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