CHAPTER 1

Introducing evolutionary thinking for medicine

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Introduction

Should doctors and medical researchers think about evolution? Does it bring useful insights? Would doctors and researchers who learned a substantial amount about evolution be more effective than a control group that learned only the usual rudiments? Would providing such education improve health enough to justify the cost?

Positive answers to these questions would have profound implications for medical education, research funding, and the future of human health. To address them, we start with examples of significant evolutionary insights into serious medical issues. We then describe the principles of evolutionary biology that produce these insights. We conclude with a summary of what doctors should know about evolution.

At the outset we acknowledge that much medical practice proceeds just fine with little need for a theoretical foundation. Medicine is a profession that offers practical help. Surgeons need to know how the organism is constructed, how it works, and what procedures work best; knowledge about how and why it evolved does not help in performing an operation. For internists, pediatricians, epidemiologists, and geneticists, evolution is more often of practical concern. Evolutionary thinking provides insight and saves lives when one is prescribing antibiotics, managing virulent diseases, administering vaccinations, advising couples who have difficulty conceiving and carrying offspring to term, treating the diabetes and high blood pressure of pregnancy, treating cancer, understanding the origins of the current epidemics of obesity, diabetes, and autoimmune diseases, and answering patients' questions about aging. Evolution is not an alternative to existing medical training and research. It is a useful basic science that poses new medical questions, contributing to research while also improving practice.

We now present some significant evolutionary insights into medical issues. The first is that our evolved state is often mismatched to our modern environment because that environment is changing more rapidly than we can adapt to it.

Mismatched to modernity

Adaptation takes time: lactose tolerance

That it takes time for a population to adapt to environmental change is illustrated by the absorption of milk sugar, lactose, by adults (Simoons 1978; Durham 1991; Mace *et al*. 2003). Like other mammals, human females provide their children with the enzymes needed to digest lactose in their milk. A minority of us now has the ability to digest fresh milk into adulthood, including populations in Europe, western India, and sub-Saharan Africa. The ancestral human condition was the inability to digest fresh milk after being weaned, and the new, recently evolved condition is the ability to do that.

How long would it take that ability to evolve? The ability to digest fresh milk after weaning behaves as a single dominant autosomal gene, and dominant genes increase in frequency under selection more rapidly than do recessive genes.

Individuals without lactase who drink milk suffer from flatulence, intestinal cramps, diarrhea, nausea, and vomiting. A mutation for lactose tolerance had an advantage for herding peoples who could use milk from their animals. Selection for lactase activity could have been particularly strong during serious famines. If the ability to absorb lactose conferred a selective advantage of 5%, how long would it take to increase from a frequency 1% to a frequency of 90%? The answer is about 325 generations or roughly 8000 years (Crow and Kimura 1970). If adults have drunk milk for only 8000 years, then it must have conferred substantial benefits for selection to increase it so quickly to its current high frequency in northern Europe. Even for a gene under strong selection—and a 5% advantage is strong selection—time is a constraint. The lactose example suggests that it is quite plausible that we are mismatched to modernity.

Birth control and cancer risk

Women in cultures without contraception and with normal birth intervals of two and a half years because of breastfeeding have about 100 menses per lifetime; in postindustrial cultures women have up to 400 cycles per lifetime (Strassmann 1997). Women who are nearly perennially cycling experience increased cell divisions, which put them at risk for breast cancer (Strassmann 1999). In the 1990s, breast cancer rates, for example, were 20–30 per 100,000 for females of all ages in Columbia, Costa Rica, and Ecuador, and 100–150 per 100,000 for females of all ages in the USA and Western Europe (International Agency for Research on Cancer, http://www.-dep.iarc.fr)—just about five times higher. Women who experience first birth at a young age and who spend most of their reproductive years pregnant or in lactational amenorrhea (a time when the ovaries shut down during breastfeeding) have demonstrably lower breast cancer rates. Although we do not recommend a return to this reproductive pattern, it is clear that Western women are experiencing too much endogenous hormone exposure and that this exposure comes from women's own ovaries rather than from external environmental sources. Contraceptives need not induce a monthly period. Hopefully a solution can be found that gives women the right level of estrogen for maintaining bone strength and avoiding osteoporosis while avoiding the risks of cancer. The first step, however, is to recognize that there is nothing biologically normal about the regular monthly period. Too many menses are harmful because they increase cancer risk, but merely suppressing them without appropriate adjustments in hormone exposure to protect against osteoporosis might not, on average, help.

Early-life events with late-life consequences

Low-birthweight infants are at higher risk of becoming obese and developing diabetes, high blood pressure, and atherosclerosis later in life. Early nutritional stress is a signal whose evolved response sets the individual on a special developmental course with a physiology effective for conserving energy but ill-prepared for abundant food (Barker *et al*. 2002). Obesity rates have risen threefold or more since 1980 in many countries, both industrialized and developing, with the rate of increase often faster in developing countries. While agencies like the WHO ascribe the worldwide obesity epidemic solely to increased food consumption and decreased physical activity (http://www.who.int/dietphysicalactivity/publications/facts/obesity), the mismatch between early- and late-life nutritional status also contributes, rendering those born in poverty and growing into plenty especially vulnerable.

