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THE MYSTERY OF DISEASE

Why, in a body of such exquisite design, are there a thousand flaws and frailties that make us vulnerable to disease? If evolution by natural selection can shape sophisticated mechanisms such as the eye, heart, and brain, why hasn't it shaped ways to prevent nearsightedness, heart attacks, and Alzheimer's disease? If our immune system can recognize and attack a million foreign proteins, why do we still get pneumonia? If a coil of DNA can reliably encode plans for an adult organism with ten trillion specialized cells, each in its proper place, why can't we grow a replacement for a damaged finger? If we can live a hundred years, why not two hundred?

We know more and more about why individuals get specific diseases but still understand little about why diseases exist at all. We know that a high-fat diet causes heart disease and sun exposure causes skin cancer, but why do we crave fat and sunshine despite their dangers? Why can't our bodies repair clogged arteries and sun-damaged skin? Why does sunburn hurt? Why does anything hurt? And why are we, after millions of years, still prone to streptococcal infection?

The great mystery of medicine is the presence, in a machine of exquisite design, of what seem to be flaws, frailties, and makeshift mechanisms that give rise to most disease. An evolutionary approach transforms this mystery into a series of answerable questions: Why hasn't the Darwinian process of natural selection steadily eliminated the genes that make us susceptible to disease? Why hasn't it selected for genes that would perfect our ability to resist damage and enhance repairs so as to eliminate aging? The common answer—that natural selection just isn't powerful enough—is usually wrong. Instead, as we will see, the body is a bundle of careful compromises.

The body's simplest structures reveal exquisite designs unmatched by any human creations. Take bones. Their tubular form maximizes strength and flexibility while minimizing weight. Pound for pound, they are stronger than solid steel bars. Specific bones are masterfully shaped to serve their functions—thick at the vulnerable ends, studded with surface protrusions where they increase muscle leverage, and grooved to provide safe pathways for delicate nerves and arteries. The thickness of individual bones increases wherever strength is needed. Wherever they bend, more bone is deposited. Even the hollow space inside the bones is useful: it provides a safe nursery for new blood cells.

Physiology is still more impressive. Consider the artificial kidney machine, bulky as a refrigerator yet still a poor substitute that performs only a few of the functions of its natural counterpart. Or take the best man-made heart valves. They last only a few years and crush some red blood cells with each closure, while natural valves gently open and close two and a half billion times over a lifetime. Or consider our brains, with their capacity to encode the smallest details of life that, decades later, can be recalled in a fraction of a second. No computer can come close.

The body's regulatory systems are equally admirable. Take, for instance, the scores of hormones that coordinate every aspect of life, from appetite to childbirth. Controlled by level upon level of feedback loops, they are far more complex than any man-made chemical factory. Or consider the intricate wiring of the sensorimotor system. An image falls onto the retina; each cell transmits its signal via the optic nerve to a brain center that decodes shape, color, and movement, then to other brain centers that link with memory banks to determine that the image is that of a snake, then to fear centers and decision centers that motivate and initiate action, then to motor nerves that contract exactly the right muscles to jerk the hand away—all this in a fraction of a second.

Parts of body & their complex functions.

Bones, physiology, the nervous system—the body has thousands of consummate designs that elicit our wonder and admiration. By contrast, however, many aspects of the body seem amazingly crude. For instance, the tube that carries food to the stomach crosses the tube that carries air to the lungs, so that every time we swallow, the airway must be closed off lest we choke. Or consider nearsightedness. If you are one of the unlucky 25 percent who have the genes for it, you are almost certain to become nearsighted and thus unlikely to recognize a tiger until you are nearly its dinner. Why haven't these genes been eliminated? Or take atherosclerosis. An intricate network of arteries carries just the right amount of blood to every part of the body. Yet many of us develop cholesterol deposits on the walls of our arteries, and the resulting blockage in blood flow causes heart attacks and strokes. It is as if a Mercedes-Benz designer specified a plastic soda straw for the fuel line!

