Dr. Darwin

With a nod to evolution's god, physicians are looking at illness through the lens of natural selection to find out why we get sick and what we can do about it.

LORI OLIWENSTEIN

Paul Ewald knew from the beginning that the Ebola virus outbreak in Zaire would fizzle out. On May 26, after eight days in which only six new cases were reported, that fizzle became official. The World Health Organization announced it would no longer need to update the Ebola figures daily (though sporadic cases continued to be reported until June 20).

The virus had held Zaire's Bandundu Province in its deadly grip for weeks, infecting some 300 people and killing 80 percent of them. Most of those infected hailed from the town of Kikwit. It was all just as Ewald predicted. "When the Ebola outbreak occurred," he recalls, "I said, as I have before, these things are going to pop up, they're going to smolder, you'll have a bad outbreak of maybe 100 or 200 people in a hospital, maybe you'll have the outbreak slip into another isolated community, but then it will peter out on its own."

Ewald is no soothsayer. He's an evolutionary biologist at Amherst College in Massachusetts and perhaps the world's leading expert on how infectious diseases—and the organisms that cause them—evolve. He's also a force behind what some are touting as the next great medical revolution: the application of Darwin's theory of natural selection to the understanding of human diseases.

A Darwinian view can shed some light on how Ebola moves from human to human once it has entered the population. (Between human outbreaks, the virus resides in some as yet unknown living reservoir.) A pathogen can survive in a population, explains Ewald, only if it can easily transmit its progeny from one host to another. One way to do this is to take a long time to disable a host, giving him plenty of time to come into contact with other potential victims. Ebola, however, kills quickly, usually in less than a week. Another way is to survive for a long time outside the human body, so that the pathogen can wait for new hosts to find it. But the Ebola strains encountered thus far are destroyed almost at once by sunlight, and even if no rays reach them, they tend to lose their infectiousness outside the human body within a day. "If you look at it from an evolutionary point of view, you can sort out the 95 percent of disease organisms that aren't a major threat from the 5 percent that are," says Ewald. "Ebola really isn't one of those 5 percent."

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The earliest suggestion of a Darwinian approach to medicine came in 1980, when George Williams, an evolutionary biologist at the State University of New York at Stony Brook, read an article in which Ewald discussed using Darwinian theory to illuminate the origins of certain symptoms of infectious disease—things like fever, low iron counts, diarrhea. Ewald's approach struck a chord in Williams. Twenty-three years earlier he had written a paper proposing an evolutionary framework for senescence, or aging. "Way back in the 1950s I didn't worry about the practical aspects of senescence, the medical aspects," Williams notes. "I was pretty young then." Now, however, he sat up and took notice.

While Williams was discovering Ewald's work, Randolph Nesse was discovering Williams's. Nesse, a psychiatrist and a founder of the University of Michigan Evolution and Human Behavior Program, was exploring his own interest in the aging process, and he and Williams soon got together. "He had wanted to find a physician to work with on medical problems," says Nesse, "and I had long wanted to find an evolutionary biologist, so it was a very natural match for us." Their collaboration led to a 1991 article that most researchers say signaled the real birth of the field.

Nesse and Williams define Darwinian medicine as the hunt for evolutionary explanations of vulnerabilities to disease. It can, as Ewald noted, be a way to interpret the body's defenses, to try to figure out, say, the reasons we feel pain or get runny noses when we have a cold, and to determine

what we should—or shouldn't—be doing about those defenses. For instance, Darwinian researchers like physiologist Matthew Kluger of the Lovelace Institute in Albuquerque now say that a moderate rise in body temperature is more than just a symptom of disease; it's an evolutionary adaptation the body uses to fight infection by making itself inhospitable to invading microbes. It would seem, then, that if you lower the fever, you may prolong the infection. Yet no one is ready to say whether we should toss out our aspirin bottles. "I would love to see a dozen proper studies of whether it's wise to bring fever down when someone has influenza," says Nesse. "It's never been done, and it's just astounding that it's never been done."

Diarrhea is another common symptom of disease, one that's sometimes the result of a pathogen's manipulating your body for its own good purposes, but it may also be a defense mechanism mounted by your body. Cholera bacteria, for example, once they invade the human body, induce diarrhea by producing toxins that make the intestine's cells leaky. The resultant diarrhea then both flushes competing beneficial bacteria from the gut and gives the cholera bacteria a ride into the world, so that they can find another hapless victim. In the case of cholera, then, it seems clear that stopping the diarrhea can only do good.

