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EVOLUTIONARY FOUNDATIONS FOR MOLECULAR MEDICINE

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Abstract

Evolution has long provided a foundation for population genetics, but many major advances in evolutionary biology from the 20th century are only now being applied in molecular medicine. They include the distinction between proximate and evolutionary explanations, kin selection, evolutionary models for cooperation, and new strategies for tracing phylogenies and identifying signals of selection. Recent advances in genomics are further transforming evolutionary biology and creating yet more opportunities for progress at the interface of evolution with genetics, medicine, and public health. This article reviews 15 evolutionary principles and their applications in molecular medicine in hopes that readers will use them and others to speed the development of evolutionary molecular medicine.

Keywords

Evolution; biology; genetics; Darwinian medicine; evolutionary medicine

FROM EVOLUTIONARY MEDICINE TO EVOLUTIONARY MOLECULAR MEDICINE

The medical importance of some evolutionary principles and methods has long been recognized. Examples include population genetics, methods for tracing phylogenies, and explanations for antibiotic resistance. Only late in the 20th century, however, were evolutionary principles applied systematically to try to understand why bodies have traits that leave them vulnerable to disease. Many traits, such as the nephron and the mitral valve, seem exquisitely designed. Others seem jury-rigged at best. Human examples include the

narrow birth canal, a back architecture notoriously prone to failure, and a vast arsenal of protective but aversive responses, such as pain, anxiety, fever, and inflammation, which often seem to be expressed excessively.

Traits that leave bodies vulnerable to disease have usually been attributed to mutations and the limitations of natural selection. Natural selection tends to make traits better suited to their functions, so it was hard to see how it could help to explain disease. Indeed, diseases are not adaptations, and they are not shaped by selection. However, traits that leave the body vulnerable to disease are shaped by selection and they do have evolutionary explanations.

This slight shift in the question, from explaining diseases, to explaining traits that leave bodies vulnerable to diseases, inspired the beginnings of Darwinian (evolutionary) medicine [1, 2]. It has quickly grown into a robust field that has expanded far beyond this original focus to include analyses of somatic evolution in lines of cancer cells, the sophisticated dynamics of host-pathogen co-evolution, and using phylogenetic methods to trace the evolutionary histories of human genes, pathogens, and populations [3, 4].

Evolutionary medicine is not a method of practice, nor is it opposed to ordinary medicine. It is, like genetic medicine, a discipline that applies the principles from a basic science to problems in medicine and public health. Comprehensive treatments of evolutionary medicine are available, many of which address medical genetics [5–7]. Several books provide overviews of evolutionary genetics [8–10], and at least one article outlines how they can be used to better understand disease [11]. A few articles integrate many evolutionary principles to offer a comprehensive treatment of a topic, such as Douglas Wallace's analysis of the evolution of mitochondria and the tradeoffs that explain their roles in disease [12]. Barton Childs should be recognized as a pioneer of evolutionary molecular medicine [13, 14].

Medical genetics has long recognized the need for evolutionary explanations in terms of the core evolutionary mechanisms of mutation, natural selection, genetic drift, and gene flow [15]. However, it is only now recognizing the world of complexity hidden in the phrase “natural selection.” If only it were as simple as genes making proteins that make phenotypes with higher or lower reproductive success! A full evolutionary explanation of genes involved in disease requires considering evolutionarily principles such as kin selection, levels of selection, segregation distortion, and antagonistic pleiotropy [8, 9, 11, 16].

The systematic exploration of evolutionary applications in molecular medicine is, however, just beginning. To encourage exploration of this new territory, we review 15 evolutionary principles and their implications for molecular medicine. The principles below are by no means exhaustive; they illustrate only some of the ways that evolutionary approaches can advance genetic understanding of disease. The list is intended to spur curiosity and efforts that will advance the continuing synthesis of evolutionary biology and molecular medicine.

1. Biological traits need both proximate and evolutionary explanations

As emphasized decades ago by Tinbergen (1963) and Mayr (1982), a full understanding of any trait requires understanding both how it works (a “proximate” explanation of the

mechanism) and the process by which it evolved (an evolutionary or “ultimate” explanation of its history and adaptive significance). Thus, understanding every physical detail of a trait and its development provides only part of a complete biological explanation. The other, evolutionary, half of a full explanation considers when the trait first appeared, the evolutionary forces that most likely maintained it in the population, its functions that increased reproductive success in the past, and how or whether it influences fitness in current populations. These analyses can be subtle; functions shift over time, formerly functional traits can become non-functional, and initially non-functional traits can acquire a function later.

Consider eyebrows as an example. Knowing every detail of their shape, color, thickness, chemical composition, development, genetic basis, and other attributes provides only the proximate half of a full explanation. We also need to know how eyebrows’ effects on fitness have influenced how they came to be the way they are. For instance, it seems likely that eyebrows give a selective advantage by keeping sweat out of the eyes; their shape fits their function nicely, and actors who shave their eyebrows conduct the equivalent of an extirpation or knock out experiment—one that often leaves them struggling to see through eyes stinging with sweat. Like many biological structures, eyebrows have multiple functions; in this case, social signaling. A proper comparative study would describe variability in eyebrow form among populations of people living in different environments, and the distribution of eyebrow-like features among non-human primates and other mammals. We might also be interested in whether eyebrows represent selective retention of previously more extensive facial hair, or whether they evolved secondarily after a period in which our ancestors lacked eyebrows. The seemingly simple example illustrates the many questions that arise.

