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REVIEW

Nothing in medicine makes sense, except in the light of evolution

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Abstract The practice of medicine is a fruitful marriage of classic diagnostic and healing arts with modern advancements in many relevant sciences. The scientific aspects of medicine are rooted in understanding the biology of our species and those of other organisms that interact with us in health and disease. Thus, it is reasonable to paraphrase Dobzhansky, stating that, "nothing in the biological aspects of medicine makes sense except in the light of evolution." However, the art and science of medicine are also rooted in the unusual cognitive abilities of humans and the cultural evolutionary processes arising. This explains the rather bold and inclusive title of this essay. The near complete absence of evolution in medical school curricula is a historical anomaly that needs correction. Otherwise, we will continue to train generations of physicians who lack understanding of some fundamental principles that should guide both medical practice and research. I here recount my attempts to correct this deficiency at my own medical school and the lessons learned. I also attempt to summarize what I teach in the limited amount of time allowed for the purpose. Particular attention is given to the value of comparing human physiology and disease with those of other closely related species. There is a long way to go before the teaching of evolution can be placed in its rightful context within the medical curriculum. However, the trend is in the right direction. Let us aim for a day when an essay like this will no longer be relevant.

Keywords Medical curriculum · Evolution · Evolutionary medicine · Selection · Holocene · Diet

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Why is evolutionary biology missing from the conventional medical curriculum?

The 1959 Rede Lecture at Cambridge by C.P. Snow resulted in his famous book [74], which discussed the "two cultures" of humanities versus the sciences, and suggested that they would never meet because of their widely disparate worldviews and differing ways of approaching questions. While the subsequent expansion of the social sciences made inroads into this divide, Snow's prescient concerns remain largely true today. One striking exception is the interface of the art of medicine with biomedical sciences. Here a divide is unacceptable, as it affects the prevention and treatment of human disease. The practice of medicine began as a diagnostic and healing art focused on a humanitarian approach to a patient, but underwent a "shotgun marriage" with science in the early 1900s [5], when emerging understanding of physiology and biology began to be directly applied to explaining disease and in developing better treatments. Thus, all of the "basic sciences" that medical students are required to learn (anatomy, physiology, biochemistry, pharmacology, etc.) became an established part of their curriculum a century ago, with cell biology and genetics evolving later from these disciplines.

However, at the time this initial revolution in medical sciences was taking place, evolutionary biology had yet to come of age as a recognized discipline. Indeed back in the

early 1900s, even basic questions about evolution could not be addressed. Mendel's laws were just being rediscovered; there was very limited understanding about mechanisms of inheritance, and there was no knowledge of what genes were made of. Thus, the teaching of evolution (the key discipline underlying all of modern biology) missed becoming part of the medical curriculum, a situation that remains largely unchanged, despite appeals and efforts by many proponents [30, 52, 56, 75, 82].

A serendipitous personal encounter with the importance of evolution in medicine

As a conventionally trained physician-scientist, I myself started an academic career with a poor understanding of evolution. I encountered the subject later, stimulated by a clinical observation (serum sickness reaction epitopes) [84], discovering the first known functional genetic difference between humans and chimpanzees [10], and then realizing I did not have a knowledge base to understand the evolutionary implications. After 20 years of subsequent self-education, I conclude that classic Dobzhansky statement that "nothing in biology makes sense except in the light of evolution" [16] can be applied to many aspects of medicine, i.e., most of the biological aspects of medicine make full sense only in the light of evolution. As with the original Dobzhansky adage, my extrapolation seems obvious, but it is rarely put into practice.

Resistance to introduction of evolution into the medical curriculum

My own experiences in discovering multiple uniquely human evolutionary changes in sialic acid biology [85] convinced me that all medical students should learn the basics of evolutionary biology. However, a suggestion that this subject be introduced in the pre-clinical curriculum at my institution was not met with enthusiasm. Besides the fact that the curriculum was packed solid, some course leaders asked what relevance the teaching of evolution had to medicine? And even if any time was allowed, which existing course did it belong in? I responded that evolutionary biology had relevance to almost every medical specialty I could think of, ranging from genetics and microbiology to orthopedics and obstetrics. Eventually, I was granted a little lecture time in the first year genetics curriculum. The response from the students was so overwhelmingly positive that the future of this topic in our curriculum was assured! A major curriculum re-organization then provided the opportunity to suggest that a lecture on human evolution be the very first one that students hear. As I told the curriculum organizers, these students have committed their lives to learning about and caring for one single species—so should they not begin their education by first knowing where that species came from, its relationships to other animals, and its evolutionary propensities for disease? The organizers agreed and the very first medical school lecture at UCSD is now about evolution!

A highly abbreviated core syllabus in evolution for the medical student

An evolutionary perspective has much to offer in understanding human health and disease, and one could easily justify a series of lectures, ideally embedded within other courses. However, modern curriculum reorganizations focus on reducing lecture time, in favor of small group teaching. But like many medical schools, ours does not have the number of knowledgeable faculty needed for group teaching in evolution. Thus, while succeeding in making evolutionary biology the first thing that medical students hear about, I must now content myself with a highly abbreviated core syllabus delivered in a single session. I had to pick and choose which topics might be most interesting and relevant. What follows in the rest of this article are some of the core concepts that I try to communicate to the students. There are obviously numerous aspects left out (especially microbiology and infectious disease), but most of the issues have been covered in detail in other writings [23, 24, 30, 48, 52, 56, 57, 75, 82], including multiple contributions to recent journal special issues [40, 56] devoted to the subject of "evolutionary medicine." The reader is referred to these writings and the references therein. Of course, as emphasized by Stearns [76], just as there is no such thing as "chemical medicine" or "biological medicine," there is in fact no such thing as "evolutionary medicine." Evolution is simply a basic science that is highly relevant to many subjects in medicine.