But the diarrhea that results from an invasion of shigella bacteria—which cause various forms of dysentery—seems to be more an intestinal defense than a bacterial offense. The infection causes the muscles surrounding the gut to contract more frequently, apparently in an attempt to flush out the bacteria as quickly as possible. Studies done more than a decade ago showed that using drugs like Lomotil to decrease the gut's contractions and cut down the diarrheal output actually prolong infection. On the other hand, the ingredients in over-the-counter preparations like Pepto Bismol, which don't affect how frequently the gut contracts, can be used to stem the diarrheal flow without prolonging infection.

Seattle biologist Margie Profet points to menstruation as another "symptom" that may be more properly viewed as an evolutionary defense. As Profet points out, there must be a good reason for the body to engage in such costly activities as shedding the uterine lining and letting blood flow away. That reason, she claims, is to rid the uterus of any organisms that might arrive with sperm in the seminal fluid. If an egg is fertilized, infection may be worth risking. But if there is no fertilized egg, says Profet, the body defends itself by ejecting the uterine cells, which might have been infected. Similarly, Profet has theorized that morning sickness during pregnancy causes the mother to avoid foods that might contain chemicals harmful to a developing fetus. If she's right, blocking that nausea with drugs could result in higher miscarriage rates or more birth defects.

Darwinian medicine isn't simply about which symptoms to treat and which to ignore. It's a way to understand microbes—which, because they evolve so much more quickly than we do, will probably always beat us unless we figure out how to harness their evolutionary power for our own benefit. It's also a way to realize how disease-causing genes that persist in the population are often selected for, not against, in the long run.

Sickle-cell anemia is a classic case of how evolution tallies costs and benefits. Some years ago, researchers discovered that people with one copy of the sickle-cell gene are better able to resist the protozoans that cause malaria than are people with no copies of the gene. People with two copies of the gene may die, but in malaria-plagued regions such as tropical Africa, their numbers will be more than made up for by the offspring left by the disease-resistant kin.

Cystic fibrosis may also persist through such genetic logic. Animal studies indicate that individuals with just one copy of the cystic fibrosis gene may be more resistant to the effects of the cholera bacterium. As is the case with malaria and sickle-cell, cholera is much more prevalent than cystic fibrosis; since there are many more people with a single, resistance-conferring copy of the gene than with a disease-causing double dose, the gene is stably passed from generation to generation.

"With our power to do gene manipulations, there will be temptations to find genes that do things like cause aging, and get rid of them," says Nesse. "If we're sure about everything a gene does, that's fine. But an evolutionary approach cautions us not to go too fast, and to expect that every gene might well have some benefit as well as costs, and maybe some quite unrelated benefit."

Darwinian medicine can also help us understand the problems encountered in the New Age by a body designed for the Stone Age. As evolutionary psychologist Charles Crawford of Simon Fraser University in Burnaby, British Columbia, put it: "I used to hunt saber-toothed tigers all the time, thousands of years ago. I got lots of exercise and all that sort of stuff. Now I sit in front of a computer, and all I do is play with a mouse, and I don't get exercise. So I've changed my body biochemistry in all sorts of unknown ways, and it could affect me in all sorts of ways, and we have no idea what they are."

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Radiologist Boyd Eaton of Emory University and his colleagues believe such biochemical changes are behind today's breast cancer epidemic. While it's impossible to study a Stone Ager's biochemistry, there are still groups of hunter-gatherers around—such as the San of Africa—who make admirable stand-ins. A foraging life-style, notes Eaton, also means a life-style in which menstruation begins later, the first child is born earlier, there are more children altogether, they are breast-fed for years rather than months, and menopause comes somewhat earlier. Overall, he says, American women today probably experience 3.5 times more menstrual cycles than our ancestors did 10,000 years ago. During each cycle a woman's body is flooded with the hormone estrogen, and breast cancer, as research has

found, is very much estrogen related. The more frequently the breasts are exposed to the hormone, the greater the chance that a tumor will take seed.

Depending on which data you choose, women today are somewhere between 10 and 100 times more likely to be stricken with breast cancer than our ancestors were. Eaton's proposed solutions are pretty radical, but he hopes people will at least entertain them; they include delaying puberty with hormones and using hormones to create pseudopregnancies, which offer a woman the biochemical advantages of pregnancy at an early age without requiring her to bear a child.

In general, Darwinian medicine tells us that the organs and systems that make up our bodies result not from the pursuit of perfection but from millions of years of evolutionary compromises designed to get the greatest reproductive benefit at the lowest cost. We walk upright with a spine that evolved while we scampered on four limbs; balancing on two legs leaves our hands free, but we'll probably always suffer some back pain as well.

