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On Darwinian Medicine

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It would appear, at first glance, that natural selection would have little to say about why organisms malfunction. Natural selection increases the frequency of genes that make organisms work better, and decreases the frequency of genes that harm organisms, so it would seem that evolutionary theory would be able to explain adaptations, but not their failures. This illusion has been so strong that even now, over a century since Darwin showed how organisms are shaped by natural selection, evolutionary biology is just beginning to be applied to the problems of medicine. (1, 1991, 2, 3, Trevathan, In press #1220) We are just beginning to learn why we are vulnerable to so many diseases. Why do we have an appendix? Wouldn't we be better off without wisdom teeth? Why does the human fetus have to squeeze through the tiny pelvic opening? Why, after millions of years of natural selection, are we still susceptible to infection by the streptococcus organism? Why do we get fevers so high they cause seizures? And why do our own immune systems sometimes attack us, causing rheumatic fever, rheumatoid arthritis, and multiple sclerosis? Why is depression so common, and why is life, in general, so full of suffering? Why is pain so often excessive? And why is it so hard for so many people to find restful sleep, to say nothing of love and sexual satisfaction?

All these questions are about the design of the organism. More specifically, they are about why our bodies aren't better designed. In many cases, such as the appendix, it would seem to be child's play to improve the design. Were we able to change the body as we see fit, we could banish much disease. Or, could we? If the problem is just that natural selection is just not strong enough to improve the design of the body, then we certainly could do better. Selection operates on random mutations that constantly slip in, so perhaps the design flaws simply result from chance. Some certainly do. The vast majority of designs that go bad, are, however, not random mistakes, but products of natural selection. This poses a central mystery. If natural selection is so powerful that it can shape bodies so perfect in so many respects, then why are our bodies also full of so many flaws and design oversights that leave us vulnerable to thousands of diseases?

There are only a few possible kinds of evolutionary explanations for such vulnerabilities. First, as already mentioned, there are random events—environmental mishaps that are too rare to be seen by natural selection and genetic changes that are outside the reach of natural selection. Second, there are problems that arise because our bodies were not designed from scratch, but from an unbroken lineage that goes all the way back to the simplest single-celled organisms. Path

dependence—the result of this continuous lineage—means that many structure designs are actually maladaptive. Third, there is competition between living organisms. Natural selection shapes predators, bacteria and viruses, and other humans, all of whom may benefit from harming us. To protect ourselves from these dangers, natural selection has shaped a wide variety of protective defenses such as pain, fever, nausea, and anxiety. These are not causes of disease, but the body's ways of preventing damage, yet because they are painful and associated with problems, we often confuse them with diseases themselves. Fourth, there are trade-offs—every trait in the body could be improved to some degree if, that is, we were willing to accept the resulting compromises in other traits. Fifth, we were not designed by natural selection for our present environment and lifestyles, and much disease results because natural selection is not had time to transform us for living in the modern environment. Finally, there are genetic “quirks”, variations that were of no consequence in the ancestral environment, but that now cause disease.

Natural selection is an extremely simple principle, but its elaborations are extremely subtle and this leads to much misunderstanding. Darwin, of course, did not know about genes—all he had to go on was the traits of organisms. As a result, he had to develop his ideas based on observations of how traits change in response to breeding, with only a vague notion about how the information that coded for an organism's traits was passed along. Now we know that the information code for organisms is stored in DNA, specifically, in approximately 100,000 protein coding sequences called genes. While much of this code is identical between two different human individuals, and, for that matter, between any two living organisms, there are also variations. If individuals with gene A, on the average in this environment have more offspring and grand-offspring than individuals with gene B, then the A gene will gradually become more common and B will, over the generations, become rare. Natural selection consists of nothing more or less than 1) variation in the information code that results in variations in phenotypes, 2) differential reproductive success of those phenotypes, with the inevitable result of, 3) changes in the information code across the generations. (4) This logic is so straightforward that it is best described not as a theory, but as a principle. When variation in an information code leads to differential reproductive success, the information code changes to whatever works best at getting copies of itself in future generations.

Despite the simplicity of the principle of natural selection, it remains the focus of many misunderstandings. (5) In particular, contrary to the beliefs of many, the path of natural selection has no goal, no direction, and follows no plan. Yes, it is true that the first organisms were small

unicellular creatures and the earth now has many large multi-cellular organisms with much greater complexity. This is not, however, because of any preexisting plan or magical force, it is simply because the first organisms were necessarily small and simple, so there was only one direction for variations to go. Organisms can evolve to simpler as well as more complex forms, as illustrated by the helminths that inhabit mammalian guts. Also, while humans are quite wonderful creatures with some unique abilities, there is no reason to think that we are a peak or a goal of this process. In fact, it appears more and more that our species is, at least in terms of the ecosystem it is ravaging, a malignantly successful replicator that is accidentally but systematically destroying most other organisms on Earth.

The key to understanding natural selection is recognizing that it changes, not organisms, but the information code that makes organisms. (4) Whatever information creates individuals who maximize copies of that information in future generations will become more common. This depends, of course, on the environment. There is no such thing as an adaptation in the abstract—traits are adaptive only in reference to a particular environment. (6)

Another common misunderstanding arises from the understandable tendency to see individuals and groups as a product of natural selection, instead of genes. Different genes cooperate to do things that benefit the individual, so intuitively, it seems sensible that individuals should make sacrifices for the benefit of the species. There is a huge difference, however, between these levels. (7) The genes in each cell of an individual are identical. Even if they were not identical, the genes in somatic cells cannot be passed on, so they get no benefit whatsoever from doing anything except helping the individual. Different individuals, however, have different genes. These genes inevitably induce behaviors that are in their own interests at the expense of other individuals. The only exceptions are in the case of identical twins or genetically identical individuals in species that can reproduce by nonsexual means.

This brings up an immediate, large, good, and unanswered question; why is reproduction sexual? Compared to simply budding, sex is expensive, troublesome, shuffles the genetic code in ways that cause unfortunate genetic combinations and, worst of all, results in related individuals with different interests who therefore are shaped to compete against one another. The very existence of sex is, from an evolutionary point of view, a mystery. (8) One plausible explanation is that the genetic code must be constantly varied, otherwise viruses and bacteria would be able to crack the code and make short work out every one of us. (9) Another idea is based on the best strategy for

winning a lottery. (10) In most organisms, the vast majority of offspring never ever get to sexual maturity. Each one is much like a lottery ticket that probably will be worthless, but may have a big payoff. In this situation, the best strategy is obviously not to buy many lottery tickets that are identical, but to spread your bets among a wide variety of different tickets in hopes that one of them will payoff. The important point here is that while it is hard to explain why sex exists, it does, and the resulting genetic variation necessarily means that individuals within a species will compete, and will cooperate only in the service of that competition. We do, however, see individuals sacrifice for the good of the group on many occasions, a phenomenon that is the deserving focus of much current work (11). It is tempting to try to explain such phenomena as a result of selection acting for the benefit of the group by selecting for traits that benefit the group even though they harm the individual. Except possibly in some very special circumstances, however, this simply does not work. The force of selection at the individual level is so much more powerful than that at the group level, that group selection can explain only traits that are of very small cost to the individual and enormous benefit to the group.