Parasite load and autoimmune disease

In the environment in which we evolved, we were frequently exposed to severe, persistent infections; most people carried parasitic worms most of the time. Worms, which inhabit their hosts for many years, evolved to down-regulate host immune responses to enhance their survival and persistence in the host. In so doing they reduced our susceptibility to autoimmune diseases by reducing the overall production of antibodies, a small percentage of which leak through our surveillance systems to react with self. Our environment is now so antiseptic that few have worms and few adults die from infection, but many have autoimmune diseases that are becoming much more common now that

children rarely have parasites. Some doctors are successfully treating autoimmune disease by injecting preparations of the coats of parasitic worms, activating an inhibitory arm of the immune system suppressed in modern populations (Michaeli *et al*. 1972). Gabonese schoolchildren with schistosomiasis have fewer allergic reactions to dust mites, and Ethiopian, Brazilian, Venezuelan, and Gambian adults have less asthma when infected with nematodes (Wilson and Maizels 2004). This idea helps to explain the current epidemics of asthma, type I diabetes, and even leukemia (Greaves 2000; Wilson and Maizels 2004). It may take hundreds of generations for evolution to bring the screening mechanisms of our immune systems, located in the thymus and bone marrow, into equilibrium with the cleanliness of modern environments.

Infection

Resistance

Most doctors and many patients recognize antibiotic resistance as an example of rapid evolution. When it evolves at all, antibiotic resistance evolves much faster than we can evolve defenses. Much work remains to understand why some bacteria remain susceptible, such as streptococcus to penicillin, while others escape a new antibiotic in just a few years. Part of the answer is that bacteria and viruses do not always have to wait for mutations; many receive resistance genes from other pathogens (Lederberg 1998). Another part of the answer is that most antibiotics, created by selection during millions of years of competition between bacteria, are weapons against which some bacteria have already evolved effective responses (D'Costa *et al*. 2006). The same principles that govern the evolution of antibiotic resistance apply also to cancer chemotherapy, where resistant cell lines displace others. Triple chemotherapy for cancer is effective for the same reasons that triple antibiotic therapy is now routine for tuberculosis.

Virulence

Virulence—the ability of a pathogen to cause morbidity and mortality—is also shaped dynamically by natural selection. It increases when infection spreads easily—by mosquitoes, fleas, lice, hands, or needles—and when pathogens compete with other pathogen strains within a host. Peaceful coexistence with the host occurs only when it benefits both parties. If the illness or death of the host increases the chances that the pathogen will be transmitted, the pathogen will evolve greater virulence. Genes that influence virulence do not need to arise by mutation; the viruses that integrate into bacterial genomes transmit them among bacteria. They include the toxin genes of cholera, botulinum, diphtheria, and scarlet fever (Waldor 1998). Plasmids, small circular genomes that inhabit bacterial cytoplasm and can induce their hosts to conjugate (have bacterial sex), also transmit virulence genes among bacteria. Thus much of the information that a bacterium needs to become more virulent evolved long ago, now exists in pre-packaged modules, and is mobile.

Emerging diseases

New diseases that emerge from other species can persist and spread in humans only if they evolve changes that allow them to enter, survive, reproduce in, and be transmitted from the new host. Without these evolutionary steps, SARS and avian flu would not be threats: to evaluate such threats, we need to understand their evolution. For some diseases, including AIDS, introduction into human hosts, by whatever route, starts the process moving. The implications for organ transplantation from other species are obvious and serious.

Reproduction

Evolved conflicts between mother and offspring

The mother is equally interested in the success of each of her offspring, for she shares exactly half her genes with each of them. The fetus, however, has evolutionary interests that differ from its mother's with respect to its siblings, because it 'shares' all of its genes with itself but only some of its genes with its siblings. Thus there is a conflict between the genes in the mother and the genes in the fetus over how much the mother invests in the fetus

(Trivers 1974; Burt and Trivers 2006), and the fetus is equipped with placental morphology and endocrine function to manipulate the physiological state of the mother to its benefit. By-products of this evolutionary conflict include increased maternal blood pressure (pre-eclampsia) and diabetes (Haig 1993).

Evolved conflicts between mother and father

The paths to reproductive success of fathers and mothers differ fundamentally. The reproductive success of a mother depends on the number of children she bears in her lifetime. The reproductive success of a father depends on the number of times he mates successfully per lifetime. Starkly put, he can father a child on this female, then go off and father another on a different female, leaving her to raise his child. This asymmetry in reproductive opportunities is ancient, predating the origin of humans by hundreds of millions of years, and we may have inherited its consequences from ancestor species. Because of this asymmetry, genes from the father have been selected to manipulate the mother to provide more nutrition to the current fetus than she has been selected to give, while genes from the mother counter this manipulation to reserve resources for her survival and her future offspring, which she may have by other males (Haig 1992). Such manipulations are possible because of a process called germ-line imprinting that inactivates some genes during early fetal development when they come through the father, and other genes when they come through the mother.