"What's really different is that up to now people have used evolutionary theory to try to explain why things work, why they're normal," explains Nesse. "The twist—and I don't know if it's simple or profound—is to say we're trying to understand the abnormal, the vulnerability to disease. We're trying to understand why natural selection has not made the body better, why natural selection has left the body with vulnerabilities. For every single disease, there is an answer to that question. And for very few of them is the answer very clear yet."

One reason those answers aren't yet clear is that few physicians or medical researchers have done much serious surveying from Darwin's viewpoint. In many cases, that's because evolutionary theories are hard to test. There's no way to watch human evolution in progress—at best it works on a time scale involving hundreds of thousands of years. "Darwinian medicine is mostly a guessing game about how we think evolution worked in the past on humans, what it designed for us," say evolutionary biologist James Bull of the University of Texas at Austin. "It's almost impossible to test ideas that we evolved to respond to this or that kind of environment. You can make educated guesses, but no one's going to go out and do an experiment to show that yes, in fact humans will evolve this way under these environmental conditions."

Yet some say that these experiments can, should, and will be done. Howard Howland, a sensory physiologist at Cornell, is setting up just such an evolutionary experiment, hoping to interfere with the myopia, or nearsightedness, that afflicts a full quarter of all Americans. Myopia is thought to be the result of a delicate feedback loop that tries to keep images focused on the eye's retina. There's not much room for error: if the length of your eyeball is off by just a tenth of a millimeter, your vision will be blurry. Research has shown that when the eye perceives an image as fuzzy, it compensates by altering its length.

This loop obviously has a genetic component, notes Howland, but what drives it is the environment. During the Stone Age, when we were chasing buffalo in the field, the images we saw were usually sharp and clear. But with modern civilization came a lot of close work. When your eye focuses on something nearby, the lens has to bend, and since bending that lens is hard work, you do as little bending as you can get away with. That's why, whether you're conscious of it or not, near objects tend to be a bit blurry. "Blurry image?" says the eye. "Time to grow." And the more it grows, the fuzzier those buffalo get. Myopia seems to be a disease of industrial society.

To prevent that disease, Howland suggests going back to the Stone Age—or at least convincing people's eyes that that's where they are. If you give folks with normal vision glasses that make their eyes think they're looking at an object in the distance when they're really looking at one nearby, he says, you'll avoid the whole feedback loop in the first place. "The military academies induct young men and women with twenty-twenty vision who then go through four years of college and are trained to fly an airplane or do some difficult visual task. But because they do so much reading, they come out the other end nearsighted, no longer eligible to do what they were hired to do," Howland notes. "I think these folks would very much like not to become nearsighted in the course of their studies." He hopes to be putting glasses on them within a year.

The numbing pace of evolution is a much smaller problem for researchers interested in how the bugs that plague us do their dirty work. Bacteria are present in such large numbers (one person can carry around more pathogens than there are people on the planet) and evolve so quickly (a single bacterium can reproduce a million times in one human lifetime) that experiments we couldn't imagine in humans can be carried out in microbes in mere weeks. We might even, says Ewald, be able to use evolutionary theory to tame the human immunodeficiency virus.

"HIV is mutating so quickly that surely we're going to have plenty of sources of mutants that are mild as well as severe," he notes. "So now the question is, which of the variants will win?" As in the case of Ebola, he says, it will all come down to how well the virus manages to get from one person to another.

"If there's a great potential for sexual transmission to new partners, then the viruses that reproduce quickly will spread," Ewald says. "And since they're reproducing in a cell type that's critical for the well-being of the host—the helper T cell—then that cell type will be decimated, and the host is likely to suffer from it." On the other hand, if you lower the rate of transmission—through abstinence, monogamy, condom use—then the more severe strains might well die out before they have a chance to be passed very far. "The real question," says Ewald, "is, exactly how mild can you make this virus as a result of reducing the rate at which it could be transmitted to new partners, and how long will it take for this change to occur?" There are already strains of HIV in Senegal with such low virulence, he points out, that most people infected will die of old age. "We don't have all the answers. But I think we're going to be living with this virus for a long time, and if we have to live with it, let's live with a really mild virus instead of a severe virus."

Though condoms and monogamy are not a particularly radical treatment, that they might be used not only to stave off the virus but to tame it is a radical notion—and one that some

researchers find suspect. "If it becomes too virulent, it will end up cutting off its own transmission by killing its host too quickly," notes James Bull. "But the speculation is that people transmit HIV primarily within one to five months of infection, when they spike a high level of virus in the blood. So with HIV, the main period of transmission occurs a few months into the infection, and yet the virulence—the death from it—occurs years later. The major stage of transmission is decoupled from the virulence." So unless the protective measures are carried out by everyone, all the time, we won't stop most instances of transmission; after all, most people don't even know they're infected when they pass the virus on.

