Why Do We Get Sick? The New Science of Evolutionary Medicine

Laith Al-Shawaf
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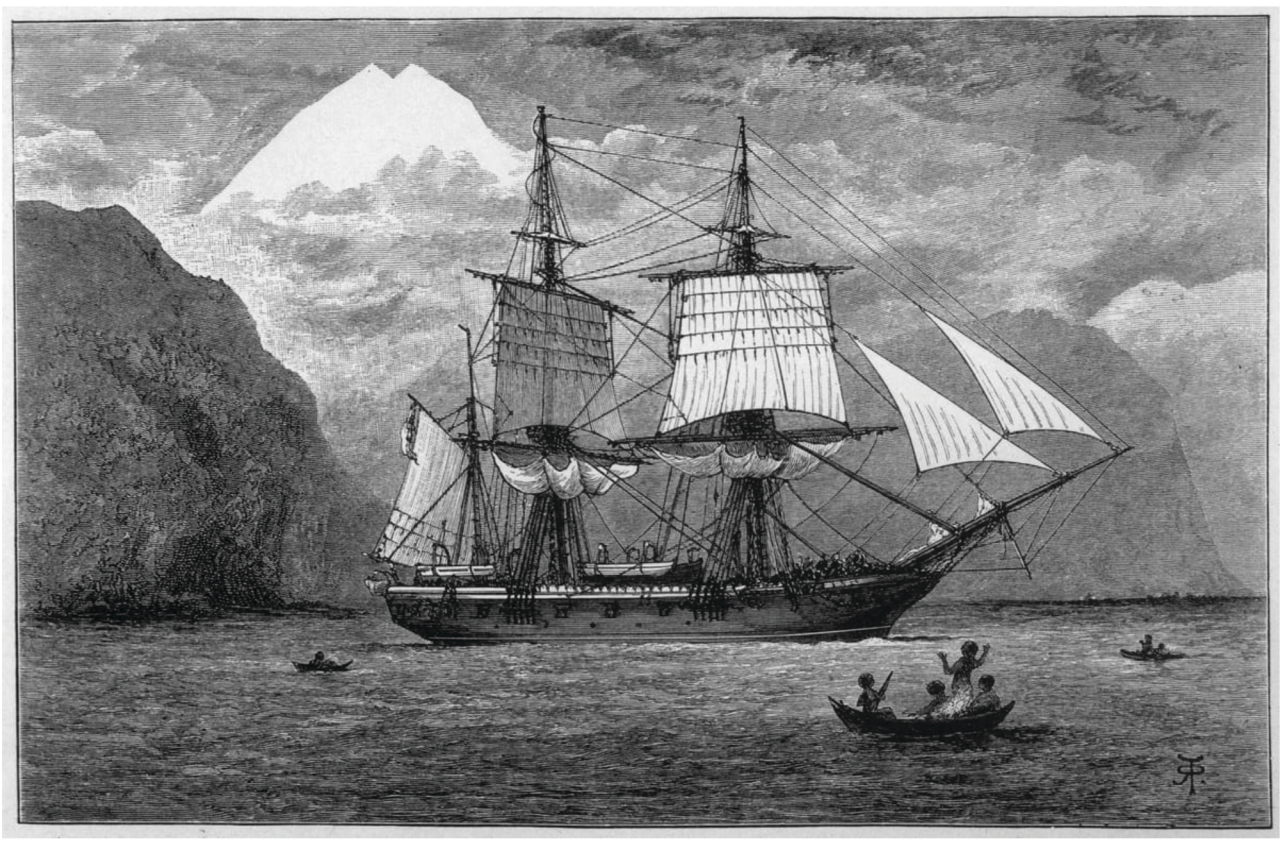

If you infect a rabbit with a virus or a bacterium, it'll start to run a fever. Why? The surprising answer is that fever is not a disease; it's a defence: a useful evolved mechanism that animals use to kill invading pathogens. Studies show that if you give fever-suppressing drugs to infected rabbits, they're more likely to die.

It's not just rabbits—all warm-blooded creatures use fever to kill invasive parasites. Animals that can't regulate their body temperature internally take a different approach. For example, infected lizards seek a hot rock on which to sunbathe,

raising their body temperature and killing the invaders that way—and research shows that disrupting their ability to do this increases their likelihood of death. Infected fish and reptiles exhibit this kind of "behavioural fever," too. In humans, some studies find that administering fever-suppressing drugs to children may worsen outcomes and prolong the period of illness.

These findings suggest that fever is not a symptom of a disease; it's an evolved defence that our bodies use to kill harmful invaders. Discoveries like this represent one small part of a larger picture emerging from the new science of *evolutionary medicine*. There's a scientific revolution brewing, catalysed by the idea that considering how our bodies evolved will help us better understand and treat disease.