One level further down the hierarchy is a parallel issue with important consequences for human health. We have already mentioned that genetic differences in somatic human cells cannot get into the genome and so act only in the interests of the individual. But are there circumstances in which genes can have effects that promote their interests in getting into the next generation even at the expense of the individual's health? Yes, indeed. In fact, such examples are common causes of much human illness and suffering. The most dramatic example is the longevity difference between the sexes. Males on the average live approximately seven years less than females. This is not true only for humans, but for essentially every species where males compete vigorously for mates. This phenomenon can be explained at one level, the proximate level, by reference to the effects of testosterone on tissues, and the effects of male aggression and fighting on accident rates. An entirely separate explanation, an evolutionary explanation, is necessary to reveal why testosterone has deleterious effects on tissues, and why men do aggressive and dangerous things. This explanation is based, like all evolutionary explanations, on how genes shape traits that influence reproductive success. Females invest more in each offspring, therefore the range of their reproductive success is narrowed compared to men. Most women have from 1 to perhaps as many as 10 children. Some men, however, will have no offspring whatsoever, while some will have far more. Some men have had hundreds of children. (12) Thus, the competition between men for mates is extreme, while women tend to be choosy. (13) A man whose physiology is set to put increased effort into this competition by sacrificing tissue

protection, tissue healing, immune function, and physical safety, will have a reproductive advantage over men who live safer, healthier, longer lives. For women, this is not true, at least to the same extent, so they live longer. This principle leads to other observable effects even in a modern civilization. People do things that are not particularly in their best interests, but are in the interests of their genes. For instance, many men will seek out additional sexual partners, despite knowing the risks of disease, jealous husbands and their own wife's wrath (14). Often they know ahead of time exactly what lies in store for them, but they go ahead, almost as if they cannot help acting in ways that benefit their genes, even when they know it will lead to their harm and ultimate unhappiness.

Still another example of genes taking advantage of individuals occurs in the process of meiosis. A gene that can somehow distort the process to get increased copies of itself into the egg or sperm will have a huge selective advantage so such genes can increase in frequency even if they do severe harm to the individual. No examples are known in humans, but the T-locus in mice and segregation-distorter locus in *Drosophila*, document the existence of this phenomenon (15). Our purpose here is not to describe such phenomena in any detail, but simply to use them as examples that illustrate the crucial principle that natural selection is a mindless process that increases the frequency of any bits of information in the DNA code that, by whatever means, are especially successful at getting themselves into the next generation, even if that harms the individual.

Still another example illustrates the idea of pleiotropy. A gene that increase the rate of implantation of a zygote on the uterine wall from the usual 25% to, say 35%, will have such a huge selective advantage that it can rapidly increase in frequency even if it causes severe problems later in life. An example may exist in the DR3 allele on the HLA system, an allele that greatly increases the risk of childhood diabetes. (16) Phenylketoneuria also may be maintained by the same mechanism, as indicated by the presence of this recessive disease in more than the expected 50% of a couple's offspring. (17)

Competition with other organisms

A large proportion of human disease results from competition with other organisms. This is most obvious in our competition with viruses and bacteria, but disease also arises from competition with predators and other humans. In all cases, natural selection is constantly improving our ability to cope with these threats, but because these organisms themselves are constantly changing products of natural selection who are in a race to escape our defenses, there is no end to the

process, and much disease results. (18, 19) To simplify, consider rabbits and foxes. If a mutation makes some foxes a bit faster than others, they will catch more rabbits, and this mutation will soon become more common in future generations. This has an obvious effect on the rabbits. Those who previously could handily escape foxes now are vulnerable. Only the very fastest rabbits can escape, so selection increases frequency of genes that make rabbits still faster, even when those genes may have other negative effects. This is a classic instance of a trade-off. A change in an organism that is all for the good with no new costs, is extremely rare. At the very least, rabbits that run faster are likely to be lighter, and therefore less likely to survive a period of food shortage. Or perhaps, the changes that make rabbits faster are also increase the speed with which energy is metabolized, perhaps with tissue-damaging side effects. As must be obvious, this competition between the rabbits and the foxes will shape both species in an escalating arms race. Such arms races result in much disease. Both foxes and rabbits could be heavier and better able to get through a harsh winter if they could just relax and cooperate. But, they can't.

Similar arms races are even more obvious in the all-out competitions between pathogens and hosts (20). Streptococcal bacteria, for instance, must somehow escape surveillance by our immune systems. One of their strategies seems to be to imitate our own cells so our antibodies against them sometimes attack our own tissues. This is obviously a tricky business, but we must do it to escape their infections. So, some people end up get rheumatic fever that damages the joints and heart valves, or obsessive compulsive disorder from damage to the basal ganglia, or scarlet fever from damage to the skin. The layer on layer of intrigue and counter-intrigue in these competitions is breathtaking in its complexity, and tragic in its results (21). Consider the organism that causes sleeping sickness, the trypanosome. Its antigen coat stimulates a healthy immune response, but just at the time when antibodies are being made in quantity, the organism exposes a completely different antigen coat, thus eluding its pursuers as effectively as a spy who completely changes his disguise. (22)

Such arms races seem to be responsible for considerable genetic variation, some of which causes disease. The sickle cell trait is a well-known example. Individuals with a single sickle cell allele are protected against malaria but do not get sickle cell disease, while those with 2 sickle cell alleles die young from sickle cell disease, and those who have no sickle cell alleles are vulnerable to malaria. This example has been widely discussed, but it is somewhat peculiar because it results from a single nucleotide substitution that apparently occurred in the neighborhood of ten thousand years ago, and, is found only in Africa and areas of the Mediterranean where malaria has

been prevalent. (23) The alpha+ thalassaemias are of particular interest because they are the commonest known human genetic disorders. They have been thought to protect from malaria, but recent evidence suggests that they are associated with a higher incidence of malaria. The explanation seems to be that by increasing susceptibility to the more mild *Plasmodium vivax* they result in immunity that protects against the more severe *P. falciparum* malaria (24). G6PD deficiency also apparently protects against malaria and has increased in frequency in the times since humans began agriculture (25). There has been wide speculation that some of the genetic diseases characteristic of the Ashkenazi Jews, such as Tay Sachs and other sphingolipidoses, may protect against tuberculosis. (26)

These genetic variations are present only in small groups, but others may have become universal genetic characteristics that protect us against other pathogens despite causing us harm. Despite the difficulty of distinguishing harmful from useful genes, (27), it is important to recognize this mechanism as a source of vulnerability to disease, especially as we begin to unravel the entire genome. Some genes will, no doubt, appear to have wholly pathological effects. Before we tamper with them, we should consider the possibility that they may have unsuspected benefits.