Genetic imprinting may also explain the genetic component of several serious diseases, including autism and schizophrenia. It is also a major impediment to cloning.

Spontaneous abortions and complementary immune genes

Early spontaneous abortions are especially common in women whose fetuses are immunologically deficient because their parents share the same versions of one or more major histocompatibility complex (MHC) genes. The immune systems of such fetuses cannot produce the recombinant antibody diversity needed to counter rapidly evolving pathogens and if carried to term would be poor at resisting infection as infants. Remarkably, the female reproductive tract can identify and discard such fetuses at a very early stage (Ober 1992) when they have not yet cost the mother much time or energy, freeing her to try again, perhaps with a different mate. Repeated spontaneous abortions are both emotionally and evolutionarily costly, and avoiding them would be advantageous. Intriguingly, humans tend to choose mates whose MHC alleles differ from their own (Wedekind *et al*. 1995; Ober *et al*. 1997), using mechanisms not yet fully understood.

The existence of this process suggests two things about the ancestral environment in which it was selected. We then lived in small, inbred groups where the probability of encountering a mate with the same MHC alleles was significant. And infectious disease then accounted for a significant portion of infant and child mortality, as it still does in much of the world.

Populations have histories

Human populations have diverged genetically since we emerged from Africa about 100,000 years ago, and nearly every human individual has a unique genome and has had a unique developmental history of environmental interactions. As we colonized the planet, each branch of our family tree encountered different pathogens and different diets, and those pathogens and diets left their traces on our innate abilities to resist disease and metabolize drugs. As a result genetic diseases vary among populations of different geographical origin and ethnicity.

Doctors practicing in South Africa, in Quebec, or on Pitcairn Island need to be aware of the high incidences of certain genetic diseases frequent in those populations but not in others because each of them was founded by a small group of people in which those genetic defects just happened to be relatively frequent.

Not all genetic diseases found at unusually high frequency in specific ethnic groups are the result of such founder events. Some confer disease resistance when present as heterozygotes, such as sickle-cell anemia and glucose-5-phosphate dehydrogenase (G6PD) deficiency, which confer resistance to malaria. In other cases such connections are suspected but not yet well established: Tay-Sachs

disease, carried by up to 11% of Ashkenazi Jews, is thought to confer resistance to tuberculosis; cystic fibrosis is thought to confer resistance to cholera; phenylketonuria to fungal toxins implicated in spontaneous abortions.

Genetic susceptibility to risk factors associated with circulatory disease also varies geographically. For example, people whose ethnic origin is closer to the equator are at higher risk of suffering from high blood pressure (Young *et al*. 2005), and susceptibility to smoking, cholesterol, and obesity is influenced by interactions among at least five genes each of which exists in several variants. Certain combinations of these variants are associated with much greater susceptibility; others with much less. This is crucial practical information for cardiac prevention.

Evolutionary technologies

Evolutionary biology has also produced technologies with medical applications. Two are particularly important: the new methods of inferring relationships and history using phylogenetic reconstruction, and the production of live attenuated vaccines through serial transfer.

Phylogenetic reconstructions

The phylogenetic methods developed to reconstruct relationships among species, and thus the history of life, have been used on RNA sequences recovered from HIV infections: they identified the Florida dentist who infected his patients (Crandall 1995) and the sailor who introduced AIDS to Sweden, and they also showed that routine dental care does not transmit HIV (Jaffe *et al*. 1994).

The same methods reveal that smallpox exists in three major lineages, one from West Africa, one from South America, and one from Asia. If smallpox is ever used as a biological weapon, knowing the strain will be crucial to developing the correct vaccine.

Attenuated live vaccines

Serial transfer is used to produce attenuated live vaccines, which are evolved by passing human pathogens through several generations of culture on tissues from other species. As they evolve to specialize genetically on the new host, they lose most of their virulence in humans. Every time this procedure succeeds—as it has for the oral polio and typhoid vaccines—it demonstrates the evolutionary principle that a jack of all trades is a master of none.

We now discuss the other basic evolutionary principles that inform the examples presented above.

The nature of evolutionary explanations

Microevolution, macroevolution, and development

To understand the current state of any population, we must consider the interactions of both micro- and macroevolutionary processes. Microevolution refers to changes in traits and gene frequencies resulting from selection and drift in each generation; its causes operate at the level of populations. Macroevolution refers to the broad patterns and deep time perceived in comparisons among species and with fossil evidence; it is revealed in comparisons at the level of the phylogenetic lineage, at and above the species level. Micro- and macroevolution explain why populations and species are the way they are, but they do not explain individuals. Understanding individuals requires adding consideration of development. In the process of development, genes and environments interact to produce the organism at all stages of its life cycle. Microevolution has shaped developmental reactions to the environment across the entire trajectory from conception to death. Those reactions also carry the macroevolutionary traces of phylogenetic history.