Dozens of other bodily designs seem equally inept. Each may be considered a medical mystery. Why do so many of us have allergies? The immune system is useful, of course, but why can't it leave pollen alone? For that matter, why does the immune system sometimes attack our own tissues to cause multiple sclerosis, rheumatic fever, arthritis, diabetes, and lupus erythematosus? And then there is nausea in pregnancy. How incomprehensible that nausea and vomiting should so often plague future mothers at the very time when they are assuming the burden of nourishing their developing babies! And how are we to understand aging, the ultimate example of a universal occurrence that seems functionally incomprehensible?

Even our behavior and emotions seem to have been shaped by a prankster. Why do we crave the very foods that are bad for us but have less desire for pure grains and vegetables? Why do we keep eating when we know we are too fat? And why is our willpower so weak in its attempts to restrain our desires? Why are male and female sexual responses so uncoordinated, instead of being shaped for maximum mutual satisfaction? Why are so many of us constantly anxious, spending our lives, as Mark Twain said, "suffering from tragedies that never occur"? Finally, why do we find happiness so elusive, with the achievement of each long-pursued goal yielding not contentment, but only a new desire for something still less attainable? The design of our bodies is simultaneously extraordinarily precise and unbelievably slipshod. It is as if the best engineers in the universe took every seventh day off and turned the work over to bumbling amateurs.

proximate & evolutionary.

TWO KINDS OF CAUSES

To resolve this paradox, we must discover the evolutionary causes for each disease. By now it is obvious that these evolutionary causes of disease are different from the causes most people think of. Consider heart attacks. Eating fatty foods and having genes that predispose to atherosclerosis are major causes of heart attacks. These are what biologists call *proximate* ("near") causes. We are more interested here in the *evolutionary* causes, those that reach further back to why we are designed the way we are. In studying heart attacks, the evolutionist wants to know why natural selection hasn't eliminated the genes that promote fat craving and cholesterol deposition. Proximate explanations address how the body works and why some people get a disease and others don't. Evolutionary explanations show why humans, in general, are susceptible to some diseases and not to others. We want to know why some parts of the human body are so prone to failure, why we get some diseases and not others.

When proximate and evolutionary explanations are carefully distinguished, many questions in biology make more sense. A proximate explanation describes a trait—its anatomy, physiology, and biochemistry, as well as its development from the genetic instructions provided by a bit of DNA in the fertilized egg to the adult individual. An evolutionary explanation is about why the DNA specifies the trait in the first place and why we have DNA that encodes for one kind of structure and not some other. Proximate and evolutionary explanations are not alternatives—both are needed to understand every trait. A proximate explanation for the external ear would include information about how it focuses sound, the tissues it is made of, its arteries and nerves, and how it develops from the embryo to the adult form. Even if we know all this, however, we still need an evolutionary explanation of how its structure gives creatures with ears an advantage, why those that lack the structure are at a disadvantage, and what ancestral structures were gradually shaped by natural selection to give the ear its current form. To take another example, a proximate explanation of taste buds describes their structure and chemistry, how they detect salt, sweet, sour, and bitter, and how they transform this information into impulses that travel via taste buds

neurons to the brain. An evolutionary explanation of taste buds shows why they detect saltiness, acidity, sweetness, and bitterness instead of other chemical characteristics, and how the capacities to detect these characteristics help the bearer to cope with life.

Proximate explanations answer "what?" and "how?" questions about structure and mechanism; evolutionary explanations answer "why?" questions about origins and functions. Most medical research seeks proximate explanations about how some part of the body works or how a disease disrupts this function. The other half of biology, the half that tries to explain what things are for and how they got there, has been neglected in medicine. Not entirely, of course. A primary task of physiology is to find out what each organ normally does; the whole field of biochemistry is devoted to understanding how metabolic mechanisms work and what they are for. But in clinical medicine, the search for evolutionary explanations of disease has been halfhearted at best. Since disease is often assumed to be necessarily abnormal, the study of its evolution may seem preposterous. But an evolutionary approach to disease studies not the evolution of the disease but the design characteristics that make us susceptible to the disease. The apparent flaws in the body's design, like everything else in nature, can be fully understood only with evolutionary as well as proximate explanations.

