



Evolutionary Medicine

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Ananth Karumanchi is a doctor at Beth Israel Deaconess Hospital in Boston and an associate professor at Harvard Medical School. He is an expert on the risks of pregnancy, including a mysterious condition known as preeclampsia, which causes a dangerous spike in blood pressure. Preeclampsia strikes about 5% of all pregnant women. Left untreated, it can be fatal;



Left: An immune cell attacks bacteria. The evolution of pathogens plays a central role in diseases. Above: S. Ananth Karumanchi of Harvard Medical School has found evidence of an evolutionary conflict underlying pregnancy disorders.

it kills about 75,000 women worldwide each year. Thanks to the level of medical care in the United States, few American women die of preeclampsia, but they can still suffer lifelong effects if their preeclampsia leads to a stroke, a failed kidney, or a ruptured liver. When a woman develops preeclampsia, there's not a lot that doctors can do for her. The one certain way to end the condition is to deliver the baby immediately. Once the baby is out of its mother's body, her blood pressure drops. As a result, preeclampsia is among the most common causes of premature birth in the United States—which puts babies at risk as well.

Doctors would love to have a better treatment for preeclampsia, one that attacked the source of the disease without endangering the baby's health. But despite the fact that physicians have been familiar with preeclampsia for more than two thousand years, they still do not know its cause. Karumanchi wants to find it. In the year 2000, Karumanchi began to suspect that preeclampsia was triggered by the release of some kind of molecule. When he compared the blood of women with preeclampsia with that of healthy women, he discovered a potential culprit: a molecule called soluble Flt-1.

Soluble Flt-1 is only known to appear in the bodies of pregnant women; in women with preeclampsia, Karumanchi found, it appears in much higher levels than in healthy pregnant women. Experiments with soluble Flt-1 have shown that it makes other proteins in the blood stick together so that they can't nourish the walls of the blood vessels. When Karumanchi injected soluble Flt-1 into rats, he found their blood pressure went up. They also suffered damage to their kidneys, which resembled the damaged kidneys seen in women with preeclampsia.

Karumanchi and his colleagues tested his hypothesis by getting their hands on a much larger set of blood samples from pregnant women. Once more, they found more soluble Flt-1 in women with preeclampsia. This time around, however, they also discovered that levels of soluble Flt-1 actually rose five weeks *before* women showed the first signs of preeclampsia.

The discovery was an important one, but it raised a swarm of new questions. No one knew what soluble Flt-1 (sFlt-1) was for. It presumably had some function in pregnancy, because healthy pregnant women make it too. Most puzzling of all was the source of soluble Flt-1. It is not made by the mother's own cells. Instead, the placenta releases the molecule. The placenta, an organ that takes nutrients from mothers and gives them to their fetuses, develops from the same fertilized egg that produces the fetus. Genetically speaking, it's part of the child, not the mother. In other words, the fetus actually gives its mother preeclampsia.

As Karumanchi was puzzling over these mysteries, he was contacted by Harvard evolutionary biologist David Haig (page 286). Haig had predicted years before that preeclampsia would turn out to be caused by a molecule produced by the baby, not the mother. He made the prediction based on his study of evolution.

Haig argued that pregnancy in mammals brings mothers and fathers into evolutionary conflict. A father benefits from mutations that allow his offspring to get more nutrients from its mother. A larger baby is healthier at birth and more likely to survive to adulthood. Mothers get an evolutionary benefit from healthy babies, but if a mother supplies too many nutrients to a single child, her health

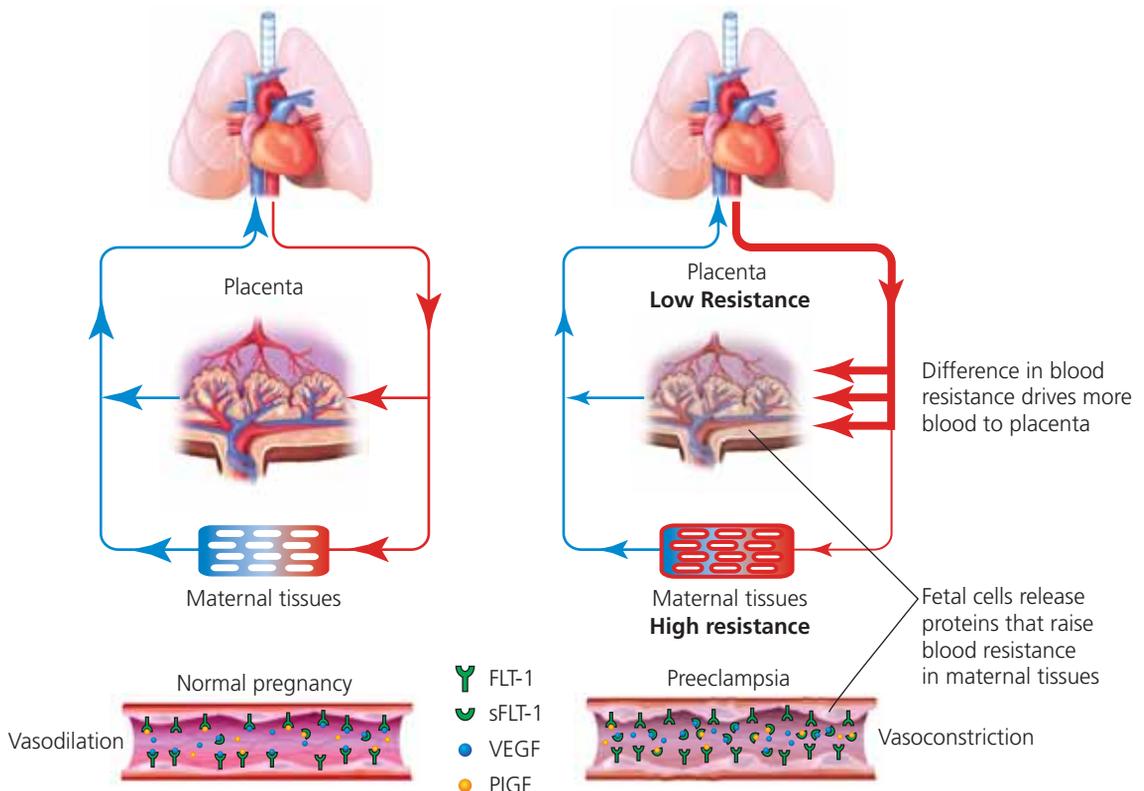


Figure 13.1 The circulatory systems of mothers and their embryos are intimately linked. According to one hypothesis, babies can increase blood flow to the placenta by releasing a molecule called soluble Flt-1 into the mother's bloodstream, raising the resistance in the mother's circulatory system. If the resistance gets too high, the mother may suffer dangerously high blood pressure. (Adapted from Koella and Stearns, 2008)

may suffer. As her health declines, she can bear fewer children. Thus, Haig argued, natural selection should favor genes in mothers that could keep the demands of a fetus in check.

In the last chapter, we saw how this conflict leads to the imprinting of genes that control the growth of fetuses. Haig also proposed that parental conflict could have other effects on pregnancy as well. For example, the amount of nutrients a fetus gets depends on how much blood flows from the mother's circulatory system into the placenta (**Figure 13.1**). If her blood pressure is high, more of her blood will get forced through it. Haig argued that mutations that allowed fetuses to raise their mothers' blood pressure would be strongly favored by natural selection. But the success fetuses had in getting more nutrients this way would favor mutations that helped the mother reduce her blood pressure. Haig argued that the opposing adaptations of mothers and fetuses are normally balanced, so that the mother and baby both survive pregnancy. But it also opened the possibility for pregnancies to go awry. If a mother could not counter the fetus's strategies for raising her blood pressure, it would shoot up to dangerous levels. Instead of simply supplying more nutrients to the fetus, the mother would suffer preeclampsia.

Haig's model of preeclampsia made a provocative prediction. If doctors ever found the factor that caused preeclampsia, they would find that it was produced in the fetal tissue, not in the mother's. Karumanchi was amazed to discover that he had unknowingly confirmed that prediction.

The two scientists began to collaborate—Haig offering insights from evolutionary biology, Karumanchi from his medical studies on pregnant women. Together, they have begun to design experiments that will allow them to test more of Haig's hypotheses about preeclampsia, so that they can better understand what triggers it in some women and not in others. For example, it's possible that genes that help produce or release soluble Flt-1 may be imprinted. In other words, the father's copies of the genes are actively boosting the mother's blood pressure, while the mother's copies are shut down. Like other insights into the basic workings of diseases, the results of their experiments may someday lead to new treatments.

Haig and Karumanchi are exploring a new kind of science—the intersection of evolutionary biology and medicine. Evolutionary medicine, as the field is known, sheds light on diseases and disorders by looking back at their history. In some cases, that history reaches back 600 million years ago, to the origins of multicellular animals. In other cases, that history reaches back over just the past few days of a virus's rapid evolution. Evolutionary medicine can lead to concrete changes in how doctors practice medicine—such as the ways in which they prescribe antibiotics to kill infectious bacteria. It also offers deeper lessons about what it means to be human. Natural selection may be able to shape complex adaptations, but it has not made our bodies perfect. We are still left vulnerable to many disorders. In some cases, evolution has actually made us more likely to get sick, not less. Evolutionary medicine doesn't just reveal our adaptations, in other words, but our maladaptations as well.