Thus, every trait in every organism arises from two interactions. One is between relatively rapid microevolutionary changes and relatively slow macroevolutionary trends and constraints in the population and lineage. The other is between genes and environments during the development of each individual. As a consequence:

- Every evolutionary change in traits involves changes in genes that influence development—for all traits develop.
- All traits arise from interactions between genes and environment; it is an elementary mistake to say

that a trait is 'environmental' or 'genetic,' the product of 'nature' or 'nurture,' for all traits are products of both. However, it is perfectly sensible to estimate what proportion of *variation* in a given population is attributable to genetic differences, to environmental differences, and to their interactions.

- An organism's traits form a mosaic: some ancient, some new, some static, others rapidly evolving.

Doctors do not treat genes; they treat traits influenced by genes expressed in whole organisms, such as infection, inflammation, blood pressure and chemistry, and anxiety. To do this well for many, if not all traits, they need to understand genetic evolution, trait evolution, and development.

Mechanistic and evolutionary explanations

Most medical research has been limited to questions about the mechanisms of the body. The evolutionary perspective asks questions about why those mechanisms are the way they are. The distinction between 'proximate' or mechanistic and 'ultimate' or evolutionary explanations was emphasized by Tinbergen (1963) and Mayr (2004) but remains unfamiliar in the medical sciences. Both types of explanations are necessary, neither substitutes for the other, and they inform each other.

In humans, the presence of some mechanisms and not others is the result of our ancestry and relationships. Like all other vertebrates, humans counter infection with an adaptive immune system and have an inside-out eye whose vessels and nerves run between the light and the receptors. Like all mammals, humans have internal fertilization, pregnancy, and lactation, and females store fat before and during pregnancy. Like all primates, humans provide extended offspring care. Like all hominids we have late maturation, a long life, and a relatively low reproductive rate. Among hominids we stand out for our relatively short interbirth intervals and a significant period of post-reproductive survival in females.

Like birds and mammals, but unlike fish and trees, humans have determinate growth: we stop growing at maturation. After maturation, energy is devoted to reproductive competition and caring for offspring as well as storing calories and resisting disease. Ancient neuroendocrine mechanisms mediate the allocations among these essential functions as well as the transition from the juvenile to the adult state. Those mechanisms have been shaped by selection to adjust allocations to the current situation. Not all such adjustments need be adaptive. For example, one seems to switch the neuroendocrine system to a premature state when nutrition is scant, a finding that helps us understand anorexia nervosa. And while seeking calories and storing them as fat was once useful in most environments, today it shortens lives (Neel *et al*. 1998).

Thus, an evolved system of proximate mechanisms interacts with environments to shape phenotypes and behavior. Individuals whose proximate mechanisms improve reproductive success pass on more of their genes to future generations. Others are selected against.

Natural selection

How selection works

Selection operates to change a trait whenever three conditions are satisfied. When a trait varies among individuals, that variation affects how many successful offspring an individual has, and the genes that vary among individuals influence at least some of the variation in the trait, the reproduction of the successful individuals then changes the frequency of the genes and traits in the next generation. As this process continues over generations, the inheritance of the changes accumulates and can be measured in changes in the genetic composition of the population. The evidence for natural selection is overwhelming.

Selection is not a theory. It is a principle that must hold when certain conditions are present: variation in traits, variation in reproductive success, correlation of trait variation with reproductive success, and inheritance of trait variation. If objects in any population vary in ways that influence which ones persist, then the population will change over time. It has to. Consider the water glasses in an inexpensive furnished apartment that has been repeatedly rented. They can be explained by selection. Some collection of glasses came into the apartment. The

fragile ones broke. The attractive ones left when renters departed. The nonfunctional ones with odd shapes were thrown out. What is left is what you find—a collection of sturdy, ugly, functional glasses. Selection can equally well account for why your coin jar is now mostly full of pennies, why the vegetables at the grocery store on a Sunday evening are mostly damaged, and why some television shows persist and spawn imitators, while others are long gone. Natural selection is just the special kind of selection that occurs when the objects are individuals in a population whose variations are caused partly by genes and whose contributions to future generations are influenced by how many of their offspring survive to reproduce in turn.

Fitness is relative reproductive success

The basic insight of population genetics is simple and powerful—the evolutionary process can be reduced to the analysis of the factors that increase or decrease the number of copies of a gene in a population from one generation to the next. It is a superb starting point. However, gene frequency change is insufficient to explain phenotype evolution. To understand some particular aspect of an organism's design for reproduction and survival, such as age at first reproduction, requires analysis of how the organism's genes produce traits that interact with environments in contributing to survival and reproduction. Natural selection improves reproduction, but the route to reproduction requires allocating effort among finding food, avoiding predators and parasites, fighting, attracting mates, and caring for offspring. The variants that selection sorts do not necessarily include the optimal type: they simply consist of the variation that can be produced by the current population, as it exists. Those that persist performed better than the others, but there is no reason to think that their performance was the best possible.