Why Do We Get Sick?

The science of evolutionary medicine asks why natural selection left us vulnerable to disease: *Why do we get sick?* It may seem like a simple question, but the answer turns out to be surprisingly complex. Everybody gets sick and takes steps to address it, but we rarely think to ask the most basic question of all: why are human bodies vulnerable to disease in the first place? Why didn't we just evolve to be immune to disease?

Evolutionary medicine identifies six reasons why our bodies are vulnerable to disease. They are: 1) defences, 2) environmental mismatch, 3) trade-offs, 4) conflict between survival and reproduction, 5) co-evolution with infectious parasites and 6) constraints on natural selection. This explanatory framework yields insights about everything from cancer to why we age and die.

Six Reasons Why Natural Selection Left Us Vulnerable to Disease

1. *Defences*

Some things that *appear* to be symptoms of disease are actually not—they're bodily defences that evolved for good reason. Fever kills invading bacteria. Cough, sneezing and diarrhoea are useful methods of expelling pathogens. Pain is not a problem *per se*; it signals tissue damage and tells us that we need to escape whatever is causing the pain. Low levels of iron in the blood are often referred to as

“anaemia” and regarded as a problem, but humans and other organisms naturally lower their blood iron levels when they’re infected because bacteria thrive on iron. When we get infected, we adaptively reduce the levels of iron in our blood, spontaneously avoid iron-rich foods like eggs and spinach, and if we do eat those foods, we absorb less iron from them. Studies of the Masai in central Africa found that when researchers gave iron supplements to iron-deficient tribespeople, infection levels spiked. We’re rapidly learning that some conditions that appear to be diseases are actually defences. This important insight has practical utility for physicians deciding which bodily reactions to suppress.

2. *Mismatch*

Some diseases are caused by a *mismatch* between the environments we currently inhabit and the ones we evolved to live in. Heart disease, type-2 diabetes, atherosclerosis and gout are not due to fundamental flaws in the human body; they’re products of the mismatch between the way we evolved and the environments we inhabit in industrialised nations, which are replete with salty, sugary, caloric foods. We crave these foods because having a sweet tooth and a hankering for calories was adaptive during most of human evolution, when calories were scarce and not getting enough food was a pressing danger. Now that food is cheap, abundant and highly processed, we find ourselves in a situation where our normally adaptive food preferences get us into real trouble. Many conditions, such as asthma, coronary artery disease, Crohn’s disease and autoimmune disorders are principally due to this kind of mismatch between the environments in which we evolved and the environments we inhabit today.

3. *Trade-offs*

The human body is a marvel, but it’s also a bundle of trade-offs and compromises. We could have thicker wrists, which would make them less likely to break—but then we’d be less dexterous. If we had longer leg bones, we’d be faster, but then our bones would be more fragile. Walking upright is pretty nifty, but the pressure on our spines causes chronic lower back pain for millions of people. Lower blood pressure would be beneficial in some ways, but it would come at the cost of less forceful, more sluggish movement.

The human body is a mosaic of trade-offs. Things that benefit us in one area often hurt us in another—and these unavoidable trade-offs mean that we’re stuck with

some built-in flaws and foibles.

4. *The bottom line of evolution is reproduction, not survival or health*

Despite the popularity of misleading taglines like "survival of the fittest," the bottom line of evolution is actually reproduction, not survival. The basic logic of evolutionary theory and a great variety of examples illustrate that when the two conflict, reproduction trumps survival. In other words, if a trait has beneficial effects on reproduction, it will pass evolution's sniff test—even if it's detrimental to our health or survival. For example, testosterone aids in reproduction, but is a powerful immunosuppressant and is thought to be one of the reasons men die several years younger than women. Oestrogen is important to fertility, but contributes to cancer risk in women. The male redback spider sacrifices himself to his mate, offering himself up for cannibalization—in doing so, he dies, but he doubles his paternity relative to non-cannibalised males because his mate uses his nutrients to produce more, and healthier, offspring.

We care about our health, but evolution doesn't. The tragic outcome is that we are fated to contend with some genes and traits that benefit our reproduction at the expense of our health.

5. *Infection: co-evolution with viruses, bacteria, and parasites*

Another reason we're vulnerable to disease is that we're locked in an arms race with viruses and bacteria. They evolve ways to parasitise us, we evolve defences to outwit them, they respond by evolving more sophisticated ways to attack us or get around our defences. In this evolutionary arms race, the parasites are often a step ahead of us because they reproduce, and therefore evolve, more quickly than we do.

The fact that we're co-evolving with bacteria is what causes antibiotic resistance—we invent new medications to kill bacteria, and they respond by evolving resistance to the new drugs. Covid and the regular flu virus also evolve via natural selection, which is why we're constantly dealing with tricky new variants. Trypanosomes, the parasites that cause African sleeping sickness, habitually change their disguises to trick our immune systems and circumvent our defences. Like the Red Queen in Alice in Wonderland, we have to keep running just to stay in the same place.