Placing the human species in an evolutionary context

An approach that assures immediate interest from medical students is to begin by placing the human species in an evolutionary context [9, 78, 93]. While this should be known from undergraduate education, it is worthwhile to reiterate. It is also important to explain basic principles of human evolution particularly specifying what we know, what we think we know, and what we actually do not know. Thus, I begin by presenting the current classification of life forms, drilling down to *Homo sapiens*, our relationships to other mammals, and our position within the primate order on the phylogenetic tree of life. A logical approach should then follow on with basics of human evolution per se. But I

find that introducing disease relevance at this point makes the students more interested in what follows.

Striding bipedal gait—an unusual human feature with medical consequences

A subset of human diseases clearly related to our evolution result from our unusual bipedal posture and striding gait. While the mechanisms of original selection of this unusual evolutionary transition remain obscure and hotly debated, it is clear that human ancestors became bipedal relatively soon after our last common ancestor with the chimpanzee [14, 44, 58], achieving obligate striding bipedal posture (likely associated with long-distance running) with the emergence of the genus *Homo* about 2 million years ago [6]. Space does not allow a discussion of the various theories for the origins of bipedalism in our lineage. Regardless, difficulties arising from this marked change in anatomy and organ physiology lie at the root of many diseases such as hernias, hemorrhoids, varicose veins, and spine disorders such as herniated inter-vertebral disks ("slipped disks"), knee joint osteoarthritis, uterine prolapse, and difficult childbirth. The last problem can be discussed as a classic example of "unintelligent design" in evolution. Achieving bipedal gait resulted in a remodeling and narrowing of the pelvis, but with no immediate consequence. However, this change resulted in serious obstetric problems many millions of years later, when brain expansion occurred, and the fetal head became larger [68, 90]. This explains the prolonged and dangerous birthing process of humans, in contrast to chimpanzees, and potentially the related uniquely human diseases [68, 73].

Other disease differences between humans and "great apes"

Comparative medicine has a long and strong tradition. However, there needs to be a greater emphasis on comparing human diseases with those of our closest evolutionary cousins, the "great apes" (chimpanzees, bonobos, gorillas, and orangutans). After all, major diseases of a given species are likely to be related to maladaptation(s) during the recent evolutionary past of that species. When I first became interested in "anthropogeny" (explaining human origins), I needed to learn all I could about differences between humans and these closest evolutionary cousins (also called non-human hominids, NHHs). It is actually more appropriate to make comparisons with NHHs in captivity, rather than those in the wild. After all, the environmental and exposures and lifestyle in captivity are more similar to those of humans—not to mention the fact that they receive medical treatment similar to that of humans (in fact, many humans in the USA do not receive as good medical care as these NHHs!).

In exploring this issue, I was struck by the fact that the primary emphasis at primate centers that house great apes (primarily chimpanzees) is on the ways in which they are *most similar* to humans [83, 87]. In striking contrast, much less attention is given to ways in which they are different. The reason is that these facilities are primarily funded by the National Institutes of Health, which has been interested in using them as "models" for human disease. Since the origins of this approach, the ethical situation has also changed [2, 12, 28], with our recognition that chimpanzees are self-aware and remarkably similar to (and yet different from) humans in many cognitive capacities [8, 61]. All of this results in an rather biased literature in which one is much more likely to find a report of the rare occurrence of a human-like disease in an ape [63] ("see, they are just like humans!"), than a paper describing an obvious and common difference [86].

There are of course disease differences that can be simply attributed to the anatomic differences between humans and great apes (including bipedal posture), and these are mentioned earlier and detailed elsewhere [87]. But there are other many definite, probable, and possible disease differences [87] that cannot be explained due by anatomical factors (see Table 1). Space does not allow a full consideration of all the diseases and of the probable mechanisms involved. I here discuss just a few of the examples from Table 1. The most dramatic difference has been known for a long time, but very poorly reported until recently. The most common cause of death in captive chimpanzees appears at first glance to be same as that in westernized humans: heart attacks and heart failure. Remarkably, it turns out that the nature of the underlying pathology is completely different. It is only over the last few years that definitive publications on the subject have appeared [41, 70, 86]. The heart attacks and heart failure of humans are primarily caused by ischemic heart disease, i.e., a decrease in blood supply to the myocardium due to blockage of the coronary arteries by atherosclerosis and its complications. Despite having many of the same risk factors as humans (including lipid profiles that would be considered quite adverse in humans) [86], it is extremely rare to find a chimpanzee who dies of a classical myocardial infarction, or who has ischemic heart disease resulting in cardiomyopathy. Instead, these individuals (particularly males) develop arrhythmias and sudden lethal "heart attacks," likely due to malignant arrhythmias (this is an assumption, as no other cause is found for the sudden death). Supporting this notion, examination of adult chimpanzees showed that ~10 % have ventricular arrhythmias, supraventricular arrhythmias, conduction disturbances, or bradycardia [15]. Likewise, chimpanzees can die of dilated cardiomyopathy, apparently as a chronic outcome of the same pathology [70]. The underlying pathology consists of interstitial myocardial fibrosis that can be

Table 1 Apparent differences between humans and "Great Apes" (non-human hominids) in the incidence and severity of biomedical conditions