The necessity of considering both proximate and evolutionary explanations applies equally to more complex traits, such as those that are only expressed facultatively in situations where they are useful. For instance, the capacity for cough requires a proximate explanation—how foreign matter in the respiratory tree is detected, how the signal is transmitted to the cough center in the medulla, and how signals from the medulla activate the phrenic nerve and chest muscles. It also requires an evolutionary explanation of how variations in those mechanisms influenced fitness in the face of specific challenges—in colloquial terms, what cough is for. Of course, coughing is not unique to humans—raising the question of when it first evolved, how broadly distributed it is, and what other traits serve similar functions in other species.

The evolutionary history of eyebrows is mainly of academic interest, and doctors already know what cough is for, but the general approach outlined above has significant implications for advancing human health [17]. Seeking both proximate and evolutionary explanations is essential for full understanding of questions such as why the appendix persists, why reproductive cells are especially prone to cancer, why major depression is so prevalent, and why autoimmune disorders are now increasing exponentially.

2. Traits that leave bodies vulnerable to disease have evolutionary explanations

Most medical research is about why some individuals fall ill while others do not. It seeks to understand the body's mechanisms, and why these mechanisms differ among individuals. Equally important, however, is the task of understanding why all members of a species are the same in ways that leave them vulnerable to disease. Taking such questions seriously and testing alternative possible explanations is one focus of evolutionary medicine [18] [1, 19]. Why do all humans have an appendix that can become infected, an esophagus that intersects with the trachea causing vulnerability to choking, a birth canal too narrow to safely deliver all babies, a spine prone to failure, and cells that sometimes divide out of control? These are evolutionary questions whose answers require tracing phylogenies and reconstructing the forces of evolution—mutation, selection, drift and migration—that explain the responsible traits [1, 18].

The potential evolutionary explanations can be organized in to six major categories. They are listed in Text Box below, and summarized in subsequent paragraphs

a. Constraints on what selection can do—Some disorders result from mutations and genetic drift. For instance, the high prevalence of hereditary deafness on Martha's Vineyard is accounted for by mutation, founder effects, and genetic drift. Are there deleterious alleles we all share that have drifted to fixation? Very likely yes, but lack of variation makes it hard to recognize them. [Maybe cross-species comparative studies would reveal such variation.]

A focus on mutations and Mendelian diseases distracts attention from other limitations of natural systems that do not apply to engineered systems. For instance, suboptimal machines can be redesigned from scratch, but organisms are path-dependent; all changes modify precursor traits. Changes in fundamental anatomic relationships that would require generations of poorly functioning individuals are not possible, no matter how beneficial. For instance, the vertebrate eye has a blind spot where vessels and nerves enter the eyeball, and a retina that can detach. Cephalopods have nerves and vessels that penetrate the eyeball where they are needed, so there is no blind spot and no possibility of retinal detachment [15]. However, the path to the vertebrate eye is a one-way street that cannot be retraced to make our eyes like those of cephalopods. Mutation and path dependence impose important constraints on natural selection, but there are five other possible reasons for vulnerability to disease. The most important is mismatch.

b. Environmental Mismatch—Natural selection is too slow to adapt populations reliably to rapid changes in environment resulting from migration, technological advances, and even climate changes, so most individuals have traits ill-suited to modern environments. Diet, hygiene, and addiction are all examples. These non-communicable diseases are fast becoming epidemic also in low-income countries.

Preferences for fat, salt, and sugar were useful a few thousand years ago, but the health effects in modern environments are displayed on inpatient wards in developed countries: obesity, atherosclerosis, hypertension and their complications are epidemic [20]. We all know what we should eat to stay healthy, but sweet, salty fatty foods still taste good and sell well.

Modern sanitation saves millions of lives, but it also results in lack of exposure to micro-organisms and worms that have lived in the guts of our ancestors for millions of years [21]. The absence of these “old friends,” organisms with which we have evolved, seems likely to explain much autoimmune disease [22]. Remissions from Crohn's disease after administration of pig whip worms provides a tantalizing hope for finding ways to minimize autoimmune diseases [23]. Likewise, lack of multiple sclerosis progression in patients who have helminths in their guts, gives hope of understanding why autoimmune disorders, have become many-fold more common in recent decades [24]. Solutions other than administering worm eggs seem likely. For instance, the Chinese herbal remedy called Chang Shan, from a type of hydrangea that grows in Tibet and Nepal, has an active compound, halofuginone, which blocks the action of Th17 cells implicated in autoimmune disorders [25].

Alcoholism and other addictions are also diseases that arise from the mismatch of our bodies and our modern environments. Natural selection shaped behavior regulation mechanisms mediated by chemicals, but there was little selection for resistance to drug abuse because pure drugs were not reliably available. Serious problems with alcohol and drug abuse arose after agriculture, and more recently with the rise of new technologies for drug manufacture, purification, transportation, and administration [26].

Atherosclerosis, obesity, and Crohn's disease are highly heritable; over half of the variation in vulnerability can be attributed to genetic variation. Does that imply that defective genes cause these diseases? No, quite the contrary. It may instead imply that the responsible alleles were nearly neutral in ancestral environments, with deleterious effects arising only when they began to interact with modern environments. Such alleles have been labeled “quirks” to avoid the implication that they are abnormal [1]. Weiss has taken this line of thinking farther, noting that most highly heritable common diseases that decrease fitness are caused mainly by novel environmental factors that expose phenotypic genetic variation that had little adverse effect on fitness in previous generations [27]. Misunderstanding of this simple point is common and serious. For instance, some interpret data demonstrating high heritability of anorexia nervosa [28] as implying that anorexia is “a genetic disease.” If so, it is one that has emerged only in the past few decades, and only in developed countries. Scientists now know better than to talk about nature vs. nurture, and most know that gene effects are manifest only in interaction with specific environments, but non-evolutionary thinking about medical genetics remains prevalent.