What is the optimum level of virulence for a pathogen? On the surface it would seem senseless for a pathogen to kill its host. Why not simply coexist with a host so that the host lives longer and the pathogen can also? But this is not how natural selection works. Whatever information code in pathogens results in the most copies in future generations will become more common. For some pathogens, such as those that cause minor upper respiratory infections, a low-level of virulence will facilitate spread. People who are too sick to leave bed will not be up and about coughing, sneezing, and touching other people. On the other hand, when a pathogen is spread by vector such as mosquitoes or dirty water, selection may favor increased virulence. Malaria may spread even better if the host is unable to slap at mosquitoes. In an environment where raw sewage may reach others, cholera may spread proportionate to the amount of diarrhea it produces. When the host is infected with a fatal pathogen, restraint by another pathogen is of no benefit. Paul Ewald has investigated such situations in detail, and predicted and demonstrated that virulence should decrease when changed sanitary conditions shift the advantage to strains of an organism that allow the victim to be up and about. (20) Indeed, when public sanitation is successful, the more virulent type of cholera is displaced by the less virulent. Likewise with *Shigella* - when public sanitation is instituted, natural selection shifts the advantage to less virulent subtype. This principle has profound implications for modern hospitals as well, since

doctor's and nurse's hands serve the same function as mosquitoes, transferring pathogens from and to passive victims in a cycle that selects for the more aggressive organisms.

Finally, we note the lengths to which pathogens go to insure their transmission. They can even take over the behavioral control machinery of the host to their own advantage. (28) Ants who are infected with a particular kind of fluke will, in the late stages of infection, climb to the top of a blade of grass and grab on in a spasm that will not let go. Why? The next phase of the life-cycle for this fluke is in sheep, so ants clasping the tip of a blade of grass are helpless prisoners doing the bidding of their internal masters. Similar pathogens induced snails to crawl up on the shore where they are exposed to sea gulls, the next stage in their life-cycle. A more common and gruesome example that affects humans, is offered by rabies. After it enters the skin, the rabies virus enters the nerves and arranges for its own transport directly to the central nervous system. There, it concentrates in the amygdala, a site that controls aggression, and in the brain locus that controls swallowing, so that the mouth fills with saliva, and in the salivary glands. Thus, the rabies virus essentially takes over the individual and turns it into a device for transmitting itself.

Defenses

Many manifestations of disease are caused directly by a pathogen or by some defect in the body. Paralysis, jaundice, and seizures, are examples. Other manifestations of disease are not themselves defects, but are defenses that have been shaped by natural selection to protect us in the face of certain dangers. Examples include pain, nausea, vomiting, diarrhea, fatigue and anxiety. It is very easy to mistakenly interpret such symptoms as pathological, when, in fact they are protections against pathology. Cough is the most obviously useful defense. The basic benefit of cough is clearing foreign from the respiratory tract. People who are unable to cough cannot clear secretions from their lungs and are likely to die from pneumonia. A variety of other mechanisms do the same thing for other passageways. Vomiting clears toxins and pathogens from the upper GI tract while diarrhea clears them from the lower GI tract. Coughing, sneezing and nasal secretions clear the respiratory passages. Inflammation leading to pus formation and extrusion on the surface of the body serves the same function for infections that have penetrated the tissue of the body.

Much of general medical practice consists in blocking the discomfort associated with these symptoms. We use medications to block cough, relieve pain, stop vomiting, and decrease diarrhea. Is this wise? Not always. In a clear demonstration of the value of diarrhea, Du Pont

and Hornick compared the outcomes in people with *Shigella* infections who took medications to decrease diarrhea and those who did not. (29) Those who are left alone recovered faster, while those who took medication had extended illness, more complications, and were more likely to become carriers. Giving cough suppressants to patients shortly after surgery is well-known to cause pneumonia, so physicians therefore avoid this. Nonetheless, in many other situations we are able to use medications to block cough, diarrhea, and vomiting with no particular apparent ill-effects. How is this possible? Consider how natural selection shaped the mechanisms to regulate these defenses. Essentially natural selection acts on the outcome of a signal detection analysis. Just as electrical engineer must set a system to decide correctly whether given click coming across a line is a signal or just noise, the body's regulation mechanisms must set the system for, say, vomiting, to expel the contents of the stomach only when that is worthwhile. But such signals are somewhat difficult to interpret. The only way to insure that no toxin is ever ingested, is not to eat all. This would not be good strategy. Conversely, to avoid wasting calories, it would be best never ever to vomit. This would not be wise either. The optimal regulation strategy depends on how likely it is that a toxin really is present, how costly it will be to mount a defensive response of vomiting, and how costly it would be to fail to mount such response if the toxin is actually present. In many instances the parameters of the system favor an apparently overly-sensitive defense responses. The cost of many defenses is relatively small—in the case of vomiting, only a few hundred calories. The cost of not responding could be death. As a result, natural selection has shaped the normal system to respond in many instances where a response is not actually necessary in order to ensure that the system will always respond when response is necessary. We call this the “smoke detector principle” because it also guides the design of smoke detectors. (2) We could design a smoke detector that would sound a warning only when the house was definitely on fire and never when the toast is burning. Such a system would, however, on occasion fail to sound off in when there was a real fire. Thus, we want our smoke detectors designed to sound some false alarms because that is what it takes to ensure that they will always warn us of a real fire.

This “smoke detector principle” also helps to explain how is possible to use medications to block defenses without necessarily causing harm. Nine times out of ten vomiting may not be necessary, so in most instances, medications to block it will cause little harm. Then again, there is that additional instance when it really is necessary. The same principle applies to many other defenses. Consider pain. Pain is a useful adaptation – people who lack the capacity for pain are usually dead by their early 20s or 30s. (30) Overall, however, it seems that most of the pain that

we experience in life, at least in the modern environment, is excessive and prolonged. Medical advances to block pain have been a great boon for humans. Furthermore, we now recognize disorders in which the pain system itself is dysregulated causing chronic pain. Defensive mechanisms, like any other real-world mechanisms, can malfunction.

Anxiety offers another instructive example. We often imagine that we would prefer life without the experience of anxiety, but people who lack anxiety entirely likely do as poorly in life as people who lack the capacity for pain. They do not come to psychiatrist's offices complaining of insufficient anxiety, but the defect is just as serious it as if their immune systems were hypofunctional. (31, 32) Therefore, while a few people may have anxiety deficiencies, the vast majority of us tend to have more anxiety that we need. Blocking this anxiety with medications only rarely leads to reckless behavior, although in case of driving automobiles, this certainly can cause accidents.

We have additional defenses that are specific against infection, including fever, inflammation and the immune response. Fever is not a simple increase in the rate of metabolism, but is a systematic and coordinated response to the presence of cues that indicate the presence of infection. (33) During a fever, the body will defend the new set point by increasing the temperature if attempts are made to reduce it and also by decreasing the temperature if attempts are made to increase it further. Pathogens are more susceptible to our defenses at the higher body temperature. Even cold-blooded animals raise their body temperature in the face of infection by moving to warmer places until the infection is controlled. All this leads to an obvious question—is it indeed wise to block fever during infection? Surprisingly, adequate studies have still not been done on this most routine medical question. Certainly in many individual instances the smoke detector principle applies, and we can block fever and rely on the body's other defense mechanisms to protect us. However, there may be situations in which we would get better faster if we did not block fever. Also, in cold climates people have repeatedly discovered the sauna bath or other ways to raise body temperature, perhaps because this helps to improve health. In the case of chicken pox, there is some evidence that antipyretics slightly prolong the cause of illness. For influenza, would people get better faster if they did not take medications block fever? We don't know.