Medical condition	Humans	NHHs
Definite differences		
Myocardial infarction	Common	Very rare
Interstitial myocardial fibrosis	Rare	Common
Plasmodium falciparum malaria infection	Susceptible	Resistant
Sexually transmitted bacterial diseases	Common	Very rare
HIV infection progressing to AIDS	Common	Uncommon
Foamy virus (spumavirus) infection	Rare	Common
Probable differences		
Alzheimer's disease pathology	Common	Rare
Epithelial cancers (carcinomas)	Common	Rare
Neu5Ac-expressing bacterial pathogens	Common	Rare?
Preeclampsia	Common	Rare?
End-stage renal disease	Variable	Common
Preterm labor	Common	Uncommon?
Human influenza A symptoms	Variable	Often mild
Hepatitis B/C late complications	Variable	Often mild
Possible differences		
Rheumatoid arthritis	Common	Rare?
Bronchial asthma	Common	Rare?
Early fetal wastage	Common	Rare?
Hydatidiform molar pregnancy	Common	Rare?
Endometriosis	Common	Rare?
Female iron deficiency	Common	Rare?
Major psychiatric diseases	Common	Rare?
Polycystic ovarian syndrome	Common	Rare?

Excludes disease differences due to obvious anatomical differences. Modified and updated from [87]. For diseases that occur at a lower frequency in humans, it is difficult to be certain about rarity. In other instances, ascertainment biases also cannot be ruled out. In these cases, the term "Rare?" is used

quite extensive [86]. The fact that this marked difference between humans and NHHs went relatively unnoticed for almost a century raises suspicions that there are other unreported differences. Of course, this overall state of ignorance is simply one aspect of our woeful lack of knowledge regarding the "phenome" of the great apes, when compared to our extensive knowledge of the "phenome" of humans [45] (Fig. 1).

Another striking difference is in the incidence and severity of retroviral diseases. While the genomes of all primates are littered with long ago "domesticated" retroviruses, humans (unlike most other African primates) did not suffer from population-wide endemic infections from retroviruses until recent times. Examples range from HIV, which causes a more severe disease in humans than in chimpanzees [71], to simian foamy virus, which is completely asymptomatic both in apes

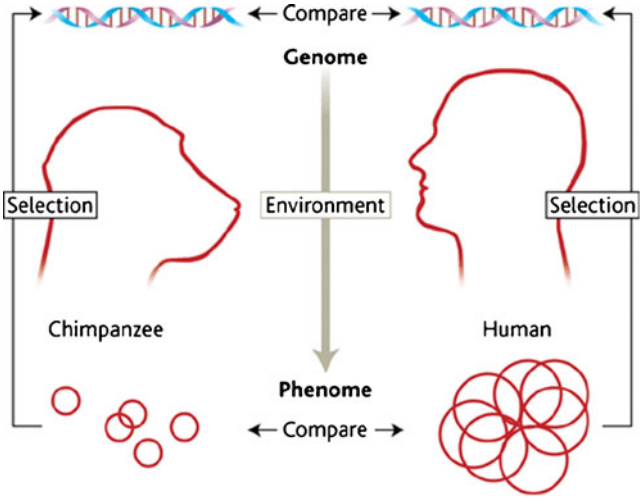

Fig. 1 What makes us human? This question may be answered by comparison of human and chimpanzee genomes and phenomes and ultimately those of other primates. To this end, we need to understand how genotype generates phenotype and how this process is influenced by the physical, biological, and cultural environment. Reproduced from [45]. Credit: Preston Huey/*Science*

and in humans (on the rare occasions that humans do get infected) [47]. But every other primate species except humans carries an endemic foamy virus that cospeciated with it [79]. This leaves a surprising and open question: It is a parsimonious assumption that the common ancestor of apes and humans had a population level prevalence of these types of infectious retroviruses. How then did the human linage "purge" itself of such viruses? Another unexplained surprise is that most of the common human bacterially sexually transmitted diseases do not have counterparts in the great apes, despite the fact that some of them are sexually promiscuous and can be experimentally infected with some human bacterial STDs [87]. Space does not allow discussion of the numerous other definite, probable and possible disease differences in Table 1. The reader is referred to a recent review on the topic, which also mentions potential explanations for some differences, based on uniquely human changes in sialic acid biology [87].

The fossil and genetic evidence for human origins

This is a subject of great interest to the students and showing pictures of timelines and fossils proves very popular. It is also important to dispel misconceptions, pointing out for example that Human Evolution is "a Bush, not a Ladder" [92] and that the lineage leading to modern humans remains somewhat unclear. Lacking sufficient time to discuss this important topic in detail, I have created a handout for individual reading by students entitled "Human Origins in a Nutshell" (see Box 1), which summarizes what we know, what we think we know, and what we need to know about where humans came from.

Box 1. "Human Evolution - in a Nutshell"