Evolving Parasites

Every year, 18.3 million people die worldwide from infectious diseases. Each of the viruses, bacteria, protozoans, fungi, and various parasitic animals that cause those diseases has its own evolutionary history. Evolutionary trees of parasites and their human hosts can reveal that history and point to new ways to treat them.

Some pathogens have been infecting our ancestors for many millions of years. Chickenpox, cold sores, and a number of other diseases are caused by a family of viruses known as herpesviruses. Herpesviruses also infect many other species of animals, including even oysters. But many strains of herpesviruses have been adapted only to humans, ever since our species evolved, and to the ancestors of humans before them. Consider human herpesvirus 5 (also known as cytomegalovirus). Most people get infected with this virus at some point in their lives. It causes fevers, fatigue, and swollen glands.

There are a number of strains of human herpesvirus 5, and they are all more closely related to each other than they are to any other herpesvirus. The closest relatives of human herpesvirus 5 strains infect chimpanzees, which are the closest living relatives of humans. Studies on other strains of herpesvirus 5 reveal the same pattern: the evolutionary tree of the viruses mirrors the evolutionary tree of their hosts (**Figure 13.2**).

This mirrorlike phylogeny suggests that herpesvirus 5 has been tracking the evolution of its host for millions of years. The common ancestor of primates and other mammals was host to a herpesvirus, and as that ancestor's descendants diverged into new lineage, the virus diverged as well. It did not leap to distantly related hosts, like turtles or sharks.

One way to test this hypothesis is to estimate how long ago the common ancestor of these viruses lived. Scientists can do this with the help of a molecular clock (page 146). Mutations accumulate in a lineage of viruses at a roughly clock-like rate. The more time passes after two lineages diverge from a common ancestor, the more mutations they will have. It turns out that human herpesvirus 5 has a large number of mutations not shared by its closest relatives in chimpanzees. That's consistent with the idea that the virus has been infecting our hominid ancestors for millions of years.

Scientists get a very different result when they look at some other viruses, such as HIV (human immunodeficiency virus, pages 143 and 147). Each of the

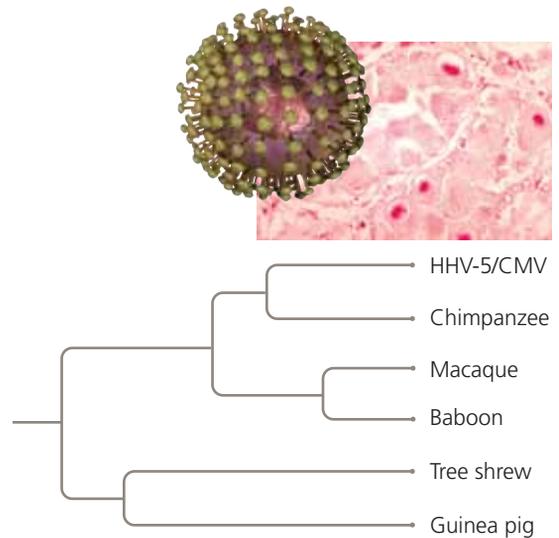


Figure 13.2 This tree shows how human herpesvirus 5 is related to other herpesviruses, with their hosts indicated on each branch. The branching pattern of the viruses mirrors that branching pattern of their hosts, suggesting that hosts and parasites have been cospeciating for tens of millions of years. (Adapted from Koella and Stearns, 2008)

major strains of HIV is more closely related to viruses that infect chimpanzees and monkeys than it is to other HIV strains. What's more, HIV strains have acquired relatively few mutations since they diverged from viruses in other primates. The best explanation for these results is that the ancestors of HIV shifted from other primates in the early 1900s.

It took nearly 20 years for scientists to pinpoint the origins of HIV after its discovery in 1983. Thanks to advances in isolating viruses and sequencing DNA, this sort of detective work now takes much less time. In November 2002, for example, a mysterious new disease began to spread through China. At first a Chinese farmer came to a hospital suffering from a high fever and died soon afterwards. Other people from the same region of China began to develop the disease as well, but it didn't reach the world's attention until an American businessman flying back from China developed a fever on a flight to Singapore. The flight stopped in Hanoi, where the businessman died. Soon, people were falling ill in countries around the world, although most of the cases turned up in China and Hong Kong. About 10% of people who became sick died in a matter of days. The disease was not the flu, not pneumonia, nor any other known disease. It was given a new name: severe acute respiratory syndrome, or SARS.

In March 2003, the World Health Organization established a network of labs around the globe to pin down the cause of SARS. Just a month later, they had identified a virus as the culprit. But what kind of virus was it?

To answer that question, Christian Drosten of the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany, and his colleagues drew an evolutionary tree based on the virus's RNA. In May 2003, they reported that the SARS virus was most closely related to pathogens called coronaviruses, which can cause colds and stomach flu.

Based on their experience with viruses such as HIV, scientists suspected that SARS had evolved from a virus that infects animals. They began to analyze viruses in animals with which people in China have regular contact. As they discovered new viruses, they added their branches to the SARS evolutionary tree.

The first big breakthrough came with the discovery of a closely related virus in cat-like mammals called palm civets. The civets are sold in animal markets in China for meat, suggesting a route the virus could have taken from one species to the other. In late 2003, a second SARS outbreak swept China, and scientists traced it to a separate invasion of palm civet viruses into human hosts. But further research revealed that civets are not the main host for the viruses that give rise to SARS in humans. Both the viruses from civets and humans belonged to tiny tufts of branches nestled in a large evolutionary tree of coronaviruses that



In 2003, panic swept southeast Asia as a new disease, known as SARS, broke out. At first, doctors did not know what caused it.

infect Chinese bats. Viruses from bats regularly infect other animals, which can then pass them to humans (**Figure 13.3**).

This rapid response from evolutionary biologists is becoming increasingly important to the world's health. New diseases continue to emerge every year, and the only way to know what they are is to know what they evolved from. This knowledge also helps doctors and public-health officials to control the outbreaks. Knowing which animals are the sources of diseases allows public-health workers to block the transmission—in the case of civets, by banning their sale in open markets.

Once scientists identify the source of new diseases, they can compare the pathogens in their original hosts and the ones in humans to see how they have evolved to adapt to our biology. Those new adaptations may provide clues to how to fight those diseases, and understanding the origin of diseases also helps scientists to predict where new diseases will come from. Scientists now recognize that Asian bats are a reservoir for many kinds of viruses, for example, and may well produce new outbreaks. Thus many scientists are now trying to discover new viruses in bats and understand how they spread. African primates, on the other hand, have proven to be the source of multiple invasions of HIV. The leap from primates to humans was probably made possible by the large-scale deforestation of central Africa, along with a growing trade in the meat of forest animals. Scientists have identified many other viruses in the same lineage that gave rise to HIV. There's good reason to expect that some of them will make the leap as well. How prepared we'll be for the next leap, however, is an open question.

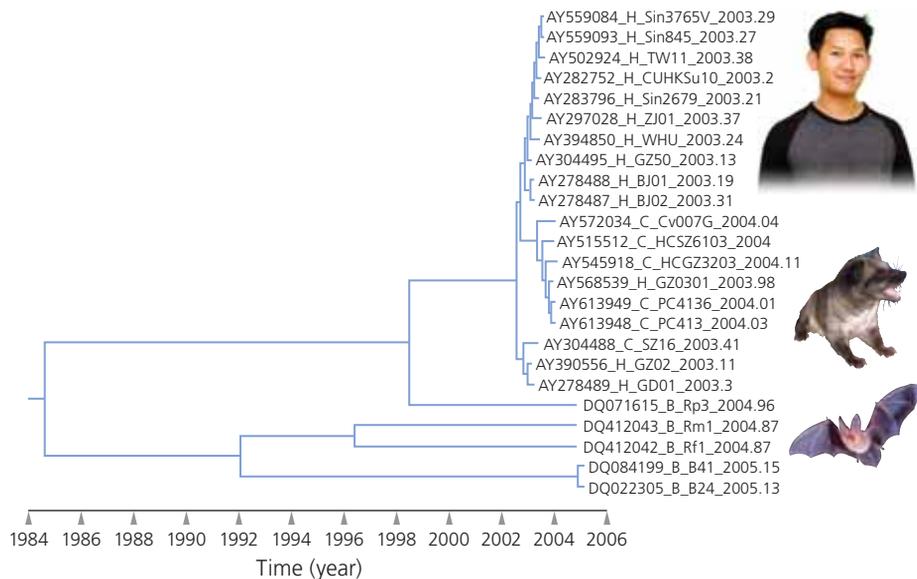


Figure 13.3 Once the SARS virus was isolated in humans, researchers searched for its closest relatives in animals. As this evolutionary tree shows, the SARS virus evolved from a family of viruses that circulates in bats. (Each branch is labeled with a strain code, followed by an abbreviation for its host: H = human, C = civet, B = bat. Adapted from Hon et al, 2008)

Human Petri Dishes

To learn about the workings of evolution, scientists have reared bacteria and viruses in the laboratory, observing how they change through mutation and selection (pages 117 and 134). But, when bacteria and viruses infect us, we become living petri dishes, and our pathogens evolve inside us.