Natural selection has several components: individual, sexual, and kin selection

The analysis of reproductive success begins with the factors determining the number of surviving and reproducing offspring produced by a single individual over its lifetime. This is the most general component of reproductive success, *individual fitness:* a shorthand way of referring to long-term reproductive success.

In sexually reproducing organisms, reproductive success depends substantially on mating success. This component of natural selection is called *sexual selection*. Sexual selection shapes traits that improve mating success even if they decrease individual health or survival. For example, the male peacock's tail improves his reproductive success by making him attractive to females but reduces his chances for survival by making it harder for him to fly. Human males have shorter lives than females; at sexual maturity in most modern cultures, mortality rates for men are three times higher than those for women (Kruger and Nesse 2004). Sexual selection can involve the two sexes in a complex interaction with fascinating properties. Females choose mates for a variety of reasons, and their preferences shape male behavior and morphology. The process stops when the costs and benefits of mating success balance. At that point, survival has often been compromised by investment in reproduction.

Organisms living with relatives experience a third kind of selection. At one level, what matters to evolution is only the relative number of copies of genes that exist in the population in the next generation. Whether those genes are contributed directly, by an individual, or indirectly, by its relatives, is of no consequence. The closer the relationship, the more genes are shared. An individual can increase the frequency of its genes if it acts in ways that increase the reproductive success of its kin whenever the benefits to the kin's reproductive success, weighted by its degree of relationship, exceed the costs to the individual's reproductive success (Hamilton 1964). This process, called *kin selection*, has helped us understand the evolution of apparently self-sacrificial, cooperative, altruistic, and nepotistic behavior. It also explains why organisms are more likely to help close relatives than distant ones; full sibs, and parents and offspring, share half their genes, but first cousins share only one-eighth. The empirical success of kin selection has convinced evolutionary biologists that their focus on genes is correct (Williams 1966; Dawkins 1976; Dawkins 1982; Williams 1992).

The gene-centered view also explains why senescence is a property of the soma (an individual body), not of the germ line. Evolution 'cares' about the germ line—the genes—whereas doctors treat the soma, which is, from the point of view of evolution, disposable. The consequence has been all the degenerative diseases associated with aging, which are becoming the bulk of medical care. Surely we should want to understand their evolutionary origins.

Traits do not evolve for the good of the species

Before the 1960s, one often heard that some adaptation had evolved for the good of the species, helping it to avoid extinction. For instance, lemmings were said to jump into fiords to commit suicide when food was scarce so the species could survive. As a general explanation, this is incorrect. The vast majority of traits evolve only if they improve the reproductive success of individuals and their kin; if they benefit the species as well, they do so only as a by-product of their benefits to the genes of individuals. Selection acting on species requires the standard conditions to be effective: variation among species in reproductive success (in this case determined by relative rates of extinction and speciation), variation in traits correlated with reproductive success, and heritability of those traits. Genes that benefit the species at the expense of individuals will rapidly disappear, for selection on individuals is much stronger than selection on groups and species. Individuals have much shorter generation times than species, and in the time that it takes for new species to form and go extinct, a process spanning many thousands of individual generations, hundreds of millions of the individuals that form those species will have lived and died. For that reason, selection has much greater opportunity to sort among individuals than it does to sort among species, and species selection simply cannot shape adaptations (Maynard Smith 1964; Williams 1966).

Random events and neutral variation: how neutral evolution works

Some changes in the genetic composition of populations occur through neutral evolution—fluctuations in the frequencies of genes whose alleles do not correlate with reproductive success. This kind of evolution is called 'neutral' because the variation is neutral with respect to selection; no variant has any systematic advantage over any other. It is also called drift to reflect the lack of direction of neutral genes drifting through the population over many generations. Drift produces random change in both large and small populations, but it works more rapidly and over a broader range of conditions in small populations.

Two processes introduce randomness into evolution: mutations and meiosis. Two other processes accentuate it: founder events and lack of correlation of genetic effects with reproductive success.

Mutations are random with respect to their effects on fitness; many are neutral or deleterious, some give an advantage. Whether the costs or benefits of a particular mutation will result in a systematic change in gene frequency depends on the number of times those effects are tested in organisms. If they are only tested a few times, then the randomness of meiosis may dominate the effects of the gene on reproductive success.