This general summary of human origins is based on the best available evidence as of the beginning of 2012. While new facts will emerge, **the text that is presented in bold below is somewhat unlikely to change in thefuture**. **Humans are living organisms that share a common genetic code with all life forms on the planet. We arose from a group of warm-blooded animals called mammals, which already existed prior to the time that the dinosaurs disappeared ~65 million years ago (mya).** Mammals at the time were probably small shrew- or rodent-like creatures. **Among the mammals we are *Primates*, which are closely related to a group called *Glires*, which includes rabbits, mice and rats. Among the primates we are part of a subgroup called the Old World primates**, which appear to have a risen in Africa and/or Asia, perhaps ~35-40 mya. **The largest subset of these are Old World monkeys, and humans belong to a smaller group called the apes, which are characterized by the lack of a tail. Among the apes we are derived from a subgroup traditionally called the "great apes", among which the currently living species are chimpanzees, bonobos, gorillas and orangutans.** While there are very few fossils of great apes, much molecular evidence indicates that **we shared a common ancestor with the common ancestor of the chimpanzee and the bonobo** (so-called "pygmy" chimpanzee) ~6-7 mya. The location and physical appearance of that common ancestor remains unknown,but available evidence from fossils of early human ancestors suggests that the common ancestor was more chimpanzee-like (this does not mean that we are derived from chimpanzees, simply that we shared a common ancestor with them). Current classification lumps all of the "great apes" and humans into"hominids", in recognition of our genetic similarities and the fact that we are closer genetically to chimpanzees and bonobos then they are to gorillas and orangutans. The term "hominoid" is therefore being used less, and the fossil species that appear after the common ancestor with chimpanzees are now therefore called "hominins", rather than hominids. The earliest hominins that have been discovered in fossil form in Africa appear to date back as far as ~5-7 mya, presumably close to the common ancestor with the chimpanzee. The best known of these is *Ardipithecus Ramidus* **The most dramatic difference from the other hominids at this early point is the emergence of bipedalism, i.e., standing upright and walking on two feet).** Although these early hominins already had the bipedal posture, limited information on the structure of their upper arms suggests that they were "facultatively bipedal", i.e., they could still use their arms to climb and swing through trees as chimpanzees and bonobos currently do. Apart from the upright posture these species do not appear to have undergone very major physical changes for the next 3-4 mya. Rather, they seem to have gone through a variety of specializations, in which some lineages developed very large jaws (*Paranthropus*) likely for chewing tough plant matter, and others (such as the Australopithecines) maintained small jaws and teeth. The best known of these species is "Lucy", who is classified as *Australopithecus afarensis*. It is important to recognize that we do not know exactly which of these various species (if they were indeed distinct species) eventually gave rise to the lineage leading to humans, but the most likely candidates are *Australopithecines*. Beginning ~2-2.5 mya, one begins to see fossil evidence of a species classified under the genus *Homo,* in which there is some increase in brain size, and the beginnings of the use of stone tools. There is some argument as to whether some of these earliest *Homo* species are still better classified as *Australopithecines*. Eventually a species called *Homo ergaster* emerges in Africa, which appears to be now committed to striding bipedal walking (and likely, running). Along with this change comes gradual increases in brain size, and some increased sophistication in the complexity of stone tools used. It is not clear whether these tools were used for hunting or scavenging, or both. Another change that becomes more apparent at this time is a decrease in sexual dimorphism, i.e., the difference in size between males and females. **Species very similar to *Homo ergaster* are then found spreading throughout the Old World, going as far as Indonesia and China in the East to current day Europe in the West. These fossils are often called *Homo erectus***. Over the next ~2 million years *Homo ergaster/erectus* seem to have undergone only minor morphological changes other than increasing brain size, and few major improvements in stone tool development. Beginning a few hundred thousand years ago we see evidence of continuing increase in brain size in African *Homo*, with the modern size being achieved

~200,000 years ago. Meanwhile, the hominin pelvis had already been much altered from that of other hominids because of the earlier adoption of bipedal gait. The resulting narrowing of the birth canal was not a major problem for the *Australopithecines,* but may have resulted in increasing difficulties in childbirth of *Homo*, associated with the much larger head of the fetus. However, despite this likely serious risk to mother and fetus, the increase in brain size continued. Given that there is still no evidence of what might be called "modern human behavior" at this time (e.g., burial, representative drawings, ornaments, complex tools etc.,) it seems likely the final increase in brain size was necessary, but not sufficient to allow the emergence of modern humans. During this period one of the most well-documented species to emerge are the **Neanderthals, who were found throughout what is now modern day Europe and the Middle East, often living in very extreme climates associated with the Ice Ages and apparently consuming a diet that consisted prominently of animal products**. The Neanderthals (our closest extinct evolutionary relatives) had brains larger than ours, had improved stone tools, and controlled fire. However, the first ~200,000 years of their existence was not characterized by many of the kinds of artifacts associated with modern human behaviors.

While skeletons anatomically very similar to those of modern humans, can be found ~200,000 years ago from the Southern end of Africa to the Middle East, these "anatomically modern humans" still did not leave behind artifacts suggestive of modern human behavior. Most evidence now indicates that the lineage leading to modern humans then emerged somewhere in Africa, perhaps ~70-100,000 years ago or so, from a relatively small effective population size of 5-10,000 or less. The first evidence for modern human behavior e.g., production of more complex tools such as harpoons, early evidence of use of decorative pigments or ordered scratch marks on objects, emerges at about this time in Africa. Thereafter these "behaviorally modern humans" began to leave Africa (note that they also could have migrated back). These migrations appear to have first occurred along the now submerged coast lines of the Middle East, India, and Indonesia, leading eventually to the first major crossing of water i.e, crossing to a point beyond which the horizon shows no evidence of land - into Australia, likely as the ancestors of modern Australian Aborigines and the Tasmanians. Around this time there is also evidence of similar species beginning to appear in Siberia and China and entering into what is now Europe. The latter group "Cro-magnon man" is incorrectly claimed to be the first human group showing evidence of modern behavior. It is very likely this is an artifact of the improved preservation and more sustained research in such geographical areas. Regardless, studies of Cro-magnon in Europe show remarkable emergences of what is unmistakably modern human behavior, with the production of bead necklaces, bows and arrows, spear throwing implements, etc., etc. As one can now move children from one part of the world and to another part and have them perform in a very similar fashion in most human activities, **it is evident that the modern human cognitive ability was established in Africa before the initial migration out of Africa**. There is some controversy as to whether these groups intermingled or interbred with the pre-existing species such as Homo erectus, but the bulk of evidence is against this possibility. Neanderthals and Denisovans seem to have contributed a very small amount of DNA to current day Europeans and Asians, but there is no evidence for positive selection of this DNA, except for a HLA allele that may reflect disease resistance. Interestingly, after coexisting for the next ~20-30,000 years, all other hominin species disappeared, leaving behind only modern *Homo sapiens*. By this point we can say that evolution of *Homo sapiens* as we know it reached its current status. Further local changes have of course occurred in adaptation to diet, weather and other selective forces. However, given continuing backward and forward migrations and admixtures, **there is no evidence for the classical concept of "race" per se.** Rather that there are "clines", with gradual differences to be found between groups as one goes in geographically different directions.