The burden of disease arising from the mismatch of our bodies with modern environments does not imply that people were healthier overall in the Stone Age, nor does it suggest we should return to an ancestral lifestyle. Nonetheless, the majority of chronic disease in modern populations comes from the mismatch between our bodies and modern environments [29].

c. Co-evolution with fast evolving microorganisms—Infectious diseases exert strong selection forces, but we remain vulnerable to infections. This should not be surprising; microbes evolve far faster than we can. They can have a new generation every few hours; our generation time is 40,000 times longer. Furthermore, microorganisms can exchange genetic material among distantly related lineages. Most of own genetic variation

comes from the much more limited source of inheritance and mutations. There is an exception, but it does not speed our adaptation very much; as much as 15% of our genome consists of incorporated viral sequences. Approximately 5% of our genome is composed of endogenous retroviral sequences [30]; researchers are now investigating if such sequences are activated in lymphomas, breast cancers, and perhaps melanomas [31].

The bottom line is that we will never be able to evolve fast enough to out-run fast-evolving microbes. The adaptive immune system, with its ability to quickly respond to a wide variety of threats, has been a key to making complex long-lived organisms possible. The effectiveness of our immune system depends on somatic selection that quickly amplifies the numbers of cells able to attack a specific pathogen, and associated immune memory that protects against reinfection and makes vaccines effective.

Many costs of infection are indirect; mechanisms that defend against infection are expensive and prone to misfire in ways that harm health [32]. Autoimmune diseases are just the tip of the iceberg. For instance, the capacity for inflammation is essential, but its inevitable side effect of damaging normal tissues contributes to many problems, including aging, cancer, and atherosclerotic disease [33, 34].

d. Trade-offs—No trait can be perfect; changes that make one trait better will usually make others worse. For instance, reducing immune responses might slow aging, but it would also increase vulnerability to infection. Making bones stronger would decrease fractures, but would also decrease mobility and increase calcium requirements. It would be wonderful to have an eagle's eyesight, able to detect a mouse from 100 meters away, but would it be worth the costs of decreased color vision and peripheral vision? Systematic consideration of the trade-offs that shape every bodily trait is one of the core benefits of an evolutionary view of the body, especially for investments in reproduction and other life history traits [35–37]. These considerations apply equally to genes and traits.

e. Reproductive success at the expense of health—One specialized trade-off deserves special mention. An allele that increases net reproductive success will spread, even if it harms health and longevity. This is illustrated by the shorter lifespan of males compared to females in species where males compete vigorously for mates. Investment in competitive ability gives fitness advantages to males who invest relatively more in it, and less in ability to repair tissues. The result, for young men in modern societies, is mortality rates three times higher than those for females, and life spans seven years shorter on average [38]. Men compete effectively, but at the cost of a shorter life. In ancestral environments, mortality rates for the sexes were more nearly equal because general mortality rates were higher for everyone, and the risks of childbirth were much higher. Reducing these general and childbirth causes of mortality has exposed dramatic sex differences that illustrate how selection shapes organisms for reproductive success, more than for health [39].

Are traits that harm health but increase reproductive success abnormal? Alas, they are normal. Do they cause problems only for men? That too seems unlikely. Women also must have traits that increase reproductive success at the cost of decreased health and longevity, but it is hard to recognize them without a contrasting group who lack such traits.

f. Defenses and their special costs—Most of the unpleasant symptoms that bring people to their physicians are not direct manifestations of bodily abnormalities, they are defenses shaped by natural selection. Examples include fever, cough, pain, vomiting, diarrhea, fatigue, and anxiety. The aversive nature of these responses is useful to the extent that it can motivate escape from dangers now, and avoidance in the future. Unfortunately, such responses often seem excessive, even when regulatory systems are normal. This is because of the “Smoke Detector Principle” [40]. Just as we put up with false alarms from smoke detectors to ensure an early warning about every fire, the body’s defenses seem to be expressed at the least provocation, causing enormous aggregate suffering. Modern medicine uses medications to block pain, fever, nausea, and vomiting. Such interventions are one of the boons of life in modern technological societies. Only now, however, is medicine appreciating how understanding the regulation of defenses can guide decisions to use such agents so that they are used to block symptoms only in situations where they [the symptoms—not the drug agents] are not needed. The Smoke Detector Principle also helps to explain why we are so vulnerable to chronic pain, clinical depression and other manifestations of dysregulated defenses.

Individuals vary widely in the responsiveness of their defensive systems. Some people experience fever, pain, cough or anxiety with only slight provocation, while others rarely experience such symptoms even when they would be useful. What level of responsiveness is optimal? It depends on the environment, so it is not surprising that selection has shaped some mechanisms to adjust expression. For instance, the responsiveness of stress systems seems to be adjusted by a developmentally plastic mechanism that adjusts the stress response according to the degree of environmental challenges [41, 42]. In modern safe environments most such responses will tend to be excessive, giving an advantage to individuals who have reduced responses. However, those with vigorous responses also have advantages in modern environments; they can take medications to block unnecessary responses. Doctors who understand these evolutionary principles are able to use their knowledge about the utility of defense responses and the smoke detector principle to individualize clinical decisions about when to block defenses.