The randomness of meiosis is like a coin flip. It consists of the 50% chance that each copy of a chromosome has of getting into a particular gamete. Since only some gametes succeed in forming a zygote, developing, and reproducing, the random effects of meiosis are particularly important in small populations. This can be seen by the limiting case of a population of two individuals, one male and one female, who produce just one offspring. Consider a new mutation sitting on a chromosome in the female. It has just a 50:50 of getting into the egg. Thus even if a new mutation gives a huge advantage, if the bearer has only one offspring, there is a 50% probability that the mutation will be lost. Most genes have effects that are not perfectly correlated with reproductive success. To the degree that they are not, those genes are subject to some influence of drift. Even advantageous genes sometimes end up in organisms that produce no children. It is therefore only in small populations that drift can overcome the effects of strong selection. As population size and number of offspring increase, so do the number of chances that genes

have of making their way into the next generation and having their effects on reproductive success register, and the effects of drift diminish.

Founder events are another source of randomness in evolution. They occur when new populations are founded by a small and unrepresentative sample of the ancestral population. They are important in understanding why certain genetic diseases are unusually frequent in the descendents of the Dutch who colonized South Africa, of the French who colonized Quebec, and of the *Bounty* mutineers who settled on Pitcairn Island. The element of randomness introduced into evolution by founder events is precisely that of sampling error.

Even in large populations drift acts on the neutral genes whose effects are not at all correlated with reproductive success. Completely neutral genes drift through both small and large populations like molecules in Brownian motion; the rate at which they are fixed determines the ticking of the molecular clocks that record the divergence times of species in DNA sequences. Thus drift does not only happen in small populations.

Both random effects and selection have had important effects on populations, but we do not yet know what proportion of genetic variation each accounts for. In humans, the amount of variation is large: about 30% of human genes coding for structural proteins have more than one allele. In many proteins only certain amino acids are critical to their function; substitutions at other positions may be selectively neutral or close to it. On the other hand, the fact that no selective function is known for most human polymorphisms does not mean that selection has not been important: absence of evidence is not evidence of absence. Modern civilization has changed our activity patterns and our diet, and has eliminated or reduced many pathogens that were selective agents in the past. Furthermore, many of the body's mechanisms are useful only in special circumstances. Shivering is useful only in cold situations and certain immune responses are useful mainly against worms that are no longer a threat. In short, the hunt for the adaptive significance of each gene, and of genetic variation, is just getting underway. That drift is real and sometimes potent should not stop us from considering possible functions. 'The neutral hypothesis, when applied to the study of human polymorphisms, might even have a counterproductive effect if it discourages the search for sources of natural selection' (Vogel and Motulsky 1997).

Trade-offs

One of the most useful generalizations evolution offers to medicine is a vision of the body as a bundle of trade-offs. No trait is perfect. Every trait could be better, but making it better would make something else worse. Our vision could be as acute as that of an eagle, but the price would be a decreased capacity to detect color, depth, and movement in a wide field of vision. If the bones in our wrists were thicker they would not break so readily, but we would not be able to rotate our wrists in the wonderful motion that makes throwing efficient. If the stomach made less acid we would be less prone to ulcers, but more prone to GI infections. Every trait requires analysis of the trade-offs that limit its perfection.

This kind of thinking is especially important as we gain more and more ability to alter our bodies. For instance, it seems like a good idea to need less sleep, but natural selection has been adjusting the length of sleep for millions of years. If we think we can take drugs to cram more into 24 hours, we had better think twice. How much testosterone is optimal? Increased testosterone levels in human males may increase strength and competitiveness, but they also decrease ability to resist pathogens and parasites (Chapter 7). How many menstrual cycles per lifetime are optimal? More cycles mean more reproductive opportunities, but they increase cancer risk. These effects of testosterone and menstruation exemplify the central trade-off shaping life span and aging: the trade-off between reproduction and survival.

Every trait must be analyzed in terms of the costs and benefits of the trade-offs in which it is involved. They limit how much fitness can be improved because every improvement in one trait will compromise some other. And those compromises can emerge as unpleasant, costly surprises when interventions are made in ignorance of the trade-offs they manipulate.

Macroevolution

Relationships and fossils reveal history

The type of explanation provided by macroevolution is essentially historical: things are now the way they are because they had a particular evolutionary history. Explaining the human pelvis, for example, begins with figuring out both how its shape changed over evolutionary time, and why it changed. To understand that history, evolutionary biologists use two methods, paleontology—the study of fossils—and the comparative method—comparisons of living species. Often they are used together.

For traits that do not fossilize, the comparative method is the only way to reconstruct the history. The first step in the comparative method is always to locate the species on the Tree of Life, to identify its relationships with other species. Those relationships are now often more precisely understood thanks to a great deal of research that has been strikingly improved by better logic and the availability of cheap DNA sequences. Many relationships are being revised because of those developments.

Given the location of the species in the evolutionary tree, one can map variations in the trait on the historical sequence of species to determine when the trait arose and how it changed in different lineages. Ancestral states can then be inferred by using several methods to search for correlated changes among traits over the portion of time, space, and biodiversity represented by the phylogeny (e.g., Felsenstein 1985; Pagel 1994). The evolutionary histories of menopause and the pelvis exemplify the power of the method; the appendix illustrates the challenges (Fisher 2000).