The problem in a nutshell is that disease-causing microbes are moving targets, not sitting ducks. We're still evolving, and we can also invent new medical technologies to target them, but *they're* evolving too—and much faster than us. As a result, while we can mitigate the problem, we can never be fully free of our microbial enemies and the pathogenic pressures they exert on us.

6. *Constraints on natural selection*

Natural selection is powerful, but it's not omnipotent. There are limits. For example, natural selection can only work with the raw material it has; if there is no genetic variation for a given trait, there's simply nothing that can be done. Natural selection is also constrained by history, or what's sometimes called "path dependence." Because of the precursor from which our visual system evolved, we are stuck with the suboptimal design of having a blind spot in both eyes. Evolution is a tinkerer, not an engineer, so it can only proceed in a gradual step-by-step fashion, and each step must be a definite improvement over the last. There's no such thing as going back to the drawing board and starting from scratch the way an engineer might. Because of this historical inertia, we're stuck with the inelegant setup of the trachea and the oesophagus, which poses a serious choking hazard. Evolutionarily, where we can go next is limited by where we've already been and the existing body plan that we're saddled with. These and other constraints limit the power of natural selection.

Since its inception, medicine has focused almost exclusively on the "how" questions of disease, largely setting aside the "why." By tackling the missing why question—*why* our bodies are vulnerable to disease in the first place—evolutionary medicine supplies an exciting new layer of understanding.

The "Why" Question Is Different From the "How"—and We Can't Afford to Ignore Either

This idea of different levels of analysis—the how and the why—is a core principle of evolutionary medicine. To understand human vulnerability to disease, we must understand both the *proximate* question (*how* the mechanism works in the body) as well as the *ultimate* question (*why* the body is built that way in the first place), and we must remember that the two levels of analysis are complementary, not conflicting. Although this key insight has been central to biology for decades, it has

taken researchers much longer to realize that the principle is equally fundamental to medicine and psychology. If we don't tackle both the how and the why, our understanding of disease will necessarily remain incomplete.

For example, suppose you want to understand breast cancer, and you know that mutations of the BRCA 1 and 2 genes contribute to breast cancer risk. That's a proximate answer—it tells us part of the story of how breast cancer arises, and it identifies a risk factor for the disease. But a key question remains: *why* do these genes persist in our species given the risk they pose for breast cancer? This is the ultimate level of analysis. It tackles the deeper question of why our bodies are like that in the first place.

In this case, the answer seems to be multifaceted. First, some evidence suggests that despite the downsides of BRCA mutations, they may simultaneously enhance women's fertility. In this apparent trade-off between health and fertility, the increased fertility may be partially responsible for why the gene persists in human populations (but see here for a conflicting viewpoint).

Second, modern humans go through vastly more menstrual cycles than our hunter-gatherer ancestors did. Rough calculations suggest that women in naturally cycling populations (for example, hunter-gatherers with no hormonal birth control) may go through 150–200 cycles in their lifetimes, with the number of cycles limited and interrupted by pregnancies and lactation. By contrast, women in industrialised nations experience closer to 500 cycles, which exposes them to evolutionarily novel levels of steroid hormones. This mismatch appears to contribute to increased risk of breast cancer later in life. Indeed, the more offspring a woman has, the lower her risk of breast cancer, and breastfeeding is also linked to reduced risk of breast cancer, findings that some researchers attribute to fewer cycles and reduced hormone exposure. Additional evidence from other sources suggests that "animals who lactate early and long" have lower rates of breast cancer.

The key point to take away here is that the proximate answer is only half the answer. Even when you know *how* it is happening in the body, the other half of the puzzle, the "why" question, remains. *Why is the body like that in the first place*? *Why did natural selection leave us vulnerable to this disease?* These fundamental questions demand an explanation.

Cancer

Cancer is one of the deadliest scourges facing humanity and one of the leading causes of death in the United States. The same is true in other countries and other age groups, including children. But why are we vulnerable to cancer in the first place?

In principle, all multicellular animals are vulnerable to cancer, and species of all vertebrate classes get cancer. Researchers have even found evidence of cancerous tumours in dinosaur fossils from the Jurassic period. From an evolutionary perspective, cancer is when certain cell lineages "go rogue," proliferating in a way that favours their own replication instead of cooperating with other cells to keep their shared host healthy. Cancer results partly from failure of the mechanisms natural selection shaped to eliminate these rogue cells. This risk of cells going rogue is always present in multicellular organisms, which is why cancer is so ubiquitous in the animal kingdom. In fact, viewed through an evolutionary lens, the more pressing question isn't: why is cancer so common? It's why isn't cancer *even more widespread*?