The above six kinds of explanations (a–f) for why bodies have traits that leave them vulnerable to disease often must be combined to offer a full explanation. Attempting to find a single explanation is a mistake. For instance, difficulties with childbirth arise from trade-offs, path dependence, and aspects of the modern environments that make babies larger. Seeking such explanations is only one area of work in evolutionary medicine, but it helps to provide a framework for organizing our understanding of diseases.

3. Testing evolutionary hypotheses about disease can be challenging

Evolutionary questions are central to genetics and medicine already. For instance, genetic knock-out studies test evolutionary hypotheses about the adaptive significance of specific genes. They are just a variation on the age-old method of studying adaptive significance in physiology, using extirpation of organs to see what goes wrong. Such methods are not always possible and, even if they are, they often do not provide a definitive conclusion about all possible functions of a trait.

Several other methods are helpful, but they are unfamiliar to many scientists [43]. The comparative method often offers the strongest evidence, quantitative predictions about a trait are helpful, and assessing the structure of a trait in light of its function and its precursors in other organisms is often essential. Using combinations of these methods and synthesizing their conclusions is difficult work, even for those who understand the method well. Several human cognitive tendencies often cause confusion.

The most problematic is a tendency to treat diseases as if they are “traits shaped by selection.” This results in wild proposals for benefits from diseases such as color blindness and schizophrenia. Diseases have not been shaped to increase fitness, so it is a mistake to try to explain them as if they were adaptations [44]. A more appropriate object of explanation is “traits that increase vulnerability to disease”.

A second cognitive problem is the tendency to look for a single explanatory factor. More often, vulnerability results from multiple factors. For instance, atherosclerosis results from a mismatch with the modern environment, but trade-offs are also involved, including the benefits of narrower vessels, and capacities for inflammation that prevent pathogens from traversing the endothelium [45].

These problems are not insoluble, they are merely difficulties that arise as scientists tackle new classes of questions. A systematic approach to formulating and testing evolutionary hypotheses about diseases can help to prevent many mistakes [44], but generic advice is no substitute for close collaborations among evolutionary biologists and medical and genetic researchers.

4. Selection is weak at levels above the gene and the individual

With the 1966 publication of *Adaptation and Natural Selection* [46], George Williams changed the way biologists think about the levels at which natural selection operates. Prior to 1966, naïve group selection was accepted widely; many biologists believed that genes deleterious to individual reproductive success could nonetheless be selected for if they benefited the group or the species. It seemed plausible to think that genes inducing lemmings to jump into fjords could spread if they benefitted the species. With a few exceptions, Williams showed that such hypotheses are incorrect. Richard Dawkins spread the word more widely [47]. Even if they do benefit the group or the species, alleles associated with decreased individual reproductive success will usually be displaced by alleles of individuals who invest in reproduction instead of benefits to the group.

Because this discovery has yet to penetrate much of medicine, medical geneticists sometimes endorse ideas that evolutionary biologists now find implausible. For instance, while reducing reproduction in crowded conditions might benefit a species [48], it would not benefit individuals, so alleles for such a trait would be selected against. Similarly, while mutations may speed the evolution of a species, they harm the fitness of individuals, so alleles that increase mutation rates are selected against; the idea that selection shapes some optimal rate of mutation that benefits the human species is incorrect. Far more plausible are mechanisms that respond to threats by increasing recombination, thereby increasing variation without corrupting the code [49].

Could alleles that predispose to a disease such as manic-depressive illness have been preserved because groups with manic-depressives somehow benefit? No, alleles persist only if fitness advantages accrue to individuals with those alleles, or their kin who share the same alleles identical by descent. What if individuals with alleles that predispose to manic-depressive illness have more offspring than others? Then the alleles will likely go to fixation, despite causing a disease.[Would it help to indicate how long that would take for a credible fitness advantage, like 1%? Of course, it is not for individuals, but for the whole subpopulation with the alleles predisposing to manic depressive illness.] One cannot help but wonder if there are some alleles in our genome, invisible because we all have them, that predispose to diseases, but persist because they increase reproductive success. Perhaps a reader will discover a way to identify such “reproduction-enhancing pathogenic alleles.”

Most references to group selection in medicine result from lack of exposure to modern evolutionary thinking, and from the confusion that surrounds this complex issue [50]. However, thinking about levels of selection is turning out to be productive in some areas, such as explaining bacteria that contribute to a biofilm in ways that reduce their direct reproduction [51, 52]. [A sentence of explanation would help. Does the biofilm expand the ecological niche into which the bacteria can grow?]

These and other useful applications of multilevel selection theory [53] should not distract from the main point that selection works mainly at the level of the gene and individual.

5. Kin selection is important

Many geneticists and physicians believe that selection cannot act after reproduction ceases. However, half of the alleles in an individual are identical to those in parents, children and siblings. As a result, alleles that decrease individual fitness can nonetheless be selected for if they increase the fitness of first-degree relatives at least twice as much as they decrease direct individual reproductive success. This is Hamilton's rule of kin selection, one of the great advances of 20th century evolutionary biology [54]. It has revolutionized the study of behavior [55, 56]. Prairie dogs who warn others about a hunting coyote are likely to be females with young pups. Groups of male grouse who cooperate to woo females are usually brothers. Humans are inordinately fond of and protective of their own offspring, as compared to unrelated children [57]. Despite such widespread applications, the principle of kin selection has yet to be fully incorporated into genetics and medicine.