Constraints: eyes and tubes

Organisms are not soft clay from which natural selection can sculpt arbitrary forms. Natural selection can only modify the variation currently present in the population, and that variation is constrained by history, development, physiology, and the laws of physics and chemistry. Natural selection cannot anticipate future problems, nor can it redesign existing mechanisms and structures from the ground up. You cannot change the basic design of a car while the car is being driven. We illustrate constraint with two examples.

The first concerns the vertebrate eye, often cited for its astonishing precision and complexity. It contains, however, a basic flaw (Goldsmith 1990). The nerves and blood vessels of vertebrate eyes lie between the photosensitive cells and the light source, a design that no engineer would recommend, for it obscures the passage of light into the photosensitive cells. Hundreds of millions of years ago, vertebrate ancestors had simple, cup-shaped eyes that detected only the direction of light and dark, not images. These simple eyes developed as an out-pocketing of the brain, and the position of the light-sensitive tissue layers happened to be beneath the layers that contained nerves and blood vessels. Once such a developmental sequence evolved, it could not be changed without intermediate forms that would be almost useless. Thus, natural selection cannot start from scratch to make the vertebrate eye more 'rationally designed.' The proof that the eye's substandard design is not necessary is found in the octopus eye, which has no blind spot because the vessels and nerves run on the outside of the eyeball, penetrating only where they are needed.

The second example concerns the length and location of the tubes connecting the testicles to the penis in mammals (Williams 1992). In the adult ancestors of primates and their relatives, and in present day primate embryos, the testes lie in the body cavity, near the kidneys, like the ovaries in the adult female. For reasons still unknown, the sperm of many mammals develop better at temperatures lower than those in the body core. This selection force moved the testes out of the high-temperature body core into the lower-temperature periphery and eventually into the scrotum (in some species they only drop into the scrotum during breeding season). This evolutionary progression in adults is replayed in the development of the testes. As they move from the body cavity towards the scrotum, the vas deferens does not take anything like the most direct route. Instead, it wraps around the ureters like a person watering the lawn who gets the hose caught on a tree. If it were not

for the constraints of history and development, the vas deferens would be much shorter and perhaps function better. Many other examples of suboptimal design are described in William Paley's book, *Natural Theology*, where they are explained as results of the Creator's intent to puzzle scientists (Paley 1970 [1802]).

Conclusion

Health, fitness, and the pursuit of happiness

Shorter interbirth intervals are associated with increased childhood mortality. Nevertheless, Hobcraft *et al*. (1983) observed: 'For what it is worth, we note that any family trying to achieve maximal numbers of surviving children at any cost would, in the light of these results, continue to bear children at the most rapid rate possible. The dramatic excess mortality is not enough to negate the extra births. However, it is hard to recommend a pattern with such disastrous human consequences.' This quotation illustrates two important distinctions. First, maximizing the fitness of a parent need not maximize the fitness of individual offspring. Second, health and fitness are not synonyms when fitness is understood in its genetic sense. Where there is a conflict between the self-defined interests of human individuals and the interests of their genes, medicine should serve the former. However, what individuals will choose for themselves does not bear any simple relation to health or fitness. Our choices sometimes promote health over fitness and sometimes fitness over health. When a woman chooses to be pregnant, she takes an action that enhances her fitness but has risks for her health. When she uses contraception, her choice may be good for her health but reduce her fitness.

Our evolved natures should be treated with respect, but not with deference. We did not evolve to be happy: rather we evolved to be happy, sad, miserable, angry, anxious, and depressed, as the mood takes us. We evolved to love and to hate, and to care and be callous. Our emotions are the carrots and sticks that our genes use to persuade us to achieve their ends. But their ends need not be our ends. Goodness and happiness may be goals attainable only by hoodwinking our genes.

Human diversity

Medicine and evolutionary biology have different approaches to variation. Medicine tends to be normative: some states (health) are better than other states (disease). Evolutionary biology is similarly concerned with the causes and consequences of variation, but particular states are not intrinsically more valuable or desirable than others. Differential reproduction is a consequence of interest but not a measure of value. Despite a common misconception, evolutionary biology is concerned with environmental as well as genetic sources of variation. Evolutionary biologists are fascinated by whether plastic human responses to different environments enhance genetic fitness and whether these responses have an evolved component (see Chapter 19). But whether a particular response is adaptive or non-adaptive (in the evolutionary sense) says nothing about the desirability of the response. The idea that some variation is 'normal' and some 'abnormal' has no place within evolutionary theory.