None of these defenses are diseases themselves, but it is easy to fall into the illusion that they are problems, instead of parts of solutions. This illusion is fostered because they are constantly associated with pathology and because they can so often be blocked without untoward effects.

The illusion is still further fostered by the psychological and physical discomfort we experience in association with the expression of defenses. We don't like fever, we obviously don't want pain, vomiting, diarrhea and coughing are extremely unpleasant, and it's perfectly understandable that we should want to minimize them. This brings us to the next question, why do humans have capacities for suffering at all?

The capacities for suffering

The capacities for suffering are products of natural selection. If pain was not useful, we would not have the capacity for pain. If anxiety was not useful, we would not have anxiety. Anxiety and pain, perhaps in concert with the awful feelings we get when we lose someone we love, are close to purely negative experiences, their aversiveness almost certainly being central to their utility. People who didn't mind tissue damage, threats, and losses, have not passed on as many of their genes as people who did everything in their power to avoid these circumstances. The reaction of people to narcotic pain-killers is of great interest. Many report that they can still experience the pain but "it no longer bothers me." In essence, they report the perception is intact, but the affective representation of the experience has been reduced or eliminated. Much of the mission of medicine is, of course, to relieve suffering. This is best accomplished by eliminating the cause that has aroused the negative feeling, but very often we can safely and effectively use medications to directly block the brain mechanisms that gave give rise to negative feeling.

Many bodily defects, such as cancer or atherosclerosis are imperceptible for years, but almost every bodily defense is associated with discomfort. Nausea precedes vomiting and inhibits eating, thus preventing further intake of toxins. Diarrhea and cough are quite annoying. The physical fatigue that follows over-exertion is unpleasant enough to motivate avoidance of the situations that gave rise to it. The malaise that accompanies infection often seems excessive, and when we take medications that block this feeling we can often go about our business much more comfortably. In the ancestral environment, however, when predators were problem, this might not have been so wise. In that circumstance, to wander far from camp when unable to run fast might have been unwise indeed. Furthermore, simply resting during infection may allow the body's full resources to be commandeered for the fight.

Many forms of human suffering are not so physical. We also experience depression, anger, jealousy, anger, embarrassment, and many other unpleasant emotions. By extension, it seems likely that the very unpleasantness of these emotions is also a product of natural selection.

Indeed, most of them are aroused by situations that are not good for our health, status, or reproductive success. (34) Work to understand the emotions in this light is just beginning, but it is needed urgently if we are to cope wisely with the development of new psychopharmacologic agents. We already have effective anti-anxiety drugs, although they all have side-effects or cause dependency. We have increasingly good drugs to block depression, although they take weeks to work and also have side effects. It seems entirely likely, however, that the combination of brain science, the genome project, and improvements in chemistry will lead to agents that are far more specific with far fewer side-effects. We are ill-prepared to decide how to use such substances. If, for instance, a pill was developed that could eliminate jealousy, how would we use it? Certainly this could prevent much suffering, and even violence, but it would also undermine some deep human impulses that are responsible, in a considerable measure, for the fundamental structure of the family and society. Or, how would we use agents that block the experiences of greed and envy? On the surface it would seem fine to eliminate these nasty emotions, but we might find that we simultaneously eliminate the motives for much human effort and entrepreneurship that makes societies successful in competition with other societies. We expect that conflicts between individuals and their societies will arise over the use of such drugs. Perhaps the current war on drugs is already an example. (35)

Trade-offs

Every aspect of the body could be designed to be more resistant to disease, but only at a cost. Why for instance are our arms not stronger and less prone to fractures? Arm bones could be made thicker and less likely to break when we fall. Because of the design of these bones, however, making them thicker would drastically decrease our dexterity and make it impossible to rotate the wrist the way we can now. We could be even better protected from infection if our immune systems were more aggressive. Then, however, the untoward effects of the system, including tissue damage and rapid senescence, would become even more prominent and we might also experience more auto-immune disease. Our vision could be still more acute, like a hawk able to see a mouse from a kilometer away. The trade-offs, however, would be a drastic loss of peripheral vision, color vision and the ability to see complex shapes all at once. Our upright posture is still another trade-off. Many explanations have been proposed to explain why we walk on two feet, from the benefits of using tools and weapons, to the need to carry infants. Whatever the benefit is, we can be sure was a substantial one, because standing upright has so many costs. The most obvious one comes from the design of our spine which is optimized for a creature that goes about on all fours. On standing upright, however, enormous pressure is put on the lower spinal discs,

causing pain and disability that is perhaps more common than any other medical disorder. On the much more mundane level it appears that hemorrhoids result from the changes in circulation that result from upright posture. The tendency to faint is greatly increased by standing upright. The tendency to lose one's balance and the need for extraordinarily complex brain mechanisms to regulate bodily position and balance are all secondary to standing upright. Even the design of the system that supplies blood to our bowel is very poorly designed for an upright posture. In an animal that goes about on all fours the omentum hangs like a curtain, supporting the bowel and providing easy access for vessels. But when we stand up, however, it is as if someone took the curtain rod and stood it upright, whereupon the folds tangle in on one another, giving rise to the possibility of bowel obstruction and arterial compromise. It's worth noting that these trade-offs can also be interpreted as novelties, in that there simply has not been enough time for natural selection to shape reliable mechanisms to protect us against of these ills. Perhaps in another million years back pain will be far less frequent. In the meantime, however, we will suffer.

Another trait that seems to be maladaptive, is our lack of hair. There is much disagreement about the evolutionary explanation for our nakedness, with proposals ranging from increased ability to sweat, to speculation that we spent much time in the water in our evolutionary past. Whatever the explanation, there are some obvious penalties, especially for paler individuals, including sunburn, and a risk of dying from malignant melanoma. Everything is a trade-off. It is foolish to describe a trait as perfect and there are few traits that are simply pathological. All have costs and benefits. All are trade-offs.

Such trade-offs also exist at the level of the gene. All genetic changes begin as new mutations, and it would be rare indeed for a mutation to have only benefits and no costs. Given the interaction effects among 100,000 genes, acting in environments that vary from year to year and generation to generation, a detailed accounting of such costs and benefits is beyond our current understanding. What we do know, however, is that a gene that gives a net selective advantage will likely be selected for, even if it causes disease in some people, or disability or decreased function in all of us. It is extremely hard to recognize genes that cause disadvantages in all of us, because we have nothing to compare them to. What we do have are a few examples of genes that have obvious benefits that explain their selection despite their tendency to cause disease. Sickle cell disease has already been mentioned. It is the only solidly documented example. In our book, we described our expectation that the allele that causes cystic fibrosis would be found have some benefit, because it was so common and so reliably fatal. This speculation has since been

supported by epidemiology (23) and by genetic studies of mice with a single cystic fibrosis allele . In more recent work, it has been discovered that this allele also inhibits *Salmonella typhi*, the cause of typhoid fever, from entering the cells in our gut. (36)

A further illustration may soon be available in the case of manic depressive illness. This illness is overwhelmingly genetic in its origins, affects approximately one percent of people worldwide with devastating consequences including a 20 percent risk of suicide and a 20 percent risk of early death from other causes. (37) The selection force acting against the genes that cause manic depression is so enormous that there is very likely some selective advantage unless a large number of genes are involved. What could the advantage be? For centuries, people have noted the increased creativity of people who have manic depressive tendencies and recent scientific evidence confirms this finding. (38) Perhaps this creativity somehow leads to selection for the manic depression genes. There's no need, however, for the benefit to accrue to people with manic depressive illness. In fact, it's more likely that their unaffected kin would experience a benefit, while those with the disease would experience mainly the costs. This general mechanism may apply to many genes, with some individuals suffering from a disease, while fitness benefits accrue to relatives who carry the same genes in combination with other different genes. The definitive test would be to look at the reproductive success, in the ancestral environment, of relatives of individuals with manic depressive illness. Such a study would be nearly impossible to do. We will likely sooner identify the specific genes. Once we have them, we will look at people who have these genes to see how they differ from other individuals. Perhaps they are more creative and perhaps this creativity does give them increased reproductive success or other advantages. Or perhaps the genes protect them from some infection. The question will be difficult to answer but important as we approach a time when genes can be manipulated.