But Ewald thinks these protective measures are worth a shot. After all, he says, pathogen taming has occurred in the past. The forms of dysentery we encounter in the United States are quite mild because our purified water supplies have cut off the main route of transmission for virulent strains of the bacteria. Not only did hygienic changes reduce the number of cases, they selected for the milder shigella organisms, those that leave their victim well enough to get out and about. Diphtheria is another case in point. When the diphtheria vaccine was invented, it targeted only the most severe form of diphtheria toxin, though for economic rather than evolutionary reasons. Over the years, however, that choice has weeded out the most virulent strains of diphtheria, selecting for the ones that cause few or no symptoms. Today those weaker strains act like another level of vaccine to protect us against new, virulent strains.

"You're doing to these organisms what we did to wolves," says Ewald. "Wolves were dangerous to us, we domesticated them into dogs, and then they helped us, they warned us against the wolves that were out there ready to take our babies. And by doing that, we've essentially turned what was a harmful organism into a helpful organism. That's the same thing we did with diphtheria; we took an organism that was causing harm, and without knowing it, we domesticated it into an organism that is protecting us against harmful ones."

We did with diphtheria what we did with wolves. We took an organism that caused harm, and unknowingly, we domesticated it into an organism that protects us.

Putting together a new scientific discipline—and getting it recognized—is in itself an evolutionary process. Though Williams and Neese say there are hundreds of researchers working (whether they know it or not) within this newly built framework, they realize the field is still in its infancy. It may take some time before *Darwinian medicine* is a household term. Nesse tells how the editor of a prominent medical journal, when asked about the field, replied, "Darwinian medicine? I haven't heard of it, so it can't be very important."

But Darwinian medicine's critics don't deny the field's legitimacy; they point mostly to its lack of hard-and-fast answers, its lack of clear clinical guidelines. "I think this idea will eventually establish itself as a basic science for medicine," answers Nesse. "What did people say, for instance, to the biochemists back in 1900 as they were playing out the Krebs cycle? People would say, 'So what does biochemistry really have to do with medicine? What can you cure now that you couldn't before you knew about the Krebs cycle?' And the biochemists could only say, 'Well, gee, we're not sure, but we know what we're doing is answering important scientific questions, and eventually this will be useful.' And I think exactly the same applies here."

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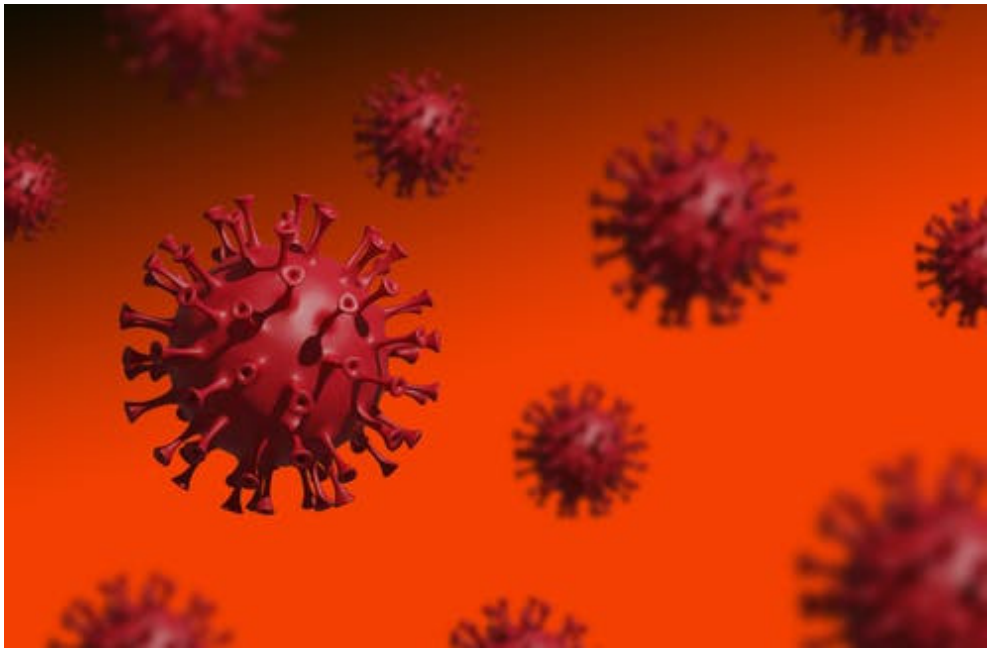

An artistic rendering of SARS-CoV-2, the virus that causes the COVID-19 illness. Getty Images / s-cphoto

How the coronavirus escapes an evolutionary trade-off that helps keep other pathogens in check

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Viruses walk a fine line between severity and transmissibility. If they are too virulent, they kill or incapacitate their hosts; this limits their ability to infect new hosts. Conversely, viruses that cause little harm may not be generating enough copies of themselves to be infectious.