Figure 13.4 shows the record of this evolution within nine people infected with HIV. Doctors took blood samples from them every few months, and James Mullins and his colleagues at the University of Washington isolated the HIV viruses from them. By sequencing a gene from the viruses, the scientists were able to draw the evolutionary tree. The viruses in all the patients descended from a common ancestor, but once they entered their hosts, they continued to evolve. Each time the viruses replicate in a host cell, many of them mutate. Most of the mutations cripple the viruses, but a few raise their fitness.

During the evolution of HIV, natural selection favors mutations that allow the viruses to copy themselves faster. The fitness of HIV can also be raised by mutations that allow the virus to escape destruction. An infected person's immune system can come to recognize parts of the surface proteins on HIV, enabling it to attack the viruses. As viruses with one kind of surface protein begin to suffer major assaults from our immune cells, other viruses with different proteins can

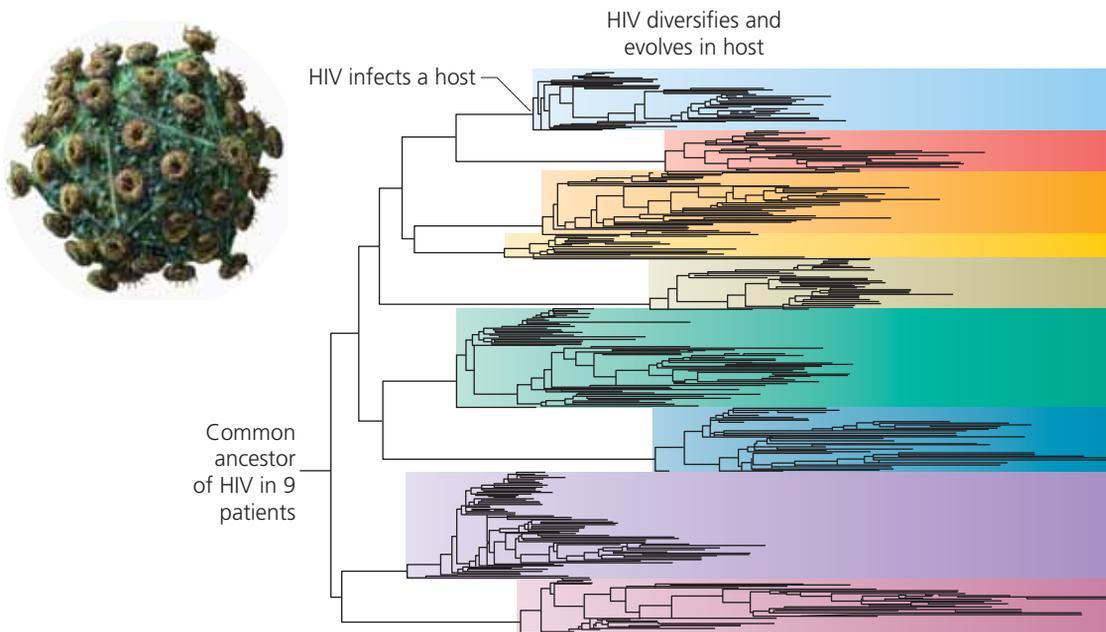


Figure 13.4 Within a single host, pathogens can replicate many times, mutate, and undergo natural selection. This diagram shows how related HIV viruses infected nine people (colored bands), and diversified inside them. These newly evolved viruses were better able to avoid the host's immune system and resist HIV-fighting drugs. (Adapted from Roualt, 2004)

reproduce more rapidly. As a result, the diversity of HIV within a single person blooms.

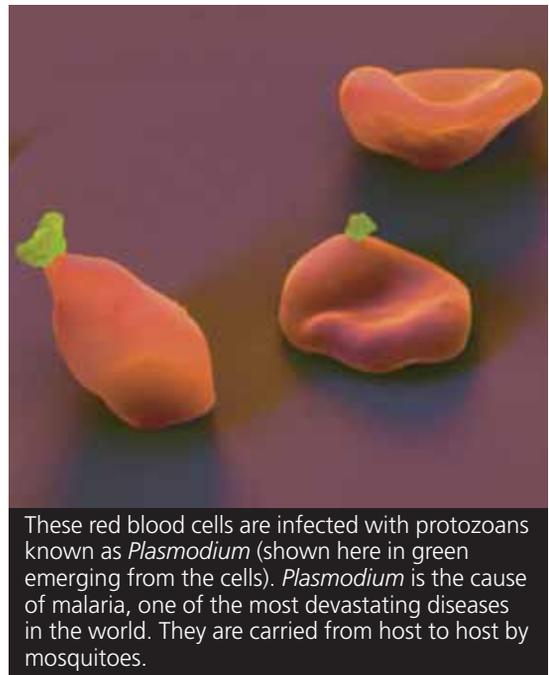
Pathogens don't make us sick and die because they enjoy it; this suffering—or, technically, virulence—is just a byproduct of the way in which pathogens grow and reproduce. Malaria, for example, is caused by single-celled parasites called *Plasmodium*. The parasite is carried by mosquitoes, which inject it into the bloodstream when they bite. *Plasmodium* can then invade red blood cells. If the infected blood cells enter the spleen, they are destroyed. *Plasmodium* avoids this fate by making sticky proteins that glue the infected red blood cells to the walls of blood vessels, so that they never pass through the spleen. Over time, these cells stick together in clumps, blocking the flow of blood and causing blood vessels to tear open.

Some diseases are more virulent than others. There are pathogens that barely slow us down, and others that can kill us in a few days. Virulence varies not only between species but within them as well. *Toxoplasma gondii*, a relative of *Plasmodium*, can live peacefully, for the most part, inside people's brains. Billions of people are infected with *Toxoplasma* without even knowing it. In Brazil, however, many strains are more likely to cause dangerous fevers and inflammation.

A pathogen's virulence can evolve over time. Rabbits provide one of the best examples of this sort of evolution. Before 1859 there were no rabbits in Australia. They were introduced by Thomas Austin, a farmer who had enjoyed shooting rabbits in Scotland before immigrating to Australia. Without predators to control them, the rabbits exploded across the continent, eating so much vegetation that they began to cause serious soil erosion. In the 1950s, scientists deployed a biological counteroffensive, known as rabbit myxoma virus.

The rabbit myxoma virus, which was discovered in South America, causes deadly infections in hares. Scientists expected that the virus would also decimate the Australian rabbits. At first, the virus worked as expected, and rabbits died in droves. But then the virus gradually became less virulent. Rabbits would get sick, but then recover. In later years, the rabbit myxoma virus became more virulent again, but it never became as deadly as the original strain. Rabbits today continue to be an ecological blight on Australia.

Scientists can also observe the virulence of pathogens as they evolve in their labs. Kanta Subbaro, a virologist at the National Institute of Allergy and Infectious Diseases, witnessed such an evolution while searching for an animal model she could use to study SARS. Mice did not get sick from the SARS virus, not even mice that had been genetically engineered so that they couldn't develop an immune system. So Subbaro and her colleagues inoculated mice with the SARS



These red blood cells are infected with protozoans known as *Plasmodium* (shown here in green emerging from the cells). *Plasmodium* is the cause of malaria, one of the most devastating diseases in the world. They are carried from host to host by mosquitoes.

virus, gave it a chance to replicate inside them, and then isolated the new viruses to infect new mice. As the virus replicated inside mice and then moved to new hosts, it evolved. Over the course of just 15 passages, it changed from a harmless virus into a fatal one. One sniff of SARS was now enough to kill a mouse.

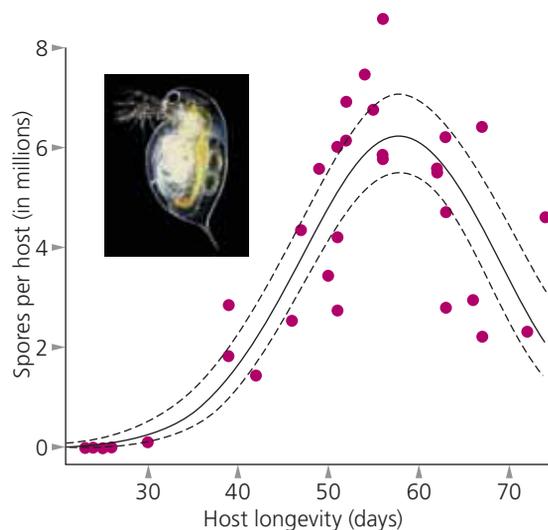
Why did the myxoma virus and the SARS virus evolve to different levels of virulence? According to one hypothesis, the answer can be found in a trade-off that pathogens face. Their reproductive success depends on both their replication within hosts and their infection of new hosts. If a pathogen multiplies too quickly, it may kill its hosts before it can spread to a new one. If it's gentle enough to keep its hosts alive, it will be rapidly outcompeted by faster-growing strains. The details of how a particular pathogen replicates and spreads may determine its most adaptive level of virulence.

Dieter Ebert, an evolutionary biologist at the University of Fribourg, has tested the trade-off hypothesis using water fleas and bacteria. The bacteria (called *Pasteuria ramosa*) infect the water fleas and produce a vast number of spores inside the animals. The bacteria eventually kill the water fleas, whereupon the spores stream out of their dead bodies.