Kin selection may help to explain clinically relevant phenomena such as menopause, and survival after menopause [58]. Many believe that reproduction inevitably ceases at some advanced age for all species, but this is true only for humans and a few other species, most of them profoundly social. George Williams proposed, in 1957, that ceasing individual reproduction might give a selective advantage by allowing increased investment in existing offspring (half of whose genes are identical to those of the mother) instead of taking the risks of having more offspring, which could threaten the welfare of existing offspring [59]. Although a consensus remains elusive, this idea has generated rich thinking and research ever since [60].

6. Conflicts at the genetic level can be important for understanding disease

Multicellular organisms can exist only because their cells cooperate, often at a cost to themselves, such as by being in the evolutionary dead-end of the somatic line, or in the extreme example of self-sacrifice, apoptosis. Such extraordinary cooperation is possible only because the cells of an individual each contain the same DNA code, and because the germ line is sequestered from the somatic line of cells. There is almost nothing a DNA sequence can do to increase its own representation in future generations except to make the phenotype as good as possible.

Of course, alleles do not actually make decisions to cooperate or not, but selection has shaped mechanisms to eliminate alleles that advance their own “interests” at the expense of the individual [61]. These mechanisms are remarkably effective. The most important are meiosis and the isolation of the germ line from somatic cells. It would be more efficient to allow several cells to pass on together to create new individuals, but instead a complex machinery has evolved to strip a cell down to a single copy of the genome, which combines, in sexual organisms, with another single copy to give rise to the new diploid individual. Why? Because if multiple copies could be transmitted, competition among them would be at the expense of the individual.

A few examples of alleles that have escaped such control mechanisms have been studied [61]. A heterozygote male mouse with a t-allele at the T locus will transmit that allele to about 90% of its offspring, but offspring homozygous for the t-allele are sterile. The segregation distorter allele in *Drosophila* is similar. Such examples are, fortunately, rare. Recombination may help to explain why they are rare. In most such cases, two linked loci interact; one is a killer locus that disrupts all gametes that lack the linked protective locus. Crossing-over separates such loci, thus protecting organisms from super selfish alleles [62], although it could also be an epiphenomenon of DNA repair [63].

Related phenomena are of wider medical importance. The interests of the maternal and paternal genomes differ. Of course, genomes don’t actually have interests, but thinking about them as agents maximizing their own transmission to future generations can help to illustrate phenomena otherwise hard to describe. For instance, in a sexually reproducing species, it is in the interest of females to retain some caloric stores during pregnancy for future survival and reproduction, while the interests of paternal genomes are advanced by exploiting more of the female’s resources now to make larger offspring that carry the paternal genes.

Haig has suggested that this competition may account for an otherwise peculiar pattern of genomic imprinting, in which the IGF-2 gene—which increases the size of offspring—has its expression inhibited by methylation at that locus when it comes via the maternal line, while the IGF-2 receptor gene—which makes a protein that degrades IGF-2—therefore making offspring smaller—is imprinted if it comes via the paternal line. The result—expression only of the paternal copy of IGF-2, and only the maternal copy of IGF2R—results in normal sized offspring. Failure of imprinting at either locus results in abnormally large or small offspring. It is difficult to conclusively demonstrate that this system has been

shaped by the differing interests of the maternal and paternal genomes, but it illustrates the heuristic utility of modern evolutionary theory [64–66].

Epigenetic effects related to genomic conflict also have substantial medical relevance [65, 67]. For instance, the cluster of imprinted genes at 15q11–12 is associated with Prader–Willi/Angelman syndromes, and imprinting abnormalities at the cluster at 11p15, which includes IGF2, are associated with Beckwith-Wiedemann Syndrome. Increased rates of these disorders in children conceived by artificial reproductive technologies have raised concerns that are confirmed by abnormal methylation patterns at IGF2 in children conceived in vitro [68]. In this active area of research, evolutionary approaches are useful to understand the origins of mechanisms that differentially imprint loci in sperm and eggs, and the disorders that arise from related epigenetic abnormalities.

7. Pleiotropy is the rule, not the exception

That one gene can have multiple effects is well known. Moreover, it is now recognized that most genes have multiple transcripts, due to alternative splicing, and then corresponding splice isoforms of the coded proteins. Some of these protein variants from the same gene have quite different functions, such as pro-apoptosis and anti-apoptosis, and have been demonstrated to be differentially expressed in specific cancers [69].

Less well known is that many genes have multiple phenotypic effects with medical consequences from conflicts among those effects. Aging offers a good example. It has posed an evolutionary conundrum. Rates of senescence are highly heritable, so why do alleles that shorten lifespan persist? One answer is that their deleterious effects occur only after the age by which almost all individuals in the population had died in the natural environment. Another answer, proposed by Williams in 1957, is that the force of selection is stronger earlier in life (simply because more individuals are alive then, even aside from the effects of senescence); therefore, an allele that increases fitness early in life will likely be selected for, even if it causes aging and a shorter lifespan [59, 70].

These theories, usually called mutation accumulation and antagonistic pleiotropy, respectively, have inspired much aging research [34, 71–73]. Experimental studies demonstrate the trade-offs: selection for early reproductive success causes faster aging, and selection for longevity causes reduced reproduction [74–76]. The relative contributions of antagonistic pleiotropy and mutation accumulation continue to spur important debate and research. Recent discoveries that single mutations can double life span in *Drosophila* and *C. elegans* have challenged previous overly-simple evolutionary perspectives on aging, and inspired new respect for the crucial trade-offs involved, many of which seem to involve insulin signaling pathways [77, 78].