This example has important implications for those who would try to improve the human species by controlling reproduction. A long-standing dream of progressives has been to eliminate defective genes and thus improve the health of the population, presumably making the world better place. While this idea recurs often throughout history, it was the subject of early public policies in the United States at the very start of the 20th-century. As everyone knows, a grander and more deadly version was practiced by the Nazis, leaving a lingering repugnance for eugenics that makes it almost impossible even to talk about the issue. (39) We will address the issue of human rights here only by saying that in our vision, Darwinian medicine is a field that benefits individuals, not nations or the species. The other issue is the scientific basis for eugenics. Much

has already been said about the lack of scientific foundation for such efforts as conducted in the past. Many supposedly genetic diseases, such as cretinism, turned out to be caused by environmental factors, and others resulted from many genes or rare recessive genes so that eugenic efforts, and the associated restrictions of individual reproductive rights, were in vain. An evolutionary view of disease helps to reveal the complexity of these matters. Population geneticists have worked out the details of how certain rare recessive genes persist in the population irrespective of their possible selective costs, and these principles show the extraordinary practical difficulties faced by anyone who would try to reduce the frequency of such genes through selective breeding. An even more important factor is that many genetic diseases involve many genes, often in complex interactions with environmental factors. Even specific harmful genes may give rise to disease in only a small proportion of individuals, so restricting reproductive opportunities on the basis of manifest disease will have little impact on the frequency of most diseases even if eugenic policies were pursued rigidly for many generations.

The case of manic depressive illness, is instructive because the responsible genes may well be helpful as well as harmful. This case is peculiarly appropriate to consider for public policy because while the individual may suffer with manic depressive illness, the society may benefit from creations by the ill individual or his or her relatives. To eliminate the genes that cause manic depressive illness without careful thought could, therefore, be a catastrophic mistake. Furthermore, other genes that appear superficially to be simple defects, will likely turn out to have unanticipated adaptive benefits, although it is still very difficult to distinguish these from others. (40) We know enough now to suggest that it would be safe to do away with genes that cause cystic fibrosis, but it will be more difficult to discover if and what benefits accrue from other genes that cause disease. Finally, it is by no means certain that the future human environment will be the environment that we live and now, so eliminating disease causing genes that protect us against infections that are now rare may seem wise, but at some future date cause new suffering.

All of this is, of course, about to be changed by the unraveling of the human genome. On one hand we will finally have accurate information about individual genotypes, and will no longer have to rely on phenotypic expression of disease. On the other hand, it's likely that medical advances arising from the human genome project will make it possible to control vastly more diseases, including genetic diseases, that has ever before been possible. This will, no doubt, give

rise to new calls for restricting reproduction among certain individuals with specific known pathological genotypes. While this argument goes on, further progress will be made in discovering ways to minimize the effects of these genetic defects or to allow people with such defects to have offspring in which manipulation of a single bit of DNA can prevent the problem. Of course, human tendencies will use these technologies to give rise to entirely new problems. People will want to have offspring with the best possible genotype. We predict that a market will soon arise in which rich people will try to control the genotype of their offspring. Such a phenomenon would likely lead to an arms race for genetic information between countries that are fearful that their populations would be left behind by genetically superior generations in other countries. This prospect seems both frightening and likely to us. While it would be easy simply to advocate for restrictions on such practices, they would both prove extremely difficult to enforce and, perhaps not in the interests of elites to enforce in their own country. What does seem likely is that the human species will, in a few hundred years, be different than it is now. No doubt it will in some ways be better, but much conflict and many mistakes lie along that road.

Novelty

The environment in which we live is considerably different from the environment in which we were designed to live. While much disease arises from environmental changes in the past 100 years, much disease also arises from changes since the advent of agriculture about 40,000 years ago (41). Prior to that, humans lived in small hunting and foraging groups of 20 to 50 people who lived largely on fruits, tubers, grains, and meat. In most locations, salt was in short supply, sugar was available mainly in the form of ripe fruits or occasionally as honey, and high levels of fat were almost always unavailable. We are living in an unnatural environment.

It is easy to over-generalize this principle. The idea of the environment of evolutionary adaptedness (the EEA), proposed by John Bowlby, (42) has been extremely useful in reminding us about the differences between then and now. As pointed out by recent scholarship, however, there was no single environment of evolutionary adaptedness, but a constellation of situations in which our ancestors lived. (43) While these environments had much in common, they also differed. When humans moved out of Africa, perhaps one million years ago, their particular ability to adapt to new environments quickly lead to spread across the Eur-Asian land mass. As they moved to new environments, new selective forces began to act. In colder climates individuals with shorter arms and legs lost heat less quickly and had a selective advantage. In environments where lack of sunshine and wearing clothes lead to light deprivation on the skin causing vitamin D depletion and rickets, there was selection for decreased skin pigmentation. (44) In settings where humans raised animals and subsisted on milk, there was selection for maintenance of lactose activity into adult life. (45)

The big environmental changes however, have been those of our own making. The giant one was the invention of agriculture. By growing their own food, people were able to insure a much more consistent supply of calories at less effort. The price, however, was immediate increase in certain diseases. Studies of Native Americans give particularly clear evidence of the rise in disease after cultivation of maize and sorgum became common. The stature of adults declined, and arthritis and tooth decay suddenly emerged because the agricultural diet provided more sugar, and far fewer and more limited phytochemicals than the diet consumed by hunter gatherers. The diets of these early Native Americans were probably also deficient in protein and certain essential amino acids.