Are evolutionary explanations mere speculations, of intellectual interest only? Not at all. For instance, consider morning sickness. If, as Seattle researcher Margie Profet has suggested, the nausea, vomiting, and food aversions that often accompany early pregnancy evolved to protect the developing fetus from toxins, then the symptoms should begin when fetal-tissue differentiation begins, should decrease as the fetus becomes less vulnerable, and should lead to avoidance of foods that contain the substances most likely to interfere with fetal development. As we will see, substantial evidence matches these predictions.

Evolutionary hypotheses thus predict what to expect in proximate mechanisms. For instance, if we hypothesize that the low iron levels associated with infection are not a cause of the infection but a part of the body's defenses, we can predict that giving a patient iron may worsen the infection—as indeed it can. Trying to determine the evolutionary origins of disease is much more than a fascinating intellectual pursuit; it is also a vital yet underused tool in our quest to understand, prevent, and treat disease.

THE CAUSES OF DISEASE

Experts on various diseases often ask themselves why a particular disease exists at all, and they often have some good ideas. In many cases, however, they confuse evolutionary with proximate explanations, or do not know how to go about testing their ideas, or are simply reluctant to propose explanations that seem outside the mainstream. These difficulties can perhaps be reduced with the help of a formal framework for Darwinian medicine. To this end, we propose six categories of evolutionary explanations of disease. Each of these will be described at length in later chapters, but this brief overview illustrates the logic of the enterprise and provides an overview of the terrain ahead.

1. Defenses

Defenses are not actually explanations of disease, but because they are so often confused with other manifestations of disease we list them here. A fair-skinned person with severe pneumonia may take on a dusky hue and have a deep cough. These two signs of pneumonia represent entirely different categories, one a manifestation of a defect, the other a defense. The skin is blue because hemoglobin is darker in color when it lacks oxygen. This manifestation of pneumonia is like a clank in a car's transmission. It isn't a preprogrammed response to the problem, it is just a happenstance result with no particular utility. A cough, on the other hand, is a defense. It results from a complex mechanism designed specifically to expel foreign material in the respiratory tract. When we cough, a coordinated pattern of movements involving the diaphragm, chest muscles, and voice box propels mucus and foreign matter up the trachea and into the back of the throat, where it can be expelled or swallowed to the stomach, where acid destroys most bacteria. Cough is not a happenstance response to a bodily defect; it is a coordinated defense shaped by natural selection and activated when specialized sensors detect cues that indicate the presence of a specific threat. It is, like the light on a car's dashboard that turns on automatically when the gas tank is nearly empty, not a problem itself but a protective response to a problem.

This distinction between defenses and defects is not merely of academic interest. For someone who is sick it can be crucial. Correcting a defect is almost always a good thing. If you can do something to make the clanking in the transmission stop or the pneumonia patient's skin turn warm pink, it is almost always beneficial. But eliminating a defense by blocking it can be catastrophic. Cut the wire to the light that indicates a low fuel supply, and you are more likely to run out of gas. Block your cough excessively, and you may die of pneumonia.

2. Infection

Given that some bacteria and viruses treat us mainly as meals, we can think of them as enemies. Unfortunately, they are not just simple pests put here to bedevil us but sophisticated opponents. We have evolved defenses to counter their threats. They have evolved ways to overcome our defenses or even to use them to their own benefit. This endlessly escalating arms race explains why we cannot eradicate all infections and also explains some autoimmune diseases. We expand greatly on these topics in the next two chapters.

becoz they evolve with us - (virus & bacteria)

3. Novel Environments

Our bodies were designed over the course of millions of years for lives spent in small groups hunting and gathering on the plains of Africa. Natural selection has not had time to revise our bodies for coping with fatty diets, automobiles, drugs, artificial lights, and central heating. From this mismatch between our design and our environment arises much, perhaps most, preventable modern disease. The current epidemics of heart disease and breast cancer are tragic examples.