Antagonistic pleiotropy also inspires thinking more generally about deleterious effects that are balanced by advantages. Crespi suggests that such phenomena should especially result in problems in strongly selected systems in humans, including those for cognition, emotion, and reproduction, life history traits related to long life span [79]. As with manic-depressive disorder, it is worth contemplating whether we all may share vulnerabilities arising from such sources. The logic against such a proposal is that antagonistic pleiotropy creates new

selection forces for modifier alleles that reduce the costs. For instance, alleles that induce persistence of fetal hemoglobin (HbF) give an advantage in individuals with sickle cell disease [80]. Understanding this phenomenon has led to extensive efforts to develop drugs that are HbF inducers to moderate the effects of HbSS disease. Modifying alleles have many and mixed effects, creating yet additional selection forces. Such complexities are the rule, rather than the exception; they illustrate how complexity in organisms is fundamentally different from complexity in machines.

Thinking about the body as a machine has been useful to purge medicine of prescientific notions of vitalism, but it now burdens us with a misleading metaphor. In particular, it encourages thinking about the genome as a blueprint, and genes as if they were machine parts designed to serve specific functions. It fosters tendencies to describe one function for a gene or a molecule. This is often a mistake. Some think of serotonin as a mood hormone, but it is equally important in gut motility, vascular tone, and even bone deposition [81]. Leptin is thought of as a fat-regulating hormone, but it has many other functions, some of which vary within a single cell [82]. Inflammation is invaluable in eliminating pathogens, but it is also crucial for healing injuries, and for regulating development. Its costs, including cancers, aging and atherosclerosis, are balanced by its benefits. Many think of stress as bad, but, like inflammation, it is an adaptive response that is essential in certain situations [83]. [You have just described pleiotropy, though it has a separate number at 14].

8. Heterozygote advantage is rare, for good evolutionary reasons

As most physicians know, alleles for sickle cell hemoglobin are maintained in populations where malaria is present because heterozygote individuals have fitness superior to both homozygotes; homozygotes for regular hemoglobin are vulnerable to malaria, while homozygotes for sickle hemoglobin get sickle cell disease. Because it explains the prevalence of alleles that cause a disease, this has become an exemplar for evolutionary medicine. However, heterozygote advantage is proposed far more often than it is confirmed. See Table S1 in Gemmell, 2006 for examples [84]. The geographically localized prevalence of hemoglobins S, C, and E, thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency alleles that protect against malaria appear to be special cases. Most are single nucleotide polymorphisms that have arisen recently—in the past tens of thousands of years. Many such phenomena are probably temporary in the history of a genome because further modifications give the same benefits without the costs to homozygous individuals [11]. While many attempts to use heterozygote advantage to explain conditions such as schizophrénias, cancers, and cystic fibrosis are unsupported by data, new examples of the role of balancing selection more generally are likely to be important, as are new methods for identifying loci likely influenced by balancing selection [11, 85]. Other related phenomena are also important, for instance, BRCA1 has been subject to positive selection, perhaps because it increases fertility [86].

9. Selection changes some traits more slowly than many expect

Myopia is highly heritable in modern societies, with over 80% of the variance attributed to additive genetic effects [87]. Could genetic vulnerability to myopia result from decreased selection since the invention of eyeglasses? No, a few hundred years is not enough time for

such deleterious alleles to drift to high-frequency. A neutral allele would, on average, take $4N_e$ generations to become fixed, where N_e is effective population size. With even a minimum estimated human effective population size of 5000, that would be 20,000 generations, while eyeglasses have been widely available only in the past 10 generations. There certainly are alleles that account for myopia, but they are not mutations that drifted to high prevalence recently, nor are they defective genes that harmed fitness in ancestral populations; they are most likely long-existing genetic quirks that have deleterious effects only in modern environments. This implies that myopia should be preventable if we can discover what in modern environments interacts with genetic quirks to cause the problem.

Some physicians worry that medical interventions may reduce the force of selection and thereby reduce the health of future populations; a common example is insulin therapy for diabetes. This general concern, prevalent even before Darwin's publications, gave rise to eugenics with its despicable consequences [88]. While lack of selection against deleterious mutations is a theoretical concern in the very long run, it seems most unlikely that medical interventions have had substantial effects on allele frequencies in the few generations since medicine has gained the power to save lives with some regularity. In contrast, public health interventions have decreased death from infectious disease dramatically, possibly relaxing selection pressure on aspects of immunologic function that could make future generations more vulnerable to certain infections. In the midst of rapid technological change, and radically changing human environments, there seems to be little reason for urgent concern about medical interventions harming the gene pool.

10. Selection changes some traits faster than many expect

The mismatch between our genome and modern environments is responsible for much disease, but the idea that our genomes are unchanged since the Paleolithic is incorrect [89]. Ten thousand years is plenty of time for substantial changes, not only in adapting to changed diets, but even in traits such as language ability. Increasing population sizes since the dawn of agriculture gave rise to new selection pressures, for instance from zoonotic diseases. Change can happen even in a single generation as a result of epidemics that preferentially affect individuals with certain genotypes. For instance, chimpanzees show evidence of a selective sweep at HLA loci caused by HIV [90]. Evidence for the effects of selection on immunity-related genes is strong in general [91], as is evidence for rapid changes in the prevalence of lactase persistence in populations that rely on nutrition from milk [92].

11. Migration, mutation, genetic drift and natural selection deserve equal consideration

Geneticists recognize the importance of all four factors, but physicians who begin trying to analyze problems in evolutionary terms tend to overemphasize selection. Lactase persistence is an exemplar for evolutionary studies of human variations, especially in view of recent evidence showing at least four different mutations, each of which has, in different human subpopulations, resulted in selective sweeps, probably during just the past 7000 years [93]. However, migration may be as important as selection to fully explain the distribution of the trait. Some research suggests that lactase persistence gave as much as a 20% fitness advantage in central European dairying populations, resulting in rapid population growth

and subsequent outmigration that carried these alleles to northern Europe where they now predominate [92].