Cultural traits can do much to compensate for such problems. For instance, many native groups in the Americas soak their maize in alkali before cooking—a process that frees the niacin, an essential vitamin that is otherwise deficient in a maize based diet. (46) and may increase lysine, an amino acid deficient in a maize diet. Other deficiencies are not so easy to remedy. When eating natural fruits and vegetables, humans get plenty of vitamin C, a chemical they cannot synthesized friends (in contrast to other primates, most of which can). Because vitamin C is a necessary substance for us, we can be confident that it was in abundant supply as a routine part of our diets for long enough to allow the synthetic mechanism to be lost over the course of evolution. When sailors began to take voyages lasting months, subsisting only on hardtack and dried meat, scurvy quickly became a major problem. When Lind discovered that giving out rations of limes prevented scurvy, the way was paved for the discovery vitamin C. In Iceland, the same problem had long been recognized and prevented by storing blueberries especially for the time in late winter when scurry became a problem

We are vastly more healthy on the average now that we were even a few hundred years ago. In most locations infection is less likely and more curable, accidents are less common and more treatable, and general health has improved thanks to more adequate food supplies and sanitation. A Darwinian approach to medicine in no way advocates reverting to some imagined ancestral time of perfect health. On the other hand, it remains true that the majority of problems we see in medical clinics today arise from novel aspects of our modern environment to which our “thrifty genotype” not yet adapted. (47) The most common and devastating of these diseases arise from our abnormal diets, and the resulting triad of hypertension, obesity, and atherosclerosis. (48) Compared to our ancestors, are diets include vastly more fat, salt, and sugar and substantially less phytochemicals and fiber. (49) The result is the current epidemic of heart disease and stroke caused largely by atherosclerosis. Such diseases claim half of individuals in most modern countries. The defect in design, however, is not simply in our metabolism and our arteries, it is also in our brains. A hunter-gatherer who did not have a taste for sugar and fat would be at a disadvantage. One could hardly ever get enough of those substances in the ancestral environment. Today, we have the same preferences as our hunter-gatherer ancestors, but the world is different. The difference, of course, is that the hunter-gatherer had to work long hours to get even occasional taste of a high-fat high-salt, high sugar food, if it was possible at all. Nowadays, we can go to the grocery store and glut ourselves on a wide variety of snack foods that satisfy these cravings instantly. In United States more than half of individuals are now overweight and a third are clinically obese, conditions that contribute to much disease.

Individuals try to diet, but rarely succeed. They know what they should eat, but they eat fat and sugar instead. They know they should exercise, but they don't. The fault is not with their will-power, but with the very design of the brain mechanisms that regulate their exercise and diet, a design that is optimized for an entirely different environment. As the diets typical in technological societies spread to developing countries, the epidemic is predicted to be the single greatest cause of human disease. (50)

Eating disorders are problems that seem to have arisen mainly in the last generation. The ability to live with very little caloric expenditure, and eat whatever one chooses whenever one chooses, interacts with evolved preferences for mates with a particular shape with unfortunate results. It appears to be a cross-cultural universal that men prefer women with a waist/hip ratio of about 0.7. (51) This has been proposed to identify women who have recently become sexually mature but who have not yet borne many children, thus making them optimal reproductive partners. Heavy women obviously do not have this conformation. Furthermore, the human tendency to attend to caricatures interacts with mass media to create images of women that are exaggerations of this ideal. In the arms race that arises from sexual competition, women try to live up to these ideals, often with tragic consequences. Attempting to diet sets off protective mechanisms that were designed to protect a person from famine. When food is in short supply, these mechanisms induce preoccupation with food and a tendency to quickly gulp down large amounts of high calorie food. Such impulses to gorge make a woman on a calorie-restricted diet even more fearful that she will be unable to control her energy intake, so she tries even harder to diet. This sets off a vicious cycle in which the impulses to eat become still stronger, causing more loss of control, thus making her feel still worse, until a serious eating disorder is established. For most women, (with eating disorders) the cycle becomes one of the bulimia, eating large amounts of food and then vomiting. For those few women with extraordinary will-power, it is possible to restrict intake entirely causing anorexia nervosa, a disease that is sometimes fatal. Eating disorders are a product of the novel environment in which we live. They can be explained by the food intake regulation mechanisms that evolved in an entirely different environment and their interactions with innate sexual preferences that are exaggerated by modern media. Such problems will become much more common as technology and easy access to variable foods spreads across the world.

On a much more mundane level, millions of people suffer from pain at the inside edge of the heel. This is sometimes called "heel spurs", because a tiny bit of calcification is visible on x-rays, but

the technical name is plantar fasciitis. The plantar fascia is a band of tough tissue that stretches from the ball of the foot to the heel—essentially it is the bow string that holds arch of the foot taut. When walking miles each day and sitting without chairs by squatting on the ground, this fascia is constantly stretched and exercised. When, however, people sit for long hours in chairs, this tissue is not stretched and contracts. When the contracted tissue is suddenly stretched by jogging or a long walk, it is vulnerable to ripping off from the heel—an injury that causes pain at the site of the injury. Certainly there are peculiarities of anatomy and walking posture that increase the vulnerability of some individuals to this problem, but the fundamental difficulty is the design of the organism and the mismatch with how we live our lives today. We are designed to seek comfort and minimize caloric expenditure. Plantar fasciitis is one of the several costs for following our evolved inclinations when they are no longer adaptive.

The invention of reliable birth control has been enormous boon, not only for individuals, but also for populations, that at last have some hope of restraining their numbers without relying on disease, war, and starvation to control populations. The availability of birth control is, however, a completely novel aspect of the environment that causes many complications. In the ancestral environment, a woman would typically reach sexual maturity at about age 17, would become pregnant within a year or two, following which she would nurse or baby for two to three years and quickly become pregnant once again. The total number of menstrual cycles in a lifetime averaged around a hundred. (52) Nowadays, women reach sexual maturity much younger, probably because of a superior diet and increased fat stores earlier in life. They may wait until age 30 to have children or may never become pregnant. After giving birth, a woman may feed the baby with a bottle, thus making it possible to become pregnant again in a matter of months, instead of the several years of infertility associated with breast feeding. The most common complication of this modern pattern is certainly iron deficiency anemia. The disorder is far more common in women than men because of loss of blood with each menstrual cycle. The system was never designed for as many menstrual cycles as now take place. High rates of breast cancer in modern societies may also be partly attributed to the use of birth control. (53) The cells in the breast that are most vulnerable to becoming cancerous begin dividing at menarche and stop dividing only with the first pregnancy. In the ancestral environment this interval lasted months to a year, but now it often lasts for decades. Studies are now being done to see if the use of pregnancy mimicking hormones for some years after menarche can prevent breast cancer in some young women whose family histories suggest a high risk.

The discovery of psychoactive drugs has also been a great boon for humankind, but like all other advances, it has brought complications, in this case drug abuse. While some individuals clearly are far more susceptible to addiction than others, and while social factors certainly help to account for why some people become addicted and others do not, an evolutionary approach to the problem highlights the universal capacity for humans to become addicted to drugs that act directly on motivational systems. (35) The ascending dopaminergic tracts that are stimulated by most drugs of abuse are intimately involved with reward mechanisms designed to control behavior. (54) Actions that led to success (as indicated by cues such as eating tasty food) are reinforced and become more common. When, however, these mechanisms are stimulated by direct action of drugs, they have no way of interpreting what is happening and they respond as if some huge bonanza of resources had just been gained. This gives a subjective enormous pleasure, the likes of which is hard to find in real life. It also entrains behavior to repeat, over and over again, whatever action brought such enormous pleasure. The great irony is that after continued drug use, the drug addict may get very little pleasure. Apparently the mechanisms that regulate subjective experience damp out after repeated exposure to the drug. The mechanisms that control behavior, however, tend to persist. Thus, the common picture of the drug-addicted individual who desperately wants to quit, who gets little pleasure from his habit, and yet who feels helplessly compelled to spend his life seeking out drugs of abuse. (55) We were simply never designed to live in an environment where drugs of abuse are readily available. It seems as if there should be some solution to the problem drug abuse, either by prevention, treatment or legalization of drugs. A Darwinian approach suggests, however, that this problem may not have any straightforward solution but may arise from an intrinsic vulnerability of organisms that reach an advanced enough state of technology if their motivational systems are chemically controlled, as ours are. In fact, we predict that when we make contact with intelligent organisms on other planets, we will discover that they either are continuing to cope with a chronic problem drug abuse or at least passed through that stage at great cost and suffering.