The particular way in which *Pasteuria* reproduces allowed Ebert's team to measure its reproductive success exactly (Figure 13.5). They infected a set of genetically identical water fleas with the bacteria and then counted the number of spores produced upon their deaths. The scientists found that the bacteria cut the life span of the water fleas roughly in half, from three months on average to a month and a half. Some bacteria killed their hosts in just 20 days, while others left them alive for more than 70 days.

At both extremes, the bacteria produced fewer spores than an intermediate host lifespan of 55 to 60 days. The fast-killing bacteria killed off their hosts before they could produce many spores. The slow killers, Ebert speculates, don't make good use of their hosts, which may get too old to provide a good supply of nutrients to their pathogens.

Figure 13.5 Like other organisms, parasites face an evolutionary trade-off. Parasites can boost their fitness by reproducing quickly inside their hosts. But if their hosts die too quickly, the parasites have less time to exploit them. Scientists documented this trade-off in bacteria that infect water fleas (inset), castrate their hosts, and then produce spores inside them that are released when the water fleas die. The bacteria that kill their host quickly or very slowly produce fewer spores than the ones that kill at an intermediate time. (Adapted from Jensen et al, 2006)



In a case like that of *Pasteuria*, natural selection will favor the pathogens at the top of the curve in **Figure 13.5**—in other words, the pathogens that reproduce the most. Exactly where the top of the curve ends up for a particular pathogen depends on its own set of conditions. Kanta Subarro's experiment may have led SARS to become more virulent because the virus no longer paid a cost for being deadly. Subarro ensured that the viruses would be able to get to another mouse, no matter how fast they replicated in their current host. Outside the laboratory, pathogens may become more virulent as it becomes easier for them to move between hosts. Pathogens can also become more virulent if several different strains infect the same host at once. If one strain of the pathogen reproduces slowly and causes little harm to its host, it will be outcompeted by the more virulent pathogens living alongside it.

Molded by Parasites

Pathogens evolve to adapt to their hosts, and their hosts, in turn, adapt to the pathogens. All living things have defenses against infections. Even bacteria can recognize invading viruses and chop up their DNA. Animals—and in particular, vertebrates—have evolved particularly elaborate immune systems, made up of many different types of cells that trade signals with one another, swallow up some pathogens, and manufacture chemical weapons to destroy others.

Despite the power and sophistication of the human immune system, our pathogens continue to thrive. One reason for their continued success is that they can evolve faster than we can. While humans may take two or three decades to reproduce, pathogens can divide in a matter of hours or less. Some pathogens, such as HIV, have very high mutation rates, which produces a great deal of genetic variation that speeds up their response to selection. Viruses and bacteria can also acquire genes through horizontal gene transfer, speeding up their evolution even more.

The high-speed evolution of pathogens means that natural selection is always favoring new defenses in their hosts. When evolutionary biologists measure the strength of selection on the human genome (page 148), immune-system genes consistently turn up near the top of the list.

Humans have evolved new strategies for fighting diseases in just the past few thousand years. One of the most devastating of these recent diseases is malaria. Scientists suspect that the strains of *Plasmodium* that cause the most harm today first evolved in Africa within the past 6,000 years as farmers began to clear forests. Malaria-spreading mosquitoes could breed in the standing water in their fields, and could then infect the farmers as they slept in their villages. The disease then spread wherever mosquitoes could carry it—even to England and the northern United States. In the mid-1900s, public-health workers eliminated malaria from the United States by eliminating breeding sites and spraying pesti-

cides in people's homes. But in Africa and elsewhere it remains a major scourge, infecting 250 million people a year and killing 880,000.

In response, humans have evolved a number of defenses to malaria in just the past few thousand years. Sickle-cell anemia (page 119) is the byproduct of one of those defenses. People suffer from sickle-cell anemia when they inherit two copies of an allele called *HbS*. If they get one copy, however, they are only one-tenth as likely to get severe malaria. It's possible that *Plasmodium* parasites can't grow as fast inside red blood cells with the *HbS* allele, or that infected cells are eliminated from the body faster.

In any case, carrying a single *HbS* allele has provided a huge boost in fitness. Neil Hanchard, a geneticist at the Mayo Clinic in Minnesota, and his colleagues recently compared the DNA of people with the *HbS* allele in different parts of Africa, as well as people of African descent in Jamaica. The scientists found that the DNA surrounding the *HbS* allele was very similar from person to person. Such a similarity (known as linkage disequilibrium) is a sign of strong recent natural selection (page 127).

As people have moved around the world, they've taken their pathogens along for the ride. Their movements have brought diseases to people who had never been exposed to them before. In some cases, the encounter has been devastating. When Spanish conquistadors arrived in the New World, they brought with them an army of pathogens that had evolved in the unhealthy cities of Europe. The conquistadors themselves had some resistance to those diseases, thanks to a long coevolutionary relationship. But the people they met in the New World had left the Old World some 20,000 years ago. They had very little resistance to the diseases of the Spaniards and died in vast numbers. If not for the coevolution of humans and pathogens, world history would have taken a very different path.

Five centuries later, HIV moved into humans in Africa and then spread out to the rest of the world. Along the way, however, some people have proven remarkably resistant to the virus. They carry HIV in their blood for years, and yet their immune system never collapses. The reason appears to be that they are missing a receptor called CCR5, which HIV generally needs to make its way into immune cells.

The CCR5 mutation is remarkably common, especially in Europe. As many as 10% of people in some regions carry it. In Africa and elsewhere, however, it's practically nonexistent. The variations in DNA around the CCR5 mutation today suggest that the mutation arose about 700 years ago. That's long before HIV ever existed. Something else must have driven up the allele to its current levels in Europe.

Experiments suggest that the mutation may have been favored originally because it protected people against another major scourge. Some scientists have proposed the original defense was against bubonic plague, which killed off roughly a quarter of all Europeans in the fourteenth century. Others have argued that repeated epidemics of smallpox were more likely to have been the cause.

Parasite-driven variations in our species cannot be ignored in the search for new treatments for diseases. Scientists may find inspiration for new treatments

by looking at the ways in which defenses have evolved naturally. However, they must also bear in mind the complexities of that evolution. While natural selection may create new adaptations, they often have many different effects, some of which are dangerous. If we could get rid of our CCR5 receptors, it's conceivable that the rate of HIV infection might go down. But we might discover an unexpected side effect. CCR5 also shows signs of protecting us from other diseases. People who carry the CCR5 mutation that protects them against HIV are more likely to suffer more from diseases such as West Nile fever.

Evolution's Drug War

Just as we are shaped by our pathogens, our pathogens are reshaped by us. Host and pathogen can evolve new adaptations to each other. One of the most remarkable sets of adaptations first came to light in the late 1980s. Michael Zasloff, then a research scientist at the National Institutes of Health, made the discovery almost by accident. At the time, he was using frog eggs to study how cells use genes to make proteins. He would cut open African clawed frogs, remove their eggs, and then stitch them back up. After he had put enough of the frogs in a tank, he'd take them to a nearby stream and let them go. Sometimes the tank water became murky and putrid, and yet his frogs—even with their fresh wounds—did not become infected.

Zasloff suspected that the frogs were defending themselves by making some kind of antibiotic. He ground up frog skin until he isolated short chains of amino acids known as peptides. These particular peptides could kill bacteria, thanks to their negative charge, which attracted them to the positively charged membranes of bacteria, but not to the frog's own positively charged cells. Once the peptides made contact with the bacteria, they punched holes in their membranes, causing the bacteria to burst open.

If frogs had these antimicrobial peptides, Zasloff reasoned, then it was possible that other animals had them too. He turned out to be right: these powerful molecules are produced in animals ranging from insects to sharks to humans. We produce many different antimicrobial peptides on our skin, in the lining of our guts, and in our lungs. Mutations that interfere with the ability to produce them can make people dangerously vulnerable to infections.

It turns out that bacteria have evolved counterdefenses against antimicrobial peptides. Some bacteria make a protein that can cut a host's antimicrobial peptide into pieces before it can do any damage. Animals, in turn, have responded by stiffening the peptides, making them harder to cut. But microbes have responded with even more counterdefenses: some species secrete proteins that grab the antimicrobial peptides and prevent them from entering the bacteria.

One of the most potent ways for animals to overcome all of these strategies is to make lots of different kinds of antimicrobial peptides. New ones can be

produced by gene duplication, or by recruiting proteins that originally had other functions. The more antimicrobial peptides an animal makes, the harder it is for bacteria to evolve counterdefenses against them all. As a result, the genes for antimicrobial peptides have undergone more evolutionary change than any other group of genes found in mammals.

Silver Bullets

Scientists discovered the first antibiotics, made by bacteria and fungi, in the mid-1900s, and they soon ushered in a new chapter in the history of medicine. Infections that once almost certainly would have been lethal simply disappeared in a matter of days. Some optimists declared that infectious diseases would soon be a thing of the past.

But not long after antibiotics first became available, doctors began reporting that they sometimes failed. In the 1950s, Japanese doctors used antibiotics to battle outbreaks of dysentery caused by *E. coli*, only to watch the bacteria develop resistance to one drug after another.