4. Genes

Some of our genes are perpetuated despite the fact that they cause disease. Some of their effects are "quirks" that were harmless when we lived in a more natural environment. For instance, most of the genes that predispose to heart disease were harmless until we began overindulging on fatty diets. The genes that cause nearsightedness cause problems only in cultures where children do close work genes have multiple functions.

early in life. Some of the genes that cause aging were subject to little selection when average life spans were shorter.

Many other genes that cause disease have actually been selected for because they provide benefits, either to the bearer or to other individuals with the gene in other combinations. For instance, the gene that causes sickle-cell disease also prevents malaria. In addition to this well-known example, many others are discussed in later chapters, including sexually antagonistic genes that benefit fathers at the expense of mothers or vice versa.

Our genetic code is constantly being disrupted by mutations. On very rare occasions these changes in DNA are beneficial, but much more commonly they create disease. Such damaged genes are constantly being eliminated or kept to a minimum by natural selection. For this reason defective genes with no compensating benefit are not a common cause of disease.

Finally, there are "outlaw" genes that facilitate their own transmission at the expense of the individual and thus bluntly demonstrate that selection acts ultimately to benefit genes, not individuals or species. Because selection among individuals is a potent evolutionary force, outlaw genes are also an uncommon cause of disease.

5. Design Compromises

Just as there are costs associated with many genes that offer an overall benefit, there are costs associated with every major structural change preserved by natural selection. Walking upright gives us the ability to carry food and babies, but it predisposes us to back problems. Many of the body's apparent design flaws aren't mistakes, just compromises. To better understand disease, we need to understand the hidden benefits of apparent mistakes in design.

6. Evolutionary Legacies

Evolution is an incremental process. It can't make huge jumps, only small changes, each of which must be immediately beneficial. Major changes are difficult to accomplish even for human engineers. Fires occurred when a popular line of pickup truck was struck from the side because the gasoline tanks were located outside the frame. But to locate the tanks within the frame would require a major redesign of everything now there, which could cause new problems and require new compromises. Even human engineers can be constrained by historical legacies. Similarly, our food passes through a tube in front of the windpipe, and must cross it to get to the stomach, thus exposing us to the danger of choking. It would be more sensible to relocate the nostrils to somewhere on the neck, but that will never happen, as we explain in Chapter 9.

WHAT WE ARE NOT SAYING

Before we discuss the details of the above causes of disease, we would like to try to forestall several potentially dangerous misunderstandings. First of all, our enterprise has nothing to do with eugenics or Social Darwinism. We are not interested here in whether the human gene pool is getting better or worse, and we are emphatically not advocating actions to improve the species. We are not even particularly interested in most genetic differences between people, but much more in the genetic material that we all have in common.

An evolutionary perspective on disease does not change the ancient goals of medicine carved on a statue honoring physician E. L. Trudeau's work at Saranac Lake: "To cure, sometimes, To help, often, To console, always." The goal of medicine has always been (and, in our belief, always should be) to help the sick, not the species. Confusion regarding this point has justified much mischief. At the beginning of the century, Social Darwinist ideology helped to justify withholding medical care from the poor and letting capitalist giants battle irrespective of effects on individuals. These beliefs were intimately linked to those of the eugenicists, who advocated sterilization of certain groups in order to improve the species (or race!). Such ideology has long ago earned a well-deserved ill repute. It made metaphorical use of some of the terminology of Darwinism but no use of the theory as biologists understand it. We are by no means advocating that medicine should assist natural selection, nor do we suggest that biology can guide moral decisions. We would never argue that any disease is good, even though we will offer many examples in which pathology is associated with some unappreciated benefit. Darwinism gives no moral guidelines about how we should live or how doctors should practice medicine. A Darwinian perspective on medicine can, however, help us to understand the evolutionary origins of disease, and this knowledge will prove profoundly useful in achieving the legitimate goals of medicine.