What about other defining human characteristics? Interestingly apart from the features such as bipedalism, larger brain size and the development of the human type of hand (all of which are detectable in the fossil record) we know little about when and where other human-specific features, such as hairlessness, emerged. Likewise fine details regarding the onset of development and use of things such as clothing, ropes, nets, etc. remain unknown. Last but not least, it is unclear when and where the abilities for human language, full theory of mind and other advanced cognitive abilities emerged, **but this must have obviously predated the initial diaspora from Africa** 50-70,000 years ago.

The origin of modern humans

Understanding the origin of modern humans is important for explaining many human diseases. On the one hand, we humans are remarkably similar to each other, having all descended from an ancestral populations with an effective population size of 5–10,000, who existed in Africa about 100,000 years ago [43]. On the other hand, there was a small degree of interbreeding with other so-called *archaic H. sapiens* species both within Africa [32] and elsewhere, i.e., Neanderthals [31] and Denisovans [66]. However, apart from HLA genes with implications for infectious disease resistance [1], this interbreeding does not appear so far to have resulted in regional selection for the novel DNA. So, as Paabo put it, "from a genomic perspective, we are all Africans, either living in Africa or in quite recent exile outside Africa." [60].

Genetic variation among modern humans

As a limited subset of humans migrated out of Africa ~50–100,000 years ago, they encountered many widely varying ecological conditions. While culture, tools, and other products of human cognition allowed substantial adjustments without genetic change, there was also local selection for some biological features particularly related to infectious diseases, nutrition, and skin color. Some examples of such genetic variation among modern humans are worth discussing. Geographic variations in skin color in relationship to latitude appear to have been selected multiple times, involving genes affecting skin melanocytes, such as the melanocortin 1 receptor locus [65]. The likely selection mechanisms relate to the fact that sunlight generates vitamin D and destroys folate [39]. It is reasonable to suggest that sexual selection played a role, in the form of local mating preferences for skin, hair, or eye color. Promoter changes that cause persistence of intestinal lactase expression in adults were selected multiple times at centers of cattle domestication likely because of a survival advantage to adult milk drinkers [81]. The extraordinary force of selection acting on this polymorphism resulted in very high rates of lactase persistence in northern Europe. Remarkably, this is not because of thousands of years of dairying there but because southern European populations with lactase persistence expanded so rapidly that subpopulations migrated north, taking the derived allele with them [29]. A more puzzling example is the alcohol intolerance found in the Far East, due to mutations in aldehyde dehydrogenase, resulting in the buildup of toxic acetaldehyde following alcohol consumption [42]. The nature of the selection mechanism remains uncertain (was it protection against alcoholism, or against liver parasites?).

The genetic non-reality of "race," as defined in US Medicine

Contrary to the popular misconception (particularly prominent in American medicine), genetic evidence does not support the concept of "race" [80]. While ethnicity certainly has relevance to behaviors impacting disease risk, the conflation of ethnic groupings such as "black" and "Hispanic" with geographic ancestry and genetic composition is deeply flawed. Space does not allow a detailed discussion here, but the bottom line can be cited from a standard textbook of human genetics: "Ultimately, the goal of personalized medicine is to tailor therapy to the individual patient, not by making assumptions about genetic make-up or environmental exposures based on labels defined by physical characteristics, but by using the most accurate predictive testing available, combined with careful attention to the patient—as an individual, as a member of a family, and as a member of society at large—to find the best preventive and therapeutic measures" [59]. And given the new genomic era of personalized medicine, we are entering "the only safe way to know what is in a person's DNA is to study that person's DNA, and this is now both feasible and cheap" [4].

Reasons why diseases exist

Having provided an overview of human evolution and its implications for disease, we need to return to a more general question that students have: If evolution is such an efficient system for optimizing biology, why do diseases even exist? The best summary of the reasons can be found in the writings of Nesse and Williams [52, 54]:

1. Natural selection is slow:
   (a) Mismatch: Our bodies are in a novel environment, different from the one it was selected for.
   (b) As slowly replicating organisms, we are always behind in competing with faster evolving pathogens (The "Red Queen" Effect).

2. Selection is constrained:
   (c) Every selected trait is a trade-off, and none can be perfect for all aspects.
   (d) Natural selection must work with existing situation and possibilities, and cannot recover something that has been lost.

3. We misunderstand:
   (e) Organisms are selected for reproductive success, and not for strength and health after the peak reproductive period.
   (f) Defenses such as pain, fever, nausea, and diarrhea can cause suffering, but may also represent beneficial

responses and/or early warning signals of pathology, i.e., the "Smoke Detector Principle" [51, 53].

It is also important to emphasize that selection does not shape diseases. Rather, natural selection left our bodies with traits that make us vulnerable to disease and also with some alternative traits that make us less vulnerable.