But SARS-CoV-2, the coronavirus that causes the COVID-19 disease, sidesteps this evolutionary trade-off. Symptoms often don't appear until after infected people have been spreading the virus for several days. One study of SARS-CoV-2 estimated that the highest rate of viral shedding, and therefore transmissibility, was one to two days before the person infected begins to show symptoms.

Put simply, you only feel ill once the virus has accomplished its evolutionary goal: to spread.

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Viruses that are good at making copies of themselves, and then getting those copies inside new hosts, are more successful and become more prevalent until host immunity or public health efforts restrain them.

As professors who study evolutionary medicine, we know the trade-off between virulence and transmissibility helps keep a pathogen in check. The very destructiveness of a virus keeps it from spreading too much. This has been the case with other pandemic pathogens, including Marburg, Ebola and the original coronavirus responsible for SARS. Outbreaks that consistently cause severe symptoms are more easily corralled by public health measures because infected individuals are easy to identify. SARS-CoV-2, however, can invade communities stealthily, because many infected individuals have no symptoms at all.

Younger people can be infectious, but they typically have milder symptoms of COVID-19. Getty Images / Justin Paget

COVID-19 behaves like an STI

Looking at it this way, COVID-19 resembles a sexually transmitted disease. The infected person continues to look and feel fine while spreading the illness to new hosts. HIV and syphilis, for example, are relatively asymptomatic for much of the time they are contagious. With SARS-CoV-2, recent research suggests that 40-45% of people infected remain asymptomatic. And those carriers seem able to transmit the virus for a longer period.

COVID-19 has another similarity to many sexually transmitted diseases. Its severity is not the same across hosts, and often it's dramatically different. There is evidence that the ability to fight the

infection differs among people. The severity among strains of the virus might also differ, though there is no solid evidence of this yet.

Even for a single strain of SARS-CoV-2, the virus can affect people in different ways, which could facilitate its spread. The SARS-CoV-2 virus – or any other pathogen – is not deliberately changing what it does in order to exploit us and use our bodies as vehicles for transmission, but pathogens can evolve to look like they are playing games with us.

Studies show pathogens can express conditional virulence – meaning that they can be highly virulent in some individuals and less virulent in others – depending on host characteristics, like age, the presence of other infections and an individual's immune response. This might explain how SARS-CoV-2 escapes the trade-off. In some individuals, virulence is maximized, such as in older hosts. In others, transmissibility is maximized.

EMTs evacuate patients from a nursing home in Riverside, California. Older people tend to have the most severe infections. Getty Images/Los Angeles Times/Gina Ferazzi

Age matters

Age, so far, seems the critical factor. Older people tend to get highly destructive infections, while younger hosts, although just as infectious, remain largely unscathed. This might be because different hosts have different immune responses. Another explanation is that as we get older, we are more likely to develop other illnesses, such as obesity and hypertension, which can make us more susceptible to harm from SARS-CoV-2.

Regardless of the mechanism, this age-based pattern permits SARS-CoV-2 to have its evolutionary cake and eat it too: ravaging older individuals with high virulence, yet maintaining younger individuals as vehicles for transmission. Some studies suggest younger people are more likely to be asymptomatic. Both presymptomatic and asymptomatic carriers can transmit the virus.

What do we know about the evolution of SARS-CoV-2? Unfortunately, not much yet. There is some evidence that the virus may be adapting to us as its new hosts, but so far no evidence shows that these mutations are causing changes in the virulence or transmissibility of SARS-CoV-2. And because SARS-CoV-2 may be able to circumvent the typical trade-off between virulence and transmissibility, there may be little evolutionary pressure to become less severe as it spreads.

For all the mysteries surrounding COVID-19, one thing is certain: We cannot be lulled into a false sense of security. As Sun Tzu warned in "The Art of War," know your enemy. There is a great deal more to know about SARS-CoV-2 before we claim any victories.

Pandemic Pathogens Coronavirus Viruses infections 2019-nCoV COVID-19 SARS-CoV-2 Transmission