Answers to other good evolutionary questions about lactase are surprisingly lacking. Why is lactase synthesized only during infancy? Several possibilities deserve consideration: the cost of synthesizing the enzyme, possible increased vulnerability to some pathogen, decreased competition for milk between close siblings, and the possibility that there has simply never been selection for ability to digest lactose in adulthood until the past few hundred generations. We understand why lactase persistence has been selected for in some populations in recent generations much better than we understand why lactase synthesis is turned off in most adults.

There is a tendency to attribute genetic variations between human subpopulations to natural selection, and to neglect genetic drift, population bottlenecks, and founder effects. In some examples the evidence for selection is incontrovertible, e.g. alleles that allow human adaptation to high altitude in the Andes, and different alleles that, by another mechanism, allow adaptation to high altitude in the Himalayas [94]. Skin color is another classic example; the covariation of latitude and skin color argues strongly for the actions of selection, and vulnerability to vitamin D deficiency, the folic acid-damaging effects of the sun, and sun-induced skin damage are all of likely importance [95, 96] .

The possibility of selection at the CCR5 locus has spurred much interest and speculation because its deletion protects against entry of HIV into lymphocytes, and thereby limits progression and transmission of HIV infection. Selection forces proposed to account for its relatively high prevalence in northern Europe include protection from plague in the 14th Century [97]; however, heterozygous mice are not protected [98], and new analyses based on denser genome mapping suggests the mutation is over 5000 years old, in a pattern that is compatible with neutral evolution [99]. Similarly, the vulnerability of Ashkenazi Jews to certain recessive disorders, especially abnormalities of sphingolipid metabolism, has spurred much interest in possible selective advantages including intelligence [100]. However, some analyses suggest that a bottleneck followed by drift may provide a sufficient explanation [101, 102]. The molecular basis of pentosuria, the only one of Garrod's metabolic diseases still unexplained in the 100 years since his report, has just been discovered; mutations of xylulose reductase [95]. The gene frequency in a North America sample is 1.7 percent, meaning that one in 3300 would be homozygotes. There is no known selective benefit from this condition; its only adverse effect was when bearers were mistakenly diagnosed as diabetic, sometimes resulting in hypoglycemia from ill-advised insulin therapy [103].

The extraordinary prevalence of alleles causing cystic fibrosis has also suggested the possibility that they may give selective advantages in some circumstances. Rodent studies show that heterozygotes have decreased vulnerability to dehydration in response to cholera toxin [104], and decreased vulnerability to penetration of the gastric mucosa by *Salmonella typhi* [105]. It is difficult to assess the possible roles of these factors in maintaining the prevalence of cystic fibrosis alleles, but a recent article has done just that to support the alternative hypothesis that heterozygotes are protected from tuberculosis [106]. This example offers an opportunity to note that such questions do not require an either/or choice.

Multiple explanations may apply; mutation/selection balance can be skewed if an allele gives some advantages in certain circumstances.

12. Signals of selection reflect the recent history at a locus

The availability of sequencing data has made it possible to identify loci that have likely been the subject of positive selection. The most obvious signal is lack of genetic diversity around a locus in a haplotype, but other methods are also available [107]. Controversy about these methods [108] has spurred efforts to devise improved methods [109] that are generating fascinating findings. For instance, a study of 53 populations from around the globe found clear evidence for selection at sites related to skin pigmentation, but no signals of selection at loci associated with disease, including those related to lipids and diabetes [110]. This leans against viewing such diseases as arising from mutations that have not yet been selected out, and towards a model in which adaptation proceeds by small allele shifts spread across many loci [111].

Other research finds high rates of Mendelian diseases associated with variations at loci where sequences have largely been conserved since the last common ancestor with chimpanzees [109]. This all becomes more important for specific findings, such as the strong signal of selection at the FHIT locus that predisposes to prostate cancer [112].

13. Variation in many complex traits arises from myriad polymorphisms with tiny effects, combined with environmental and behavioral variables

Only a decade ago, many expected that reliable genome sequencing would soon reveal the mutations responsible for highly heritable conditions such as schizophrenia and diabetes. Now that it has been possible to scan the entire genome looking for them, we can be confident that common alleles with major effects on complex diseases are rare. This has been a great disappointment. Some have claimed that we should have expected it [27]. After all, common variations that decrease fitness should have been selected out long ago. The rarity of common alleles with large effects on common diseases is nonetheless a profound discovery.

Recent research on the genetics of height illustrates the situation. About 90% of human height variation is attributable to genetic variation, so it would seem straightforward to find the responsible alleles. A succession of smaller studies has culminated in a collaborative genome-wide association study of 183,727 individuals showing that the 180 loci with the greatest influence on human height together account for only about 10% of the variation [113]. The 180 loci are not random; they are enriched for genes that are connected in biological pathways and that underlie skeletal growth defects; at least 19 loci have multiple variants associated independently with height, reflecting allelic heterogeneity.

These results have implications for other highly heritable complex traits, such as blood pressure. Most of their variation is accounted for by myriad genes with tiny effects, and it is increasingly clear that even combinations of relatively rare alleles will not reliably predict the trait. Why? Because their effects are moderated via gene x gene and gene x environment interactions, whose effects are counted in estimates of broad heritability [114]. High

heritability does not imply that specific alleles or combinations of alleles will predict the phenotype.