Some popular misconceptions about biological evolution

There are also some popular misconceptions about biological evolution that can confuse a student trying to understand implications for medicine and disease. Examples of misconceptions (also partly based on Nesse and Williams) [52] are:

1. "Natural selection operates primarily by survival of the fittest". The reality is that selection works primarily on reproductive success. "Fitness" is also relative to the population under study and the environmental situation.
2. "Selection shapes traits to benefit the species." The reality is that selection has no "plan" to make species, nor to benefit them. In situations of evolutionary conflict, all parties can suffer.
3. "Natural selection usually leads to optimal design." The reality is that natural selection proceeds by tinkering with what is currently available. It also cannot recover things that were lost, nor anticipate future problems. And neutral evolution is also a strong force.
4. "Imperfections cannot be eliminated because natural selection is too weak." The reality is that imperfections are present for multiple reasons—and evolution is still in progress, it is not over!
5. "Pathogens evolve primarily to co-exist with hosts." The reality is that pathogens usually evolve to maximize their replication.
6. "Natural selection shapes health and longevity". The reality is that natural selection maximizes reproductive success across generations, and health and longevity are only relevant if they affect reproductive success.
7. "Genetic disease results from mutations that natural selection cannot eliminate". The reality is that most common diseases result from multiple existing genes interacting with novel environments.
8. "Aging results only because body parts wear out ("Disposable Soma")." While this is a contributing factor, the reality is that selection operates on reproductive success, and there is no selection against aging, i.e., selection is weak against deleterious effects of genes expressed late in the life span. Genes favoring aging could even be positively selected, if they benefit reproductive success, earlier in life.
9. "Natural selection cannot influence anything after reproduction ends." While generally true for other species, kin selection and cultural selection can be strong forces in humans. The "grandmother hypothesis" is relevant here but we will return to this later, in the section on longevity.

The value and risks of inductive reasoning and speculation in evolutionary thinking

Also to be briefly considered are value and risks of inductive reasoning and speculation in exploring human origins and disease. Since the evolution of long-lived animals like humans is not amenable to experimental replication, one must use inductive reasoning with available facts, thus develop theories, test them against other existing facts, and then seek some indirect experimental verification if possible. And pure speculation is worthwhile, to the extent that it encourages novel thinking and new theories. However, one must keep in mind the danger of developing "just-so" stories that seem to make perfect sense, but neither consider alternative explanations nor care about testing them. It is also worth pointing out that "although no biological explanation makes sense except in the light of evolution, it does not follow that all evolutionary explanations make sense." [11]. Regardless, one can still be productive in this approach without lapsing into making broad generalizations about "adaptationism", i.e., falsely assuming that all traits are adaptive [55].

The end of the Last Ice Age and the current Holocene epoch

Perhaps the greatest impact of human evolution on modern human disease relates to dramatic changes that occurred with the onset of the current Holocene epoch. About 11,000 years ago, our planet came out of multiple cycles of ice ages and developed a relatively stable and warm climate [37]. The reasons for this stability are a matter of current debate. Regardless, this climate allowed the spread of humans across the planet and a gradual switch from the traditional hunter–gatherer, foraging type of subsistence, toward agriculture, settled villages and cities. This in turn caused a massive population boom due to shortened inter-birth intervals, along with dramatic changes in lifestyle and biology, all with potential implications for disease. The related changes in human diet are of particular note, and it is now well recognized that the mismatch between our current lifestyles and diet relative to our genetic origins is a major source of disease [19, 30]. Thus, prior to 10,000 years (~400 generations) age, most humans very likely lived in small groups or tribes of "hunter–gatherers." The ~100,000-year period prior to the Holocene epoch is thus sometimes considered the "environment of evolutionary adaptation" in which most of our genes were selected, across ~5,000

generations [19, 30]. Of course there was no single definable environment, so the term "adaptively relevant environments" may be more appropriate [38]. While one has to be careful in making generalizations and extrapolations, studies of current-day hunter–gatherers (particularly in Africa) may shed some light on these environments, and useful principles may emerge.

Post-Paleolithic changes in human diet

Fruits represent the majority of food intake for most primate species [18, 64, 91], with the exception of leaf-eating monkeys that do not have tri-color stereoscopic vision (which other primates use to find fruit) [17]. This large-scale primate frugivory has been lost in most human populations, and it is unclear if humans have yet adapted to that loss. Conversely, very few primates eat mammalian meat, and those that do so consume it as a minor source of total calories [25]. In contrast, most humans consume large amounts of red meats, with the total bulk (as well as saturated fat content) increasing markedly in modern times. Animal milk drinking by adult humans provides many valuable nutrients, minerals, and water (likely explaining why it was so strongly positively selected for) [81]. However, it is also true that no other mammal steals the mammary secretions of another mammal after it is finished with its own mother's milk! And the question is whether the mass production capabilities of the dairy industry have converted this valuable food into a nutritional problem, in its excess (after all, milk is a form of beef!). These and other factors (see Table 2) can help explain the severity and frequency of some modern human diseases. An added factor could be our recent discovery that a non-human sialic acid enriched in red meats is being incorporated from the diet into human tissues, generating a xeno-autoantibody response that can fuel inflammatory aggravation of red-meat-related diseases [36, 62, 85].