The startling answer is that cancer *is* more common than we know—but many of our cancers never see the light of day because we have evolved cancer-suppression mechanisms that kill them quite effectively. Evidence from various sources, including autopsies of animals that died for other reasons, show numerous cancerous growths that don't get counted in cancer tallies and don't make it far enough to become a problem. Thank goodness for our immune systems!

But despite our marvellous defences, we still sometimes succumb to cancer. Why? The answer involves co-evolution with viruses and bacteria, mismatch, trade-offs and the conflict between survival and reproduction.

Co-evolution with viruses and bacteria is important because some cancers are actually caused by infection—by some counts, as many as 15–20%. Examples include schistosomiasis and bladder cancer, *Heliobacter pylori* and gastric cancer, and HPV and cervical cancer.

Environmental mismatch plays a role because, as noted above, modern women go through many more menstrual cycles than our hunter-gatherer ancestors, which

exposes them to much higher levels of key hormones. Additionally, evidence suggests that our modern diet is carcinogenic, with factors such as reduced fibre in the diet, increased meat consumption, smoking and excess alcohol intake relative to the way our bodies evolved.

Trade-offs in the human body make us vulnerable to cancer, too. Stem cells pose a tragic trade-off: they're great at tissue healing, but having more of them increases our vulnerability to cancer. We benefit from the enhanced wound healing and tissue repair but suffer from the increased likelihood of cancer.

Finally, some cancer can be traced to the *conflict between survival and reproduction*. Certain gene variants appear to contribute to both cancer risk and enhanced fertility. Although the jury is still out, in one study, carriers of BRCA gene mutations were at higher risk of cancer, but had nearly two more children (on average) than did non-carriers. A similar link may exist between testosterone and prostate cancer in men. According to this idea, high levels of testosterone persist partly because they enhance men's reproductive success early in life even though they contribute to greater cancer risk later in life. Indeed, studies suggest that young men with higher testosterone have higher rates of prostate cancer later in life (see also here).

What this example shows is that the "why" answer can be multifaceted. The brief answer sketched above involves four of the six factors identified by evolutionary medicine: the inescapability of trade-offs, the primacy of reproduction over survival, co-evolution with pathogens, and the problems caused by environmental mismatch. And this is not an exhaustive answer—cancer is a complex collection of diseases underpinned by a variety of factors. But the key point shines through: if you want to understand the body's vulnerability to disease, you can't just address the how (the proximate mechanism); you need to address the why (the evolutionary basis) as well. Unless you tackle both, your answer remains incomplete.

Evolutionarily informed cancer research is still in its infancy, but even so, it has already led to many new findings, and it promises more insights and practical applications over the next few years. As researchers Athena Aktipis and Randy Nesse note,

> An evolutionary approach can help us understand why cancer exists and how it progresses (somatic evolution), how cancer cells interact with environments (ecological approaches), why it is not more common (natural selection for cancer suppression mechanisms), and why cancer suppression mechanisms can never be perfect (constraints, trade-offs, and other evolutionary reasons for vulnerability to disease). Evolution is essential for understanding cancer.

And It's Not Just Cancer

Evolutionary medicine extends far beyond cancer and illuminates a wide range of health conditions. The science of why we get sick offers new insights into cardiovascular problems, tooth disease, blood iron deficiency, breastfeeding, pregnancy and miscarriage, pain, Alzheimer's disease, aging and senescence, sepsis and even psychological disorders. We are only in the beginning stages of a revolution that is already transforming how we think about medicine, health and disease.

Does Medicine Really Need Evolution?

Just like tardigrades and jellyfish, humans are evolved animals. If we want to understand them—if we want to understand *ourselves*—we simply can't afford to ignore evolution. From infancy through to the end of life, and from physiology to mental illness, an evolutionary perspective illuminates how our bodies work, why they're built like that and why they go awry. Evolutionary medicine pinpoints the ways in which our bodies are bundles of trade-offs and compromises—and how we can use this information to stave off disease and better treat it when it occurs.

Perhaps it's obvious that this applies to our hearts and livers. It is less obvious that it applies with equal force to how our emotions work, why we suffer from anxiety and depression and why we are so tragically xenophobic as a species. From the urgent problems of antibiotic resistance to the crushing weight of psychiatric illness to the fatal omnipresence of cancer, we're quickly learning how indispensable evolution is to a deep understanding of human health and disease.

The new science of evolutionary medicine is growing fast, and interested readers may wish to consult the International Society for Evolution, Medicine and Public

Health for more information and new discoveries. This new science provides a roadmap for how we can achieve a deeper understanding of the slings and arrows of human frailty—and importantly, for how we can use this knowledge to best our illnesses. Don't miss this exciting scientific revolution.

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