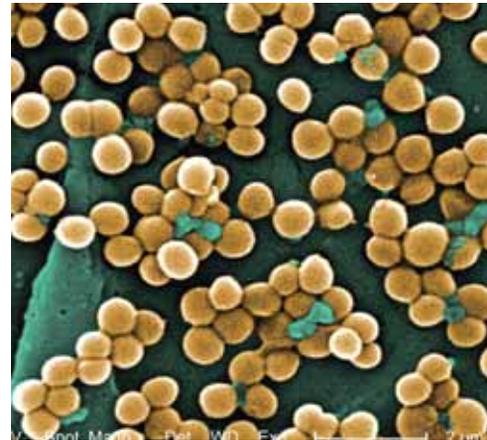
The Japanese doctors had come face to face with one of evolutionary medicine's most sobering lessons: medicine itself can drive the evolution of disease. The microbes that breed in an infection also mutate, and some of those mutations may help the microbes to resist an antibiotic. In the absence of an antibiotic, those mutations may not increase their fitness. In fact, they may even make the microbes grow more slowly. As a result, those mutations will remain rare. But antibiotics can alter the evolutionary landscape in a flash. If a mutation provides a microbe with even a little resistance, it will have more reproductive success than vulnerable microbes that die off altogether.

Resistance can evolve in many ways. Some mutations can make it harder for antibiotics to attack their targets inside the microbe. Some alter membrane pumps so that the microbes can flush the antibiotics out quickly before they can cause serious harm. As a lineage of resistant microbes takes over a population, new mutations emerge, some of which can make them even more resistant. The evolutionary costs of these mutations can be eliminated by new mutations, which allow the microbes to reproduce just as quickly as vulnerable strains. These compensatory mutations allow resistant microbes to survive when there are no antibiotics to give them an edge.

Much of what scientists understand now about the evolution of resistance has come from watching it take place in their laboratories. When Michael Zasloff discovered antimicrobial peptides, he immediately wondered if they might prove to be resistance-proof antibiotics. He teamed up with Graham Bell, an evolutionary biologist at McGill University in Montreal, and Bell's student Gabriel Perron to test his new drugs.

The researchers began by exposing *E. coli* to very low levels of an antimicrobial peptide. A few microbes survived, which the scientists used to start a new

colony. They then exposed the descendants of the survivors to a slightly higher concentration of the antimicrobial peptide. Again, most of the bacteria died, and they repeated the cycle, raising the concentration of the drug even more. After only 600 generations, 30 out of 32 colonies had done the impossible: they had become resistant to a full dose of antimicrobial peptides.



A human body can also serve as a living flask in which bacteria can become more resistant. Alexander Tomasz, a microbiologist at Rockefeller University, and his colleagues have tracked the evolution of resistance in a single patient, known only as JH (Figure 13.6). In 2000, JH developed an infection of *Staphylococcus aureus* bacteria in a heart valve. He was treated with an antibiotic called rifampin, which failed to work; his doctors



Figure 13.6 In 2000 a patient known as JH developed an infection of *Staphylococcus aureus* (top right). Doctors took a series of blood samples and identified the new mutations that arose in the bacteria over the course of the infection. Mutations that conferred more resistance to antibiotics were favored by natural selection. (Adapted from Mwangi et al., 2007)

then gave him heavy doses of more powerful antibiotics, such as vancomycin, which failed as well. After three months of treatment, surgeons replaced his heart valve, but he died two weeks later.

Tomasz and his colleagues were able to isolate the bacteria from a series of five blood samples that doctors had taken from JH over the course of the infection. They sequenced a *Staphylococcus aureus* genome from the first sample and then analyzed the DNA from later samples. The bacteria from the later samples shared a set of genetic markers with the original one, demonstrating that they were their descendants, rather than new arrivals from a separate infection.

Over the course of the infection, Tomasz and his colleagues found, the bacteria evolved increased resistance to three out of four antibiotics. The bacteria became eight times more resistant to vancomycin, for example, and 1,000 times more resistant to rifampin. These changes were the result of mutations that arose in the bacteria and were favored by natural selection. In all, Tomasz and his colleagues pinpointed 35 mutations that distinguished the bacteria in the last sample from those in the first. They could even see the mutations accumulate from one sample to the next. Some of the mutations are familiar to scientists from other resistant strains of bacteria; others are new, altering the bacteria in ways the scientists have yet to understand.

The bacteria in JH built up new mutations through vertical gene transfer. But bacteria can also acquire genes through horizontal gene transfer, which can speed up the evolution of antibiotic resistance dramatically. Many species of bacteria that live in the soil have genes that can, by coincidence, provide resistance to antibiotics; from time to time, they can pass those genes on to bacteria that cause human infections. Once genes evolve high levels of resistance, they can move from one species to another, either in the soil or in our bodies.

Resistance genes may start out being transferred individually, but over time they can be combined. Some of them are carried on ringlets of DNA called plasmids that bacteria exchange. Those plasmids sometimes mutate, splicing together their DNA so that resistance genes from separate plasmids can end up together on one. A plasmid resistant to two antibiotics may raise the fitness of bacteria much more than a plasmid with just one. And if it should pick up a third resistance gene, its fitness rises even more. This is probably what happened in Japan during the dysentery outbreaks: drugs fostered the evolution of *E. coli* resistant to several antibiotics.

Today, new strains of pathogens are emerging that are resistant to just about every antibiotic on the market. The only way to cope with the crisis is to treat it as an evolutionary phenomenon. It's not enough to recognize that evolution is taking place; doctors need to understand the complexities of that evolution. Some hospitals have tried to fight resistant bacteria by rotating their antibiotics over the course of a few months, so that the bacteria don't have much time to evolve increased resistance. That strategy hasn't worked, and mathematical models of evolution show why: a more promising strategy, according to the models, is to give different antibiotics to different patients, to slow down the transmission of bacteria between them.

Nature may be able to give scientists some clues to new strategies. It's striking, for example, that Zasloff, Bell, and Perron were able to observe bacteria evolve high levels of resistance to antimicrobial peptides in a matter of weeks, while bacteria have not evolved such resistance over millions of years in the natural world. That's because the scientists exposed *E. coli* to an intense dose of a single kind of molecule. Our bodies, on the other hand, have evolved many different antimicrobial peptides, all of which were modified into more effective forms.

Unfortunately, modern medicine tends to work more like Zasloff's experiment than like our own evolution. It may be time to find a new, more complex strategy. At the same time, however, some old-fashioned strategies still work well. Washing your hands with soap is a very effective way to avoid getting infected, and it does not foster the evolution of resistant strains.

Genetic Drift and Disease

In every generation, many harmful mutations spontaneously arise. They may produce life-threatening genetic disorders, or they may make people more prone to diseases like cancer later in life. Natural selection can eliminate many of them because they have such strong effects on reproductive success. But natural selection's broom doesn't sweep perfectly clean. Because natural selection favors sickle-cell heterozygotes, for example, it cannot eliminate sickle-cell anemia. Natural selection is also weak in small populations, where genetic drift can allow even harmful alleles to spread to high frequencies.

On the remote Pacific island of Pingelap, for example, 5% of the population is completely color-blind. By comparison, only 0.003% of the United States population suffers from this condition, called achromatopsia. Historical research indicates that, around 1775, a typhoon reduced an already small population down to just 20 survivors. One of those survivors carried one copy of the achromatopsia allele. Thanks to that fluke of history, 5% of the island's current residents now suffer from the disease because they carry two copies of the original allele, while 30% carry a single copy.

Islands are not the only place where genetic drift drives up genetic disorders. In the late 1600s, a small group of closely related farmers traveled from Switzerland to Germany and finally to the United States, where they became known as the Amish. Shunning intermarriage with other groups, they kept to themselves, and they still do today. In effect, they've created a genetic island in the middle of a continent. Not surprisingly, the Amish suffer high rates of certain genetic disorders, such as Ellis-van Creveld syndrome, which leads to extra fingers and dwarfism (**Figure 13.7**). Scientists have been able to trace that disorder to a single Amish couple who immigrated to Pennsylvania in 1744.

Genetic drift's biggest impact on human health probably occurred about 100,000 years ago. *Homo sapiens* evolved in Africa about 200,000 years ago (page 139). For at least 100,000 years, our species remained on that continent,

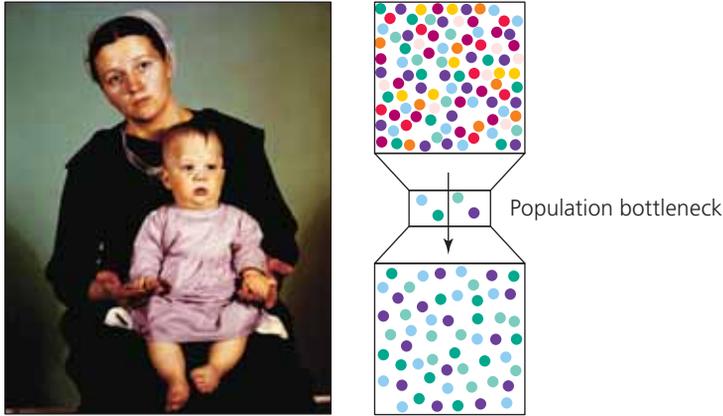


Figure 13.7 Some human populations suffer from high rates of certain genetic disorders. The Amish, for example, are unusually likely to suffer from Ellis–van Creveld syndrome, which causes deformities to the skeleton. The Amish descend from a small group of immigrants from Europe who settled in the United States. Because their population was so small, their genotypes were not a representative sample of the genotypes in their homeland. Even one person with genes for a rare genetic disorder could make it much more common in the population.

evolving an increasing level of genetic diversity. Then a very small number of Africans—probably originating in or around Ethiopia—migrated out of Africa. Their descendants would people Europe, Asia, and Australia. This migration out of Africa is recorded in the collective DNA of our species. The genetic variation among populations in Africa is much larger than the diversity found on the rest of the planet, even though Africans only make up 13% of the world’s population.