Industrial age behavioral changes affecting disease incidence

Examples of such changes abound, but a few dramatic ones can interest the student in exploring the matter further. Myopia (shortsightedness) increases from near 0 % in aboriginal peoples to the very high rates seen in Westernized individuals who do a lot of reading or other near vision activities [27]. While genetic factors contribute, it seems that the way in which we use our eyes in childhood can affect ocular growth and refractive error. Another modern behavior is the loss of traditional mother-infant co-sleeping and on-demand nursing, a change which had been associated with the increased incidence of sudden infant death syndrome [46]. Reduced toughness of food makes chewing easier and may be associated with less gingivitis, but reduced jaw size, dental crowding, and impacted molars seem to be a consequence [89]. Another dramatic change in more recent times is the alteration of the female reproductive schedule, with the attendant implications for disease. In times past most women had relatively large numbers of children (many of whom did not survive). Taken together with the fact that they breast-fed to support these infants for extended periods of time, they had a much lower number of lifetime menstrual cycles [20]. Meanwhile, the age of menarche has been progressively going down in developed countries likely due to environmental endocrine-disrupting chemicals and improved nutrition [22] (perhaps the latter is a human evolutionary adaptation that maximized female reproductive fitness during times of plenty?). Meanwhile, there is an increasing frequency of women having either no children or one late child, coupled with the decreasing frequency and duration of breast-feeding. These changes (while socially considered positive and empowering for women) may have negative effects on the health of reproductive organs. Indeed as pointed out many years ago [20] and reiterated in various forms since then [7], this combination of early menarche, late first child, or no child, and limited or no breast-feeding

Table 2 Post-Paleolithic changes in human diet, activity, and disease

Food	Hunter–gatherer	Agrarian	"Western"
Fruits	++++ (variable)	++	+
Nuts	++++ (variable)	++	+
Tubers	++	+++	++++
Corn	+	+++	+++
Rice	−	+++	+++
Wheat	−	+++	++++
Red meat	+ (lean)	++ (fatty)	++++ (very fatty)
Milk and milk products	−	+++	++++
Soluble fiber	++++	+++	+
Physical activity	++++	+++	+
Obesity/diabetes/heart disease	Rare	Variable	Common

Space considerations limit the ability to fully reference the points made in the table. However, many of them are covered by citations in the main text

constitutes some of the major risk factors for breast and ovarian cancer. No one is suggesting that the successes of the women's liberation movement should be reversed. However, a research agenda focused on understanding how these modern changes increase cancer risk would be worthwhile, with intent to intervene in some practical manner, perhaps related to selective use of hormones.

The hygiene hypothesis

Another consequence of our cultural evolution may be the increasing risk of autoimmune diseases, i.e., the "hygiene hypothesis" [67, 77]. The success of epidemiology and public health in reducing infections has markedly increased longevity. On the other hand, the increasing cleanliness required for this success story has left our microbiomes and immune systems in a rather unnatural state, in which allergies, autoimmune disease, and unexplained immune processes like inflammatory bowel disease appear to be increasing in frequency [21, 67, 77]. These are certainly potential mechanistic connections that need to be further evaluated. But if a clean environment is definitively proven to increase the risk of autoimmune disease, what are we going to do about it? Should we increase our risk of waterborne diseases in order to restore our microbiomes? Or should this be done in some artificial manner? Claims for success of probiotics [26] and such unusual therapies as deliberate worm infestation [21] and fecal transplants into the colon [26] give one pause and suggest that such approaches should be considered seriously.

The "thrifty gene" hypothesis

Another concept that has stood the test of time to some extent is the so-called thrifty gene hypothesis [49, 50] that suggests the following logic (updated and modified from Greg Wray) [3]: Prior to modern civilization, it was helpful to crave nutrients, such as saturated fats. It was useful to eat a lot of them when food was available because these are limiting for growth and physiology and thus for reproductive fitness, especially during subsequent periods of famine. It is suggested that genetic alleles that encouraged craving/eating such foods were adaptive, and we still crave them. But these nutrients are now superabundant in our environment, and the result may be the increasing incidence of insulin resistance, obesity, diabetes, and their complications. The same logic could be applied to other key nutrients such as salt and sugar. While the specific genes and regulatory elements involved are yet to be clearly defined (and are likely a large complex of interacting genes), the concept is supported by the high incidence of metabolic syndrome and diabetes in populations that were agrarian for a long time (e.g., Middle Easterners, South Indians, and Native American) and likely went through many cycles of nutritional boom and bust [30, 49] Interesting correlations have also been proposed with the human propensity for chronic inflammation [69] and polycystic ovarian disease [13].

Human longevity: implications for the future of medical practice

Of very practical relevance to modern medicine is the evolution of our lifespans and increasing selection for longer life. From the evolutionary perspective, greater longevity should be of little benefit unless there is also an improvement in reproductive success. In this regard, it has been noted that although median lifespans in hunter–gather tribes tend to be very short, all such societies have some individuals living for a long time [33, 34]. This is in striking contrast to the situation in great apes, wherein life span is consistently curtailed at about the fifth to sixth decades, regardless of medical intervention [35], implying that there was prior selection for longevity in humans. This may relate to the grandmother hypothesis (that post-reproductive women can contribute to the survival of their genes in their grandchildren) [33, 34] and/or the change in the early life history of humans (a prolonged helplessness and dependence prior to late maturity), which may have accidentally generated the potential for long life. Regardless of which hypothesis explains the human potential for longevity, the modern diminution in early deaths arising from malnutrition, infectious disease, trauma, and violence has greatly increased the number of individuals living well past prime reproductive age, and there is no clear inflection point in the life expectancy curves [88]. In some Western countries, the number of centenarians has increased by 5,000 %! While this is a great success for public health programs and modern medicine, it also generates huge social, fiscal, and medical issues for the future. Essentially, if adult humans in developed countries have the benefits of modern preventive health and medical care and then escape the "three big Cs": cardiovascular disease, cancer, and car (automotive accidents), they will run up against the big A (Alzheimer's disease has a frequency of ~50 % in those who reach age 80) [72]. Those who also escape this fate then emerge as "the frail healthy elderly," with well-functioning brains and other organs, but now at risk of falls and injury due to poor musculature and/or osteoarthritis. The vicious cycle of fractures, hospitalization, and hospital-acquired infections are

