribution to medicine may be replacing the analogy of body as machine with a feeling for the organism as a product of natural selection.

OBSTACLES

The application of evolutionary principles to the problem of medicine is slowed by several factors: first is general ignorance about how natural selection works, even among medical researchers, second is difficulty grasping the distinction between proximate and evolutionary explanations, and third is the lack of agreed-upon methods for testing evolutionary hypotheses.

How Natural Selection Works

Many readers of this book have never had a course in evolutionary biology, and some will never have read a book describing natural selection in depth. Like other volumes on evolution and medicine, this one provides no overview of how selection works for the very good reason that there is too much to cover. However, without the basics, confusion is inevitable. Little can be done about the problem here except to note it and to recommend reading an engaging authoritative text (e.g., Bell, 1997; Futuyma, 2005; Stearns & Hoekstra, 2005).

Well, perhaps one recommendation may be worthwhile. Many students learn about natural selection by memorizing answers to exam questions. The currently popular mnemonic is VIST (variation, inheritance, selection, time). This static approach does little to impart a feeling for the dynamic process that is evolution. It is far better to encourage students to look for nonbiological examples of selection (such as what television shows persist and which are dropped) and examples of breeding (everyone knows breeds of dogs). Then, after the general principle of selection is vividly illustrated with many examples, students are ready to grasp natural selection with the help of dozens of examples from the natural world.

*The Need for Both Proximate and
Evolutionary Explanations*

It is as difficult as it is essential to get across the idea that every biological trait needs an evolutionary as well as proximate explanation. Students have spent years thinking there is only one explanation for one phenomenon, and many suffer from the misconception that all explanation involves reduction. Here again, examples and discussion prove more helpful than lists and lectures. One student names a trait such as the do not explain the behavior, instead explain how squirrel's tale or the dog's ears or the firefly's glow, and others are invited to propose proximate and evolutionary explanations. I spend a full hour on this exercise in my classes with undergraduates and doctors in training, which is enough for only about half the students to get a secure grasp of these crucial concepts.

How to Test an Evolutionary Hypothesis About Disease

Discussions about evolutionary explanations tend to generate wild speculations. One student may suggest that nearsightedness exists so that that some members of the group stay home to make tools, another that diabetes is useful to keep blood sugar levels elevated to increase energy, and another may hypothesize that cancer cells are reproducing for their own advantage. While these wild ideas are disturbing to listen to, they also provide a valuable reminder about how difficult it is to think clearly about evolution and disease. I have tried to forestall such excesses by emphasizing experimental and comparative methods, the need to test alternative hypotheses, and the scientific method. Students dutifully listen, but this approach does little to make their thinking more critical. Instead, I now encourage students to consider one aspect of the body that makes it vulnerable to disease, and to come up with as many hypotheses as possible. We then go through possible explanations, one by one, showing why most are false, and discussing what it would take to assess the rest. Most proposals are incorrect because the student has either formulated the hypothesis incorrectly or misunderstood a core concept. Correcting these and other errors in example after example is frustrating, but it helps students to develop their critical skills. It encourages a deep feeling for science in general, as well as better understanding of evolutionary principles.

Developing these critical skills is by no means easy, however. If the task is left half-finished, students are liable to leave a class on Darwinian medicine with severely mistaken notions about evolution and disease. In an attempt to provide secondary prevention, I give students explicit instructions on how to test an evolutionary hypothesis about disease (Tables 23–4 and 23–5). This cookbook set of guidelines helps to encourage clear thinking about how to assess hypotheses about why selection has left the body vulnerable to a disease.

CONCLUSION

Evolution is important for medicine. Its full range of possible applications is, however, just now being appreciated. The value of evolutionary medicine in providing direct

clinical advice is real, but limited so far. Its heuristic value is enormous, as is its potential to offer a framework for deeper understanding of bodily systems, as documented by the chapters in this volume. However, its greatest contribution may be to foster a deeper feeling for the organism as a bundle of trade-offs that emerges from varying environments interacting with those genes that have given rise to individuals who have had the most offspring in past generations. From so simple a beginning in the principle of natural selection, endless ideas most beautiful and most wonderful have been, and are being, applied to medicine.