The amount of anxiety we experience nowadays is greatly excessive for the dangers we encounter. (31) Most of us would be better off cutting down our anxiety level by several notches. In this sense, anxiety can be seen as excessive, given that we live in novel environment. It also seems possible, however, that the anxiety system was fine-tuned during a life-time in ancestral environments by exposure to things that actually were dangerous. A modern person may see snakes only in zoos and so fear of snakes can become quite generalized and lead to a tendency to avoid any place a snake might conceivably be seen. If that same person had been living in an

ancestral environment, however, there would be great pressure to keep going to places where snakes would be seen despite the fear, a process that which soon extinguish unwarranted fear. Furthermore, exposure to different kinds of snakes would soon lead to stimulus discrimination between snakes that are harmful and those that are harmless. Many modern phobias may, paradoxically, result from lack of exposure to different kinds of dangerous objects.

Genetic quirks

We have emphasized diseases that arise from novel aspects of the environment and diseases that arise from genes that may have benefits as well as costs. Much modern disease arises, however, from interactions between genetic variation and environmental novelty. Genes that had no ill effects in our ancestral environment now reliably cause disease. Myopia is an excellent example. Nearsightedness is a genetic disorder. If your parents have it, you almost certainly will as well. This prevalence is approximately 25 percent in all modern populations. How could such a serious defect be maintained despite the force of natural selection? The answer comes from recognizing that this is not purely a genetic defect, but a genetic variation that was harmless until people began doing close work, such as reading at an early age. Such early reading, in people who have the genes, reliably cause is myopia. People who do not have the genes, or do not do close work, never get nearsighted. Attempts to decide if it is a genetic or an environmental disease are confused. Like many other diseases, it is both.

Much atherosclerosis is probably the same. The genes that increase vulnerability to heart disease probably were not harmful in an environment where no one had high cholesterol. To call these genes defects is vastly simplistic. These variations were of minor consequence in the environment we were designed to live in. Genes that make some individuals especially susceptible to drug abuse, are still another example of “quirks” that caused no harm in the natural environment.

Path dependence

We have emphasized design features of the human body that offer some advantages as well as disadvantages. Other features are, however, simply mistakes. The eye, for instance, that wonder of wonders, is inside out. The vessels and nerves enter at the back of the eye ball causing a blind spot, and they spread out of the inside of the retina casting shadows. The eye of an octopus is, in contrast, much better designed. The nerves and vessels run along the outside of the eyeball, penetrating where they are needed. This octopus has no difficulty with a blind spot, no shadows

cast by the retina, and is protected against detachment of the retina. In this respect, the design of the octopus eye is extremely sensible, ours is a mistake. Why doesn't natural selection fix it? Because the process of evolution is not based on planned design, but on continual tiny modifications in which each generation must survive and prosper. Once some semblance of a working eye gave a selective advantages to our ancestors, the process moved forward steadily until our eyes were as good as they could be, despite the gross disadvantages of having vessels on the inside. As Jacob Monod has put it so clearly, "Nature is a tinkerer, not an engineer."

Many other examples illustrate other anatomical difficulties that arise from path dependence. (56) The vas deferens, for instance, instead of going directly from the testicles to the penis, makes a long detour into the pelvis, looping around the inguinal arteries, and only then returning to the urethra. This path makes it vulnerable to damage, at least in surgery. But, because the original routing of the vas deferens and the iliac vessels was the it was, there is no going back.

The recurrent laryngeal nerve offers another example. This nerve controls some motions of the vocal cords and muscular contraction of the upper eyelid and the pupil. It descends from the brain down into the neck and proceeds immediately behind the thyroid gland on the surface of the trachea. From there, it does its work at the vocal cords and goes back up to the eye. All along this long course it is subject to injury, especially at the hands of surgeons working on the thyroid gland. It is a faulty design that cannot be changed.

Choking is the cause of death for many people worldwide each day and it too is simply a design defect resulting from path dependence. It would be ever so much better if the trachea and the esophagus were completely separate, however, some of our amphibian ancestors seem to have swum at the very surface of the water so their nostrils could take air into a common passage way shared by the food and air. That common cavity has never been eliminated, thus there is always the possibility of aspirating food that will clog the wind pipe and cause death.

Finally there's a matter of the appendix. A very thin blind loop of gut, it extends from the large bowel and seems for all the world as if it is there just to cause problems. In our ancestors it may have been a larger cavity that which useful in digestion, but for us, it appears to be nothing but a potentially fatal nuisance. Its tendency to cause problems is directly proportional to its narrowness. Any minor bit of inflammation can compress the artery that supplies it with blood and this lack of blood supply that opens the way to further bacterial invasion unencumbered by

protective defenses. Such infection further compresses the blood supply, at which point bacteria can grow completely unhindered until the appendix bursts, whereupon the patient very often dies. Has natural selection simply not had enough time to eliminate this troublesome organ? It certainly does not seem to give any selective advantage. Paradoxically, however, the appendix may be maintained by natural selection precisely because it causes appendicitis. People who have an appendix that is somewhat larger are less likely to get appendicitis, while people who have a long thin appendix, are more likely to die. This is perhaps the ultimate example of a “blind loop” in the process of natural selection, an organ that is wholly useless for any task, but is nonetheless maintained by natural selection because as it gets smaller, it increased the risk of death. Such examples suggest that the very idea of a normal, perfect body is probably incorrect. The body is a bundle of trade-offs and problematic arrangements jury-rigged into a miraculous machine.

Random events

We began by emphasizing the randomness of natural selection and we return to this theme here at the end. There are many accidents and diseases for which natural selection can offer no protection. If an asteroid hits our neighborhood, there's nothing natural selection can do to protect us. If we are exposed to high levels of radioactivity, we have no way of detecting the danger, so would likely go about our business with possibly fatal results. Many toxins, especially novel toxins, are colorless and tasteless, thus making it difficult for us to protect ourselves. Events that are very rare, or that we cannot detect, do not shape protection and simply must be chalked up to the unfortunate randomness and uncontrollability of life.

Likewise, the genetic code can never be perfect. Mutations are always creeping in, at the rate of approximately one per individual per reproductive episode. Selection will gradually eliminate some of these, but some, even some that cause decreases in reproductive success, will become more common or even widespread by the mere process of genetic drift and there is no rhyme or reason or controlling such mutations, they are simply random events that happen.