The migrants who left Africa were not a representative sample of the continent’s population. Like the settlers of islands, they had unusually high numbers of certain alleles, including some that cause diseases. One of these diseases is myotonic dystrophy, a genetic disorder that causes muscles to waste away slowly. It’s triggered by a sequence of repetitive DNA near a gene for a muscle protein, known as DM. On rare occasions, the repetitive DNA is accidentally mutated into a longer segment of repetitive DNA. In later generations, that longer segment can become longer still. Eventually, it becomes so long that it disrupts the gene.

Myotonic dystrophy is rare in most of the world, but in sub-Saharan Africa it’s practically nonexistent. To investigate why, Sarah Tishkoff (page 140) and her colleagues analyzed the stretch of DNA that includes the DM gene, comparing segments from 25 different populations around the world. They found that most Africans had only a few copies of the repetitive DNA. In Ethiopia, however, some populations had longer chunks of repetitive DNA, and these longer chunks are even more common out of Africa.

Tishkoff concluded that a mutation arose in an early Ethiopian, expanding the repetitive DNA near the DM gene. That Ethiopian’s descendants were part of the

migration out of Africa that led to the peopling of Europe and Asia. As the migrants rapidly expanded across the other continents, they passed down this repetitive DNA, which then mutated again in some people into a form that caused myotonic dystrophy.

Maladapted

Natural selection can adapt organisms to their changing environments, but it does not produce perfect forms of life. In many cases, natural selection actually leads not to adaptation but to maladaptation—the source of many of our medical problems.

Some of our maladaptations are the result of tinkering with old body plans for new environments. Evolution can modify only what already exists, rather than ripping up old plans and creating new ones from scratch. As a result, many structures have glaring weaknesses. When male human embryos develop, for example, their testes start out high up in their bodies. Over time, the testicles descend. As they migrate, they push down on the body wall, creating a weak spot. It is here that a loop of intestine can slip through, creating an inguinal hernia.

Why should the testicles make such a strange journey? A comparison with a shark shows why. Shark testicles develop in the animal's abdomen and stay there. As a result, sharks don't get hernias, because the wall of muscle surrounding their bodies is intact. But when mammals evolved a warm-blooded metabolism, a problem emerged. Sperm are delicate, and overheating them can kill them off. Mammal testicles descended until they had formed a sac outside the body wall. There they could stay cooler than the core of the body.

Some diseases emerge from natural selection when it favors genes that come into conflict, as in the case of babies and their mothers. Preeclampsia in pregnant women is not the inadvertent side effect of some adaptation that benefits a woman's health; if David Haig is right, it is the direct effect of natural selection on the genes that babies use to get nutrients from their mothers.

The Natural Selection of Cancer

Darwin first recognized that natural selection could operate in a population of individuals. But selection can also operate at other levels. Cells, for example, can compete with each other within our bodies. We know this particular kind of natural selection as cancer.

Every time a cell divides, there's a tiny chance that it will mutate. In some cases, those mutations strike genes that control the rate at which cells divide. These gatekeeper genes ensure that cells divide only when they need to, and not when they shouldn't. For example, when you cut yourself, cells in the skin and other tissues rapidly divide to heal the wound. If they were to keep dividing, they'd create an expanding mass of flesh. Mutations to these gatekeeper genes allow cells to grow faster than their neighbors. In some cases, these runaway mutant cells can form a tumor.

Within a developing tumor, cells continue to mutate, and cells with mutations that speed up their growth come to dominate the population of cancer cells (**Figure 13.8**). Some genes, for example, normally only become active in sperm cells, helping them to grow rapidly throughout a man's adult life. Normally these sperm-growth genes are kept silent in other parts of the body. But mutations can switch them on in cancer cells, making them divide faster.

Natural selection not only allows cancers to become more aggressive, but also to become harder to treat. As tumors grow, some mutations may make them resistant to drugs. Much like bacteria, those resistant mutants will be able to grow faster than susceptible cancer cells. The same mathematical models that help evolutionary biologists to understand the rise of antibiotic-resistant bacteria are now being adapted to shed light on the evolution of resistance to anti-cancer drugs in tumors.

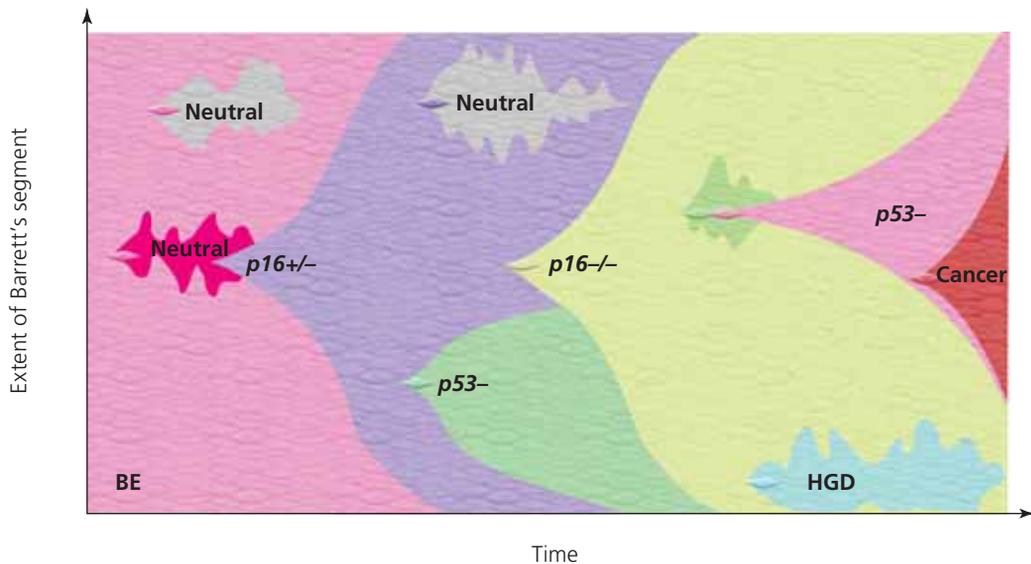


Figure 13.8 Cancer biologists have come to view tumors as the result of a special form of natural selection. This diagram shows how cancer can arise in the esophagus. In a condition known as Barrett's esophagus, a segment becomes precancerous (indicated here by the pink "BE" cells). Over time, as the esophagus cells divide, mutations arise. Many mutations are neutral, and some slow down a cell's rate of division. But every now and then mutations arise that speed up a cell's growth rate. The cell's descendants come to dominate the surrounding tissue. Later, a new mutation arises in one of its descendants, raising its fitness even further. Eventually a cell acquires enough mutations to develop into full-blown cancer of the esophagus. (Adapted from Crespi and Summers, 2005)

The fact that cancer cells follow the rules of natural selection suggests that it's important to start treating tumors as early as possible, because the longer they evolve, the more likely a resistant mutation may spontaneously arise in a cell. Evolutionary theory has led some researchers to explore using continuous, low-level treatments of cancers instead of a large pulse of drugs.

Defending Against Our Own Imperfection

Like hernias, cancer is a maladaptation of our bodies. It is the inescapable risk of being a multicellular animal. In order to make our bodies function properly, the cells inside them must cooperate. But cooperation always opens the way for cheating to evolve (page 250). Cancer, in other words, is a tragedy of the commons.

Because cancer can be lethal, natural selection has produced defenses against it. If a cell becomes precancerous, for example, proteins within the cell detect the change and trigger it to commit suicide. Some precancerous cells evade this checkpoint, however, but the vast majority of them are killed off by the immune system.

The very architecture of our bodies shows signs of having adapted to fight against cancer. One of the best defended organs is the colon, which is not surprising because it's so vulnerable to the disease. Every day, 100 billion cells lining the inner wall of the colon are shed, replaced by new cells generated from underlying stem cells. They continue to proliferate throughout our lifetime, and all that cell division provides a tremendous opportunity for a cell to turn cancerous.

Instead of a smooth sheet of cells, the colon's inner wall is made up of hundreds of millions of tiny pockets, called crypts. Each crypt contains about 2,000 cells. Stem cells at the bottom of each crypt continually divide, each time producing a differentiated cell and another stem cell. The new cells get pushed up the sides of the crypt until they reach the top and are shed.

Natalia Komarova, a mathematician at the University of California, Irvine, and her colleagues sought to understand the anatomy of the crypts by building a mathematical model of the colon. Different arrangements of cells in the crypts lead to different risks for cancer. If the cells go through many divisions over a person's life, they have a higher chance of mutating and turning cancerous. One alternative would be for stem cells to produce only a single generation of differentiated cells, which would then be shed. But that arrangement would create a risk of its own: it would require a vast number of stem cells, each of which would have to divide rapidly to produce a differentiated cell and a new stem cell.

Komarova found that the actual shape of crypts is a good solution that avoids these two extremes. Cells in crypts get to be only a few generations old at most before they are shed, and it takes relatively few stem cells to keep each crypt regenerating itself. Colon cancer is the third most common form of cancer in the United States, but, if Komarova is right, the architecture of the human colon keeps it from being far more common.