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TABLE 23-4 How to Test an Evolutionary Hypothesis About Disease

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1. Define the object of explanation with great specificity.
 - a. A trait shaped by natural selection will usually be the object of explanation.
 - b. A disease is an appropriate object only if the hypothesis is that the “disease” is actually a defense, or otherwise increases fitness.
 - c. Usually the object is a trait that is universal in the species and that makes an organism vulnerable to a disease.
 - d. If the object is not a universal trait, justify the exception.
 - i. The most common exceptions are traits that reflect genetic differences in subpopulations responding to local environment, e.g., sickle cell alleles that protect against malaria.
 - ii. Other exceptions are facultative adaptations that explain individual differences, e.g., the number of sweat glands increases as a function of early exposure to high temperatures.
 - iii. If the trait is a behavior, do not explain the behavior, instead explain how selection shaped the behavior regulation system.
 - e. Do not propose an evolutionary explanation for why one individual gets a disease and another does not. Evolutionary explanations are about populations. They may however, predict who get a disease.
 - f. Evolutionary explanations are not alternatives to proximate explanations. Evidence about proximate mechanisms is often useful in assessing a hypothesis, however, especially when the hypothesis is that vulnerability to disease results from constraints or trade-offs.
 2. Specify all possible alternative hypotheses for why the trait is apparently suboptimal. There are six main possibilities (see Table 23-2):
 - a. The environment has changed faster than selection and the disease results from this *mismatch*.
 - b. The relevant environmental factor is a *pathogen* that evolves faster than host defenses.
 - c. *Constraints*, e.g., natural selection’s limited ability to clear mutations or correct a fundamentally defective design, leave the organism vulnerable.
 - d. The trait offers *trade-off* compensatory benefits that account for apparently suboptimal features.
 - e. The trait offers *benefits to reproduction or to kin* that are greater than the costs to the individual.
 - f. The trait is not a disease at all, but a useful protective response such as pain or fever.
 3. Make explicit predictions from each possible hypothesis.
 - a. If relevant data from other species can be obtained and analyzed, use the comparative method.
 - b. Otherwise, try to make predictions about aspects of the trait or its regulation, preferably previously unrecognized and quantitative.
 - c. Other useful predictions may be made about the relative fitness of individuals with and without the trait in different environments.
 - d. Predictions about proximate aspects of the trait may be possible.
 4. Use all available evidence to test the predictions from all alternative hypotheses to arrive at a judgment about the contributions of different factors.
 - a. Note that multiple factors often operate together to explain an apparently suboptimal trait. This is quite different from proximate explanations where evidence for one alternative usually weighs against others.
 - b. Many hypotheses can be falsified because they are inconsistent with evolutionary theory.
 - c. Others can be falsified by experiments that show that a trait does not serve the proposed function.
 - d. Assess the overall plausibility of the proposal and the relative viability of alternative hypotheses.
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TABLE 23-5 Some Common Mistakes in Testing Evolutionary Hypotheses About Disease

The guidelines in Table 23-4 tacitly describe a variety of possible errors, some of which are made explicit below.

1. Attempting to explain a disease: Instead, reformulate the question as an explanation for vulnerability to a disease.
2. Proposing an explanation based on what is good for the species: This is group selection, an elementary error. Almost all evolutionary explanations must be based on advantages to genes or individuals.
3. Proposing adaptive functions for rare genetic conditions: There are sometimes evolutionary reasons why deleterious mutations stay in the gene pool, but the explanation is hardly ever some useful function of the disease itself.
4. Confusing proximate and evolutionary explanations: This is a common and serious mistake. Knowledge about how the body works can be very useful in assessing an evolutionary hypothesis, but it is no substitute for an evolutionary explanation.
5. Thinking that evidence for learning influencing a trait indicates that no evolutionary explanation is needed: Learning is a capacity shaped by natural selection, and the pathologies that arise from learning mechanisms, such as phobias, are likely to harm fitness.
6. Thinking that evidence for environmental or cultural differences in a trait is evidence against evolutionary influences: Natural selection shaped the behavioral mechanisms that give rise to culture, and environments and culture influence human behavior and fitness strongly. An evolutionary approach to behavior does not imply that behavior is somehow “determined by the genes,” only that the mechanisms that give rise to behavior and culture were shaped by natural selection. These mechanisms obviously are capable of profound flexibility, with attendant major benefits and costs.
7. Confusing genetic explanations, especially behavioral genetic explanations, with evolutionary explanations: Traits need evolutionary explanations whether or not individual variations arise from genetic variations.
8. Failing to consider all of the alternative hypotheses: This is very common and very serious. All too often an author will propose one possibility without making the alternatives explicit.
9. Assuming that evidence for one hypothesis is evidence against another: Multiple factors may all contribute to a complete explanation and they may interact in complex ways. Correct explanations often incorporate multiple explanatory factors.
10. Presenting all the evidence in favor of a pet hypothesis and all of the evidence against other hypotheses, instead of offering a balanced consideration of all evidence for and against all hypotheses: This is rhetoric, not science. It is observed commonly, for good reasons arising from human nature, not just in testing evolutionary hypotheses but across the range of sciences. Nonetheless, such advocacy should be avoided.