Critics often object to the application of evolutionary theory to our own species because they fear that the theory has normative implications, or will be *perceived* as having such implications. However, normative questions are not the province of evolutionary biology. If it were convincingly shown that some men have a genetic predisposition to homosexuality, then the discovery would raise interesting evolutionary questions but there would be no reason to treat sexual orientation as a medical problem, just as few people would now see left-handedness as a problem needing correction. On the other hand, if it could be shown that variation in growth between human populations is an adaptive response to different levels of nutrition the response would be of evolutionary interest but its existence would not absolve us of asking why some people should have more food than others.

Evolutionary biology is not going to provide easy answers to medical dilemmas, nor provide a simple guide for intervention, but a dialogue between evolutionary biology and medicine should nevertheless be of benefit to both disciplines. Most immediately, the vast database of medicine provides unparalleled opportunities to test evolutionary theory and suggest new avenues of evolutionary research.

We hope that evolutionary biology will be able to repay some of this debt by providing medicine with new hypotheses for answering old questions.

Implications for medical practice, research, and education

Clinicians can profit from viewing infection from the pathogen's point of view and being able to anticipate the evolutionary responses of pathogens to treatments with antibiotics and vaccines. The coevolution of pathogens with our bodies, our behaviors, our interventions, and our drug industries is ongoing, incessant, and inescapable (Chapters 10–17). The evolutionary view helps clinicians dealing with reproductive medicine, cancer, and autoimmune disease to understand how our bodies are mismatched to modernity and how far biological adaptation lags behind cultural change. The diseases of civilization include significant proportions of cancers, allergies, asthma, obesity, diabetes, and cardiovascular disease (Chapters 8, 9, 19–23).

For medical researchers evolution provides a continuing supply of a key limiting resource: new questions posed from a different point of view leading to alternative explanations that suggest new lines of research on tough problems. We recommend considering graduate research programs that bridge medical school departments with departments doing basic research in evolutionary biology.

For medical education, the engagement with evolution does not necessarily imply any new courses or any fundamental restructuring of the premedical or medical school curricula. Both are already packed with useful information that would be a mistake to discard. Instead, we suggest fitting evolutionary material into roughly 10% of that subset of courses where such material is relevant and clearly beneficial.

What doctors need to know about evolution and why

1. How natural selection works—By this we mean not just memorizing 'variation, inheritance, and differential reproductive success' but being able to describe, with examples, how natural selection explains why organisms are the way they are. The body is not a machine designed from first principles by an omniscient engineer. Evolution has assembled it by tinkering with the variants available, every step of the way.

2. Trade-offs and constraints are ubiquitous—Because selection has pushed the design of organisms to limits determined by trade-offs and constraints, improving one thing often makes something else worse. Because some trade-offs are not obvious, unpleasant surprises are possible. Because constraints are real, the optimal has often not been attained.

3. The distinction between proximate and evolutionary explanations and how they combine to explain traits—Those who do not understand this distinction will waste time on futile arguments and will not grasp the importance of evolutionary explanations. For instance, those who think that type I diabetes is caused only by genes and autoimmune reactions have often not considered why those genes persist and why the autoimmune reactions evolved as they have.

4. The distinction between micro- and macroevolution—Some think that evolution is only about anthropological studies of bones and primates and confuse that with studies of changes in gene frequencies.

5. The distinction between evolution and natural selection—Evolution is more than just natural selection. It includes gene drift, gene flow, founder events, speciation, and all of their consequences.

6. Group selection is weak—Many who do not know this is a problem offer explanations for traits such as aging that are inconsistent with evolutionary mechanisms. The correct explanation of aging follows as an example of explanations based on individual selection.

7. Aging is a by-product of selection operating on the whole life cycle, from birth to maturity to death—Selection pressures drop with age and disappear in post-reproductive individuals, and up to a point more fitness can be gained by investing in reproduction than in maintenance that would improve survival. Therefore all organisms must evolve senescence. By understanding why we age, we can better appreciate the consequences of

treating the symptoms of aging and attempting to prolong life (Chapters 18, 23).

8. Each human individual has had a slightly different evolutionary history, and each has a different genetic makeup—This leads to important differences in the way that different human individuals react to drugs and to diseases (Chapters 2, 3, 4, and 5).

9. Microorganisms and cancer cells rapidly evolve resistance to drugs—This has important implications for drug design and the management of treatment (Chapters 10, 21, and 22).

10. Evolutionary theory tells us why virulence evolves to a certain level and no further and what measures could be taken to reduce it—Changes in our lifestyle, in treatment, and in public health measures such as vaccination all cause virulence to evolve, for better or for worse (Chapters 11, 12, 16, and 17).

11. The evolutionary analysis of genetic conflicts tell us why both the placenta and the ovary make high concentrations of reproductive hormones during pregnancy and why some fetal proteins are derived only from the father's genes while others are derived only from mother's (Chapter 6).

12. Selection is everywhere in everyday life, including what drugs physicians use, which patients keep coming for treatment, and which insurance companies stay in business—Understanding selection in general is the foundation for understanding natural selection. Doctors need to understand this to help explain evolution to their patients.