At the next stage, selection, there is further randomness. Some genes that cause harm will drift to a higher frequency despite the harm they cause. Some genes that would protect us or otherwise be beneficial may nonetheless be eliminated from gene pool by simple stochastic accident. Such random factors are real and important, but they are not as all-important as they have sometimes been portrayed. Many of the body's vulnerabilities are, by contrast, direct products of natural

selection. There is no such thing as one universal normal genome, there is no such thing as a perfect body, there is no such thing as a perfectly safe diet, and there is no such thing as life without senescence, but there are a remarkable number of humans who have miraculously healthy periods in their life. Given the myriad vulnerabilities and the number of things that can go wrong, this is astounding indeed.

Senescence

Perhaps the most serious trade-off at the level of a trait is that of aging. More specifically, there is the mystery of senescence. Why should individuals age and inevitably die? It is perfectly possible for organism to recreate body parts that have been lost, so why isn't it possible to systematically and steadily replace every body part as it ages so that the individual can be eternal? The explanation here is very similar to the explanation offered earlier for why men die younger than women. While it might be possible to design a body that would be eternal, this individual would not be as effective a replicator as an individual that put more resources into competition and less into preservation of the body. (57)

Actually, genes that cause aging can be assigned globally to just two categories. Some have simply never been exposed to the force of natural selection because they cause disorders that are too rare and too late in life for selection to have had much of any effect in the natural environment. Certain diseases that become extremely common for people in their 90s, for instance, would have had only a minuscule effect on natural selection in the natural environment and so it's not surprising that we remain vulnerable. The same is observed in laboratory animals who are fed and protected so they can grow to ages that they would never reach in the wild. On the other hand, the effects of aging may well influence fitness in the wild for some species. Alex Comfort, going along with ecologists of previous generations, believed that there was no evidence for aging in wild animals because he had never seen a decrepit animal in the wild. However, most animals in the wild are prey for other animals. Long before they become decrepit, they become a meal for some other predator. Thus, just because we do not see feeble old rabbits, does not mean there is no senescence for wild rabbits

The other explanation for the continued presence of genes that cause aging is that they give some pleiotropic benefit. (58) By this we mean that the very same gene that offers a benefit, for instance, strengthening bones during childhood and early adulthood, may also cause some disadvantage that causes disease or even death later in life, for instance, calcification of the

arteries. While no such specific gene has yet been identified in animals, the likelihood of such genes has been demonstrated in fruit flies and other insects. (59) Before we began to tamper with genes that appear to be causes of aging, we should look carefully to see if they perhaps have been maintained because of some pleiotropic benefit.

An evolutionary view gives a somewhat pessimistic outlook on the possibility of eliminating senescence. If genes cause disadvantages in midlife this will select for other modifier genes that postpone the expression of the deleterious effects to later in life. At some point, the expression of many of these genes will seem to be coordinated in later life because the force of selection will fall quite rapidly at the age when they are expressed. One can thus imagine their manifestations as grains of sand that have been swept to later in the life-span by other modifier genes so that they now form something of a hill beyond which it is impossible to go.

This is not to say that much may not be accomplished by gerontologic research and by slowing some aspects of aging. For instance, taking a small dose of aspirin each day decreases risk of dying from heart attack. Does this have disadvantages as well? Yes, it thins the blood somewhat and that makes death from bleeding more likely. However, injuries are less likely now, and medical care is available, so on the whole we benefit by having blood that is a bit thinner than that designed for the natural environment. These circumstances offer an example where taking medications regularly may improve our adaptation to the current environment. Likewise, a tendency for rapid oxidation may be essential to destroy certain bacteria but toning down this capacity may currently not harm us much at all, but may protect our tissues from aging. In fact, it appears that this may be the explanation for gout. Gout occurs when crystals of uric acid precipitate in the joint fluid, causing excruciating pain. So why don't humans have lower levels of uric acid, like other primates do? A cross-species comparison shows a very strong linear relationship between plasma uric acid levels and longevity in different species. Uric acid turns out to be a potent antioxidant, and may well have been selected for to help make our long life spans possible. A few people, the unfortunate ones, get gout.

Implications

Natural selection and our evolutionary history has been well understood for nearly a hundred years now. Why is it only now being applied to the problems of medicine? In part, the explanation probably depends on the illusion that we referred to at the beginning of this article. Natural selection shapes things that work, so it is a bit hard to see on first glance how can also

help explain why things don't work. There also more practical reasons, however, why it is only now that evolutionary biology is being recognized as a basic science for medicine. Medicine is a practical endeavor. Doctors treat individual patients with individual diseases and are usually far more interested in why this patient is sick now and what to do about it, than they are about why all members of the species are vulnerable to a particular problem. The patient comes in with a painful gouty big toe and the physician wants to help that individual immediately. The possibility that high levels of uric acid protect all of us from aging is not especially relevant at that moment.

Nonetheless, an evolutionary approach to medicine can be profoundly relevant. For instance, some well-meaning genetic engineer might well decide to adjust things so that we all have lower levels of uric acid in order to protect us from gout. This would be fine, except for the possibility that we would probably all begin aging more quickly. Natural selection creates many designs that are substandard, but when it has a chance to act on some variable parameter, that shows continuous variation, such as the circulating level of uric acid, it will usually approach an optimum, given trade-offs, and given the specific environment in which the trait was shaped.

Even in everyday practice, however, there is much that is immediately useful from an evolutionary approach to medicine. Recognition that diarrhea, fever, pain, nausea, vomiting and anxiety are useful defenses allows us to treat them in a far more sophisticated way. On the one hand, it helps us to hesitate and think carefully about the normal function of the defense before we block it. It also may allow us to feel comfortable that in this particular instance, blocking the defense is of no consequence to the person's health so we can act aggressively to make the person feel better more quickly. This is especially common in the case of pain.

In the area of public health, an evolutionary approach is of great importance in assessing environmental changes that might influence changes in virulence. In particular, settings in which vectors can transmit pathogens between passive hosts are recognized as particularly dangerous for shaping more virulent organisms, whether the vector is a mosquito or a doctor's hands. The use of condoms not only prevents transmission of sexual diseases, it also can decrease their virulence. A sexually transmitted disease that causes quick death or incapacitation will tend to increase in virulence if the person is having many sexual partners, but if the person uses protective devices or abstains from dangerous sexual practices, this will tend to select for strains of the pathogens that are less virulent. Similar principles may also be useful for vaccine design.

We could go on at great length about other potential benefits from an evolutionary approach to medicine but we wish to emphasize that most of the relevant research has not yet been done. Evolutionary questions have not been asked systematically about disease, and the methods for testing them are still being developed. What is needed now is not to jump quickly to a new theory of medical practice based on evolutionary biology, but to begin to educate physicians and patients about the evolutionary nature of the body and its vulnerabilities to disease. This will, we believe, quickly lead to specific advances in the treatment of individual diseases that will benefit individual patients. Even before that, however, it will help us all to a deeper understanding of the nature of the organism, and the nature of its vulnerabilities to disease. From this viewpoint, the body is not a Platonic ideal, and the genetic code is not correct in any one particular version. Instead, genes, with considerable variation, makes phenotypes, that interact with environments and other individuals, to result in more or fewer offspring depending on the genes, the environment, their interactions, and chance factors. An extraordinary number of people are blessed with years and even decades a good health, and sometimes even happiness. Despite all our knowledge about how this is possible, it still seems nothing short of miraculous, even though no miracle is needed to explain.

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