Old Age: Evolution's Side Effect

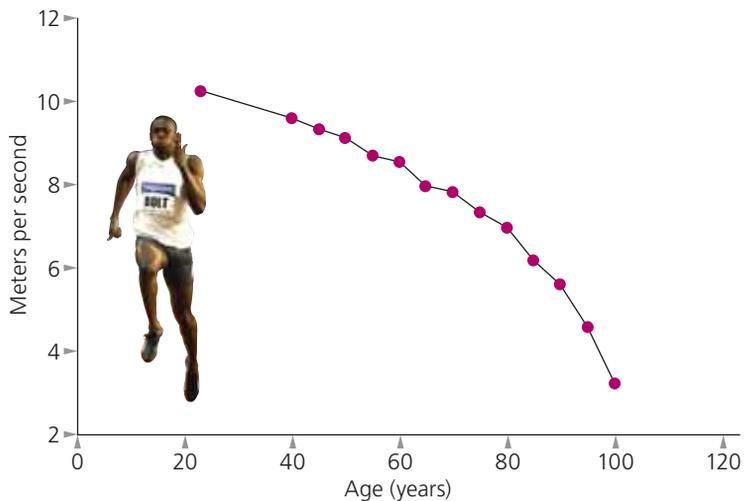
A child born in 1900 could expect to live, on average, for 47 years. A child born today can expect to live 78 years. Much of that change can be credited to clean drinking water, decent sewer systems, a steady supply of food, and improved medical care. But there's actually less to our longer lifespan than meets the eye. Most of the progress has come from saving the lives of children, as well as young mothers who used to die in childbirth. At the other end of life, people today still age in much the same way people did a hundred years ago. Their bones get brittle, they lose their stamina, and they lose their ability to fight infections. The decline begins in middle age and continues gradually for decades (**Figure 13.9**).

Most animals age in much the same way, although some get old faster than others. Blue whales may live 200 years, while fruit flies live for only a matter of weeks. Our closest relatives, the chimpanzees, rarely survive past 50 years, even under the best conditions. In the past, scientists speculated that the particular lifespan of each species was itself an adaptation, set by natural selection. But the evidence now shows that that's not the case. Aging is one of the unpleasant byproducts of natural selection, much like sickle-cell anemia.

The English biologist J. B. S. Haldane was the first to recognize the evolutionary nature of aging. In the 1930s he studied Huntington's disease, a genetic disorder that slowly destroys the nervous system. It is unusually common for a devastating genetic disorder: about one in 18,000 people suffers from the disease. If Huntington's disease resulted only from spontaneous mutations in sperm or eggs, Haldane realized, it should be much rarer than that.

Haldane proposed that the reason for Huntington's disease being so common was its late onset. It does not begin to cripple most people until they are in their forties. That would have provided them with plenty of time to raise children, passing on the disease-triggering alleles to the next generation before they died.

Figure 13.9 This graph illustrates how the human body declines with age. Scientists produced it by gathering the world records for the men's 100 meter run by age groups. They then calculated the average speed of each champion runner. The maximum speed starts dropping in the third decade of life. Evolutionary biologists seek to understand how this decline evolved. (Adapted from Koella and Stearns, 2008)



If Huntington's disease claimed its victims when they were teenagers, it would have been much rarer.

Haldane recognized an important feature of natural selection: it has different effects at different times in life. It acts weakly on mutations with effects in old age, and it acts strongly on mutations with effects in childhood and the prime reproductive years.

Since then, evolutionary biologists have recast Haldane's ideas in more precise terms, building mathematical models to calculate how natural selection fades with age. George Williams (page 279) also proposed that a mutation that benefits an organism while it's young, will be favored by natural selection, even if it becomes harmful in old age. Its benefit outweighs its cost. Thomas Kirkwood, an evolutionary biologist at Newcastle University in England, argues that organisms face a trade-off between reproduction and repairing their cells. If they put all their energy into repairing their cells, they will slow down the aging process, but they won't be able to produce as many offspring as other organisms. Fast-breeding individuals pass down more of their genes, and as a result the population cannot repair its cells very well. They get old.

To test these ideas, scientists have run experiments on animals. Stephen Stearns, an evolutionary biologist at Yale University, and his colleagues wondered if they could alter the longevity of fruit flies. They reared hundreds of fruit flies in two sets of vials. Twice a week, the scientists killed most of the flies in one set of vials and replaced them with some of their offspring. The other flies in the other vials could live longer, because, twice a week, the scientists only killed a small fraction of the flies.

The flies getting killed off faster didn't benefit as much from mutations that acted on them late in life. There were just too few of them left alive by then. In fact, mutations that caused harm late in life could be favored by natural selection if they boosted the reproductive success of the flies while they were still young.

That was the prediction, at any rate—and that's what Stearns and his colleagues discovered. After killing off the flies for generations, they relented and let the flies live out their natural lifespans. The flies that suffered high mortality evolved to grow up faster and to become ready to mate sooner. They were also more likely to die sooner than the flies that didn't face such high mortality.

This trade-off can explain how our bodies have ended up defending us from diseases in a less-than-perfect way. One of the most important controls against cancer is the p53 tumor-suppressor protein. It responds to stress inside cells, particularly to damaged DNA, which may signal the first steps towards cancer. It can cause a cell to die or to stop dividing. In either case, p53 prevents the cell from possibly growing into a tumor, but it takes a toll in the process. As the years pass, p53 can kill or stunt so many cells that tissues can no longer renew themselves. By forcing cells into early retirement, p53 may prevent them from becoming tumors, but the cells may damage surrounding tissue and release abnormal proteins that stimulate the growth of cancer cells.

In other words, p53 is a very effective stopgap defense against cancer. It helps keep young people relatively cancer free. But it also damages the body in the

process. The damage accumulates slowly, over the course of many years. By the time it has an impact on us, we're so old that natural selection cannot alter it.

None of this means that we can't hope to extend the human lifespan. Some of the most promising results in the study of longevity have come from experiments in which scientists reduce the amount of food animals can eat. If they cut the normal number of calories in an animal's diet, it often lives much longer. Some experiments suggest that restricting an animal's diet triggers a special response in its cells. They begin to produce proteins that can repair the damage caused by the stress of not getting enough to eat.

This response appears to be an ancient strategy, given that the same stress-fighting genes can be found in animals ranging from nematode worms to mice. These genes may have evolved as a way to cope with short-term stress, such as famines and droughts. Scientists who study nematode worms have found that they can double the lifespan of the animals with mutations that keep these genes switched on. The genes may be able to continually repair damage to cells, fighting the effects of aging. Restricting calories may have the same effect, by keeping the genes switched on permanently.

David Sinclair, a Harvard biochemist, and his colleagues have discovered that certain chemicals can turn on these genes, and they have been trying to turn one of those compounds, resveratrol, into an anti-aging drug. Resveratrol may well do what they hope it will, but it may also have unexpected side effects. Nicole Jenkins, a biologist at the Buck Institute for Age Research in California, and her colleagues have found that mutations that bring long life to nematode worms actually lower their fitness. The scientists put 50 of the long-lived worms in a dish with 50 normal worms and then let them breed. Jenkins then randomly picked out 100 of the eggs and used them to rear the next generation. The long-lived worms were just as fertile as the normal worms, Jenkins found, and yet within just a few generations they had vanished from the dish. They had been outcompeted by the shorter-lived worms.

Natural selection, once again, did not favor long life simply for long life's sake. Jenkins's experiment raises the possibility that taking resveratrol or some other medication to prolong aging may bring with it some kinds of side effects. It would be nice to have an elixir of life, but an understanding of evolution's trade-offs shows why that's so unlikely.

Sick from Sexual Conflict

The best strategy for mating and rearing offspring is not the same for males and females. As a result, sexual conflicts can evolve, producing traits and behaviors that can seem downright destructive—such as the habit some birds have of abandoning their young (page 285). David Haig and other researchers are now investigating the impacts of sexual conflict on human health. Sexual conflict can

help to explain preeclampsia as a tug-of-war between mothers and fetuses. In cases such as these, different genes come into conflict.

But sexual conflict can also leave a mark on a single gene. Scientists have identified dozens of genes that are imprinted (page 286). Animals inherit two alleles of a gene from their parents, but the copy from one parent is almost always silenced. Gene imprinting may be a strategy that has evolved to let one parent reduce the effect of a gene that benefits the other parent. In mice, for example, a gene called *Igf2* stimulates the growth of fetuses. The female's copy is silenced. Likewise, a gene called *Igf2r* limits the growth of fetuses. The father's copy, not the mother's, is silenced.

Scientists learned about the roles of these genes by disrupting them. If a mouse's paternal copy of *Igf2* is disabled, for example, the mouse develops to be 40% smaller at birth. If its maternal copy of *Igf2r* is disabled, it is 25% bigger than average. But nature, it turns out, has also produced this experiments in humans.

Sometimes a child is born expressing both copies of *Igf2*, instead of only the father's. The child will be born unusually big—weighing 50% more than an average baby. The child will also suffer a range of other symptoms of unchecked growth. Its heart and other organs are often enlarged, causing them to malfunction. Its tongue may grow so big that the child has trouble breathing, eating, and speaking. Sometimes one half of the body grows faster than the other, and the child may suffer tumors in the liver and kidneys. This condition, which strikes 1 in every 35,000 children, was recognized long before it was linked to *Igf2*. Doctors dubbed it Beckwith-Wiedemann syndrome.