Box 2: Evolution: A Proof By First Principles

- Over time, humans in most societies have classified living organisms into groups such as animals, plants, fungi (and more recently "microbes"), based on observations of similarities and differences.
- Some humans further divided such groups into subgroups and into subgroups of subgroups, again based on observational criteria (initially external appearance, and later on, other internal features).
- When a particular sub-group shows great similarities between individuals and they breed and reproduce to give rise to similar individuals in the next generation, we humans called such a group a "species".
- Much later humans found that all known life forms require DNA as a "genetic code", a system by which specific "letters" of a code direct the addition of specific amino acids into proteins.
- It then emerged that the genetic code lettering system of DNA is essentially the same in all life forms.
- When DNA from different species was then sequenced the relatedness of the sequences was almost exactly in line with the prior classification of species based on general observation. i.e., there is a "tree of life" in which living things appear related to one another by their DNA.
- At the level of populations, all species show individual variations in their DNA, their bodies and/or behavior, which can be beneficial, neutral, or detrimental, depending on the environmental conditions.
- Such variation is also common in the DNA of different individuals within natural populations.
- During reproduction, the DNA of one generation must be passed on to offspring. This process introduces such variation into the progeny by less-than perfect replication of DNA.
- Ongoing random mutations also introduce further variations and changes into DNA.
- Most species produce far more progeny than can possibly survive. What prevents natural populations from explosive expansion is that only a small fraction of all progeny survive and reproduce.
- Individuals who reproduce (pass DNA on to progeny) are likely to be those whose variations were most beneficial and least detrimental under the circumstances (a non-random process).
- Thus over time, populations will change, as DNA variations beneficial to prevailing environments accumulate in a given population over generations. This process can be called "natural selection", and it results in "adaptations" to environmental conditions.
- Many such adaptations eventually appear like very exquisite designs, but on closer observation, they are still imperfect and/or seemed constructed in an "illogical" fashion.
- Mate choice can influence whose DNA is passed on. This is called "sexual selection", and can lead to astonishing features of no apparent survival value to the individual e.g., the male peacock's tail, or the male moose's antlers.
- In addition to natural and sexual selection, the distribution of DNA variations and imperfections across populations can occur randomly, without selection. This is called "neutral drift".
- Working together, natural selection, sexual selection, and neutral drift can lead to differences between populations that are eventually large enough to represent barriers to successful mating.
- Such "reproductive isolation" will eventually give rise to new species, as newly isolated populations accumulate independent DNA changes and cease to have any DNA exchange.
- Once a beneficial DNA change becomes critical for survival and reproduction, any further changes tend to be detrimental, and cannot be tolerated without losing the individual in whom the change occurs (and hence that individual's DNA). Thus some aspects of DNA remain "conserved" during passage to the next generation. This is called "purifying selection".

Taken together, all this information *can only be explained by assuming that all life forms are related by a single genetic code and have diverged over time into the different species we see today*, via processes such as natural selection, sexual selection, neutral drift and purifying selection. The sum total of all these processes can be called "biological evolution". It is today the *only possible fact-based explanation* for the existence of so many life forms on earth, with all their remarkable variations and imperfections. No other explanations come even close. The evidence for evolution is now as strong as the evidence that the earth is round (not flat) and that the earth revolves around the sun, and not the other way around.

familiar to many. This suggests that much greater effort should be taken not only to improve the cardiovascular and nutritional status of the elderly but also the physical condition of their musculoskeletal systems. Overall, the apparent "unmasking" of the human evolutionary propensity for human longevity has huge implications for the future of medical practice.

Creationism: a fly in the ointment

The overall responses to my lectures to medical students on this topic were overwhelming positive. But I later heard that student discussion blogs discussed differing views about evolution, including creationism. I therefore conducted a single question multiple-choice anonymous survey of the

students who had recently heard my lectures and obtained the following results:

Question: *Which one of the following answers best characterizes your understanding of the origin and diversity of life forms on earth*? The suggested options and the resulting answers were as follows:

66 %—evolution over time from ancestral life forms
14 %—evolution over time from ancestral life forms, initiated by a Creator, who did not interfere
8 %—evolution over time from ancestral life forms with limited interference by a Creator
14 %—created directly by a Creator
0 %—produced by an unknown Intelligent Designer
2 %—Not sure

I cannot quibble with students who took the option of "Pascal's Wager" and hedged their bets as to whether or not a Creator was involved in the evolutionary process. But I was shocked to find that almost 1/6th of this class of future physicians completely denied the reality of evolution, in favor of pure creationism.

A proof of evolution from first principles

To avoid the non-scientific arguments that can surround this issue, I decided to derive a proof of evolution from First Principles, i.e., simply using well-known facts in biology, and without alluding to specific theories, nor to any of the existing literature on evolutionary biology. As you can see in Box 2, such a proof is easy. I asked the next class of students to judge for themselves and said I would be happy to organize a separate session to discuss it with anyone who disagreed. But no one took me up on the offer.

Conclusions and perspectives

I hope that this somewhat personal view of the critical importance of teaching evolution to medical students has been convincing and provides an impetus for every medical school that currently has a deficiency to correct it. We owe it to future generations of physicians and patients to ensure that this fundamental keystone of biology takes it rightful place as an integral part of the curriculum.

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