Identifying alleles with small but definite effects, can, however, implicate specific gene networks and biochemical systems whose functions can then be connected to disorders [115]. The major international research efforts to catalog gene variations that affect human health, e.g. “The Human Variome Project,” testify to the promise of this field [116]. These massive amounts of data they generate will only be fully understandable in the light of dynamic evolutionary descriptions of how environments have interacted with genetic variations in world populations to make humans generally healthy, but nonetheless vulnerable to disease. Traits like height, blood pressure, diabetes, and obesity are surely greatly influenced by diet, physical activity, and other behavioral and environmental variables, called risk factors by epidemiologists, which, as noted, contribute to heritability through gene x environment interactions.

14. Genes can influence phenotypes via myriad indirect routes

The tendency to look “under the street lamp” for genetic causes of diseases is often justified, as exemplified by spectacular success in identifying loci responsible for Mendelian disorders. For complex traits, candidate genes are a good starting place. For instance, searches for the causes of mood disorders have focused on genes for neurotransmitters and their receptors. However, many important causes may be outside of the street light’s circle of illumination.

For instance, genetic variations may influence vulnerability to mood disorders via influences on scores of phenotypes that do not even qualify as endophenotypes. Vulnerability to depression would likely be increased by alleles that induce a preference for alcohol or for very exciting mates. It would also be increased by a tendency to persist in pursuing unreachable life goals, a tendency to anxiety that impairs the ability to make needed major life changes [117] or tendencies to be unfriendly or socially isolated. Such examples suggest that we should not be looking for “the genes that cause depression,” we should be looking for alleles whose variations influence the risk of mood disorder via many separate but overlapping and interacting pathways. This perspective suggests considering subtypes of disorders based not only on genotypes and brain findings, but on a deeper understanding of the functions of the disordered systems [118].

15. Organic complexity is fundamentally different from complexity in designed machines

The most profound advance evolution offer molecular medicine may be its assistance in throwing over the outmoded metaphor of the body as machine. The metaphor should not be given up lightly; it helped to extricate us from vitalism. It is misleading, however, because it conceals fundamental differences between bodies and machines. Blueprints describe uniform components with specific functions that influence other components by well-defined pathways. There is one design, and all normal machines are the same. Bodies, by contrast, arise from genomes whose variation is intrinsic. There is no such thing as the normal genotype, and therefore, no such thing as the normal body. Organisms have systems with blurry boundaries and multiple overlapping functions that develop from alleles

interacting with each other and environments to give rise to phenotypes with tiny variations that influence fitness by their interactions with varying environments, in ways that can be nearly indescribably complex.

Models of bodily systems represented as boxes, pathways, and arrows are helpful for understanding and teaching about biochemical and physiological systems. As we gain the ability to look at details, however, it becomes clear that such models often misrepresent organic systems. They are not only more complex than we had imagined; they are complex in ways that are fundamentally different from machines. This is by no means nihilistic. It does not imply that we should stop research to describe the body's mechanisms; it simply reminds us of the need to keep looking for new ways to describe biologically complex systems in ways that recognize their differences from designed machines.

The difference is made clearer as designed machines begin to evolve. For instance, no individual can understand the 50 million lines of code in some versions of the Microsoft Windows Operating System. Therefore, edits to correct identified bugs have unanticipated effects elsewhere, requiring additional one-off fixes, in cycles that create kinds of complexity somewhere in-between ordinary machines and evolved bodies. Despite thousands of incremental fixes, such machines often fail. As they evolve further and become more like organisms, they will fail less often, but their vulnerabilities to failure will need evolutionary as well as proximate explanations.

CONCLUSION

The above principles and examples illustrate only a few of many opportunities for applying evolutionary principles in molecular medicine. We hope this article inspires some readers to work at the interface of evolution with genetics, medicine and public health, thereby speeding the evolution of evolutionary molecular medicine.

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Possible evolutionary explanations for traits that make bodies vulnerable to disease

- a. Constraints** on what natural selection can do, e.g., because mutations occur, genetic disease is inevitable; major design revisions are impossible, so spine problems will persist
- b. Mismatch** with fast-changing environments, e.g. atherosclerosis, allergies, and substance abuse are new problems
- c. Co-evolution** with fast-evolving pathogens, e.g. the inability to evolve perfect immunity, the costs of immune responses
- d. Trade-offs** that leave every trait suboptimal, e.g. stronger bones would be heavy, stronger immune responses would damage tissues
- e. Selection for reproductive success at the expense of health**, e.g. human males die, on average, 7 years earlier than females
- f. Defensive capacities** and their special costs, e.g. fever, pain, cough, anxiety

Table 1

Evolutionary principles useful for molecular medicine

1	Biological traits need both proximate and evolutionary explanations
2	Traits that make bodies vulnerable to disease have evolutionary explanations
3	Testing evolutionary hypotheses about disease can be challenging
4	Selection is weak at levels above the gene and the individual
5	Kin selection is important
6	Conflicts between genes can harm health
7	Pleiotropy is the rule, not the exception
8	Heterozygote advantage is rare, for good evolutionary reasons
9	Migration, mutation, drift and natural selection deserve equal consideration
10	Selection changes some traits more slowly than many expect
11	Selection changes some traits faster than many expect
12	Signals of selection reflect recent evolution at a locus
13	Variations in many traits arise from myriad polymorphisms of small effect
14	Genes can influence phenotypes via many indirect routes
15	Organic complexity is fundamentally different from complexity in machines

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