One in 75,000 children suffers the opposite problem. In these children, the father's copy of *Igf2* is silenced, so that they produce no *Igf2* at all. This silencing leads to Silver-Russell syndrome. Children suffering this condition are born small, without much fat underneath their skin. After birth, they grow slowly, ending up far shorter than average at maturity.

Modern medicine may also be disrupting the delicate balance that has evolved between maternal and paternal genes. A growing number of couples who have trouble having children turn to in vitro fertilization (IVF): doctors inject sperm directly into eggs in a dish. Once the eggs start dividing, they implant them in the woman's uterus. Jane Halliday, a geneticist at the University of Melbourne, and her colleagues surveyed 1.3 million birth records from the Australian state of Victoria, comparing children conceived through IVF with other children. They found that children conceived by IVF were nine times more likely to develop Beckwith-Wiedemann syndrome than normal children.

IVF may raise the risk of Beckwith-Wiedemann syndrome because it bypasses the normal process by which genes are imprinted in fertilized eggs. When a sperm delivers its DNA into an egg, the methyl groups that cap both male and female genes are stripped away. Only then do special proteins in the fertilized egg put methyl groups back on its DNA.

Eamonn Maher, a geneticist at the University of Birmingham in England, has suggested that this imprinting requires a special set of compounds made by the

uterus, compounds that are missing from the medium in which IVF eggs are kept.

Another possible explanation is that the risk of Beckwith-Wiedemann syndrome may have something to do with the infertility of the women who resort to IVF. Whatever makes it hard for them to conceive may also impair their eggs' ability to imprint genes.

In either case, it's clear that gene imprinting is a delicately balanced process, and disrupting it can have lifelong effects on people. Evolutionary medicine can explain why this part of development is so fragile and so susceptible to malfunctioning: because evolution did not find an optimal solution. In fact, thanks to sexual conflict, it *could* not.

Mismatched with Modern Life

For people in the United States and other developed countries, it's nearly impossible to imagine the suffering infectious diseases brought a century ago. Along with tremendous outbreaks of such scourges as influenza, many other diseases also steadily killed off people year in and year out. Since then, the death rate from infectious diseases has dropped dramatically (**Figure 13.10**).

Yet, in the countries that have experienced these drops in infectious diseases, people have seen an increase in another kind of disease. Rather than being caused by pathogens, these rising diseases are caused by our own immune sys-

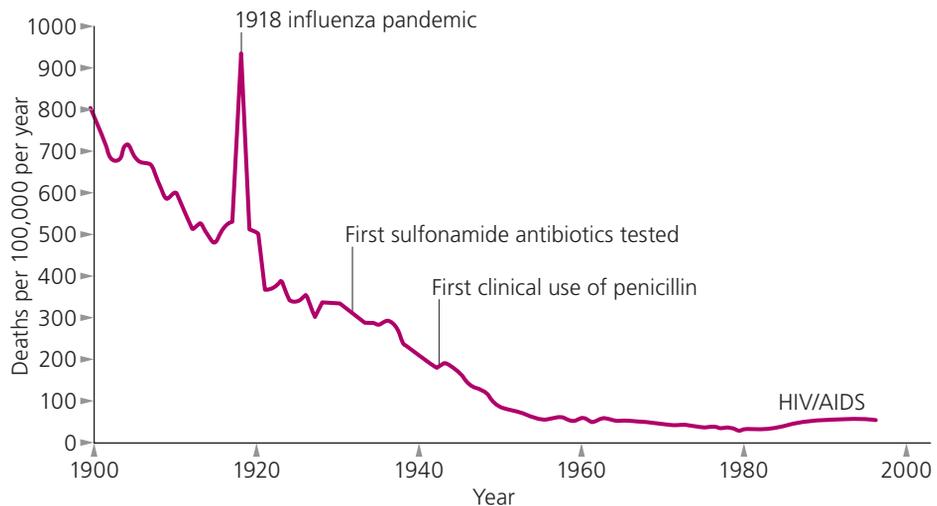


Figure 13.10 The death rate from infectious diseases dropped dramatically in the United States over the twentieth century. It began to decline thanks to better hygiene, clean drinking water, and better food. The invention of antibiotics in the mid-1900s helped push the death rate even lower. The HIV epidemic that began in the late 1980s raised the death rate, although it remained far lower than at the beginning of the century. (Adapted from Koella and Stearns, 2008)

tems. Crohn's disease, for example, occurs when the immune system attacks the lining of the intestines. Asthma is caused by inflammation in the lungs. Type 1 diabetes occurs when immune cells attack insulin-producing cells in the pancreas. All these diseases were once rare in the United States and other developed countries, but now are increasingly common.

It's intriguing to note how these diseases seemed to have followed in the wake of affluence. They first emerged in countries such as England and the United States, which were among the first nations to go through an industrial revolution and then improve their public health. Later, when other countries went through the same transition, they also saw a rise in autoimmune diseases. Within countries, a similar pattern can be found. In Venezuela, for example, the population is split mainly between cities and farms, with some Indians still living in isolated villages in the rain forest. Venezuelan city dwellers have higher rates of allergies than Venezuelan farmers, and Venezuelan Indians have no allergies to speak of.

In 1989, David Strachan, an epidemiologist at the London School of Hygiene and Tropical Medicine, suggested that these autoimmune diseases were breaking out because children had become too clean. They were not being exposed to dirt and dust, and they were not being infected by bacteria and parasitic worms. As a result, their immune systems were attacking themselves, rather than pathogens. Today, scientists refer to this as the hygiene hypothesis.

The hygiene hypothesis builds on the fact that life in the twenty-first century is very different from what it had been for most of our 200-million-year history as mammals. Our ancestors were under constant assault from pathogens. They could not respond with antibiotics or bandages. Instead, natural selection responded by fine-tuning the immune system, which became better able to cope with the infections. But if the immune system became too aggressive in fighting infections, it could actually do more harm than good. If it attacked any peculiar-looking cell, it might wipe out the intestinal bacteria we depend on for our nutrition. It might even damage our own tissues by releasing too many toxic chemicals.

It appears that the immune system has evolved to an uneasy truce with pathogens. When the immune system encounters certain kinds of bacteria and intestinal worms, it becomes subdued. In effect, it learns to tolerate our inner companions. This truce is an ancient one, shared by other vertebrates. If you dissect a healthy opossum or gorilla, you'll find not just bacteria but several species of worms living inside it without triggering a major reaction from the immune system.

When our own species first emerged 200,000 years ago, our ancestors inherited this tolerant immune system. But suddenly, in just the past few decades, a large fraction of our species has entered into an entirely new relationship with the life within us. Many children do not get exposed to many microbes, playing inside houses rather than out in the dirt. When they get sick from bacteria, they are treated with antibiotics that kill many harmless bacteria along with the pathogenic ones. Intestinal worms are now a thing of the past.

According to the hygiene hypothesis, our bodies are maladapted to this kind of upbringing. The immune system is primed to receive calming signals from bacteria and

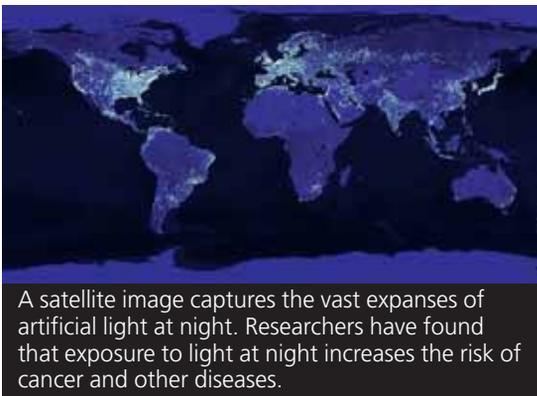
worms, but it gets none. In some individuals, it begins to overreact, either to their own bodies or to normally harmless substances such as peanuts or cat dander.

Scientists have been testing the hygiene hypothesis from many different directions, and their results are encouraging. Martin Blaser and Yu Chen, microbiologists at New York University, have been looking at the effects of one particularly important species of bacteria called *Helicobacter pylori*. *H. pylori* lives in the stomach, and it's had a particularly intimate relationship with our species. Its phylogeny mirrors our own. *H. pylori* strains that live in Native Americans are more closely related to the ones in Asian people; African strains of *H. pylori* are more diverse than strains on other continents.

H. pylori was ubiquitous in our species before the advent of antibiotics, but it's now on the decline. Only one in five American children now carries it. Blaser and Chen analyzed the medical histories of more than 7,400 people who took part in a nutrition survey. As part of the survey, researchers collected stool samples. Blaser and Chen checked the samples for signs of *H. pylori*. In 2008, they reported that children between three and 13 years old who carried *H. pylori* were 59% less likely to have asthma than children who were free of the bacteria. They were also less likely to have hay fever or eczema. Other experiments suggest that *H. pylori* triggers the body to make certain kinds of immune cells, known as Th17 cells, which regulate the way the body will respond to invading bacteria.

On the whole, the public is healthier, thanks to antibiotics and better hygiene, but that's small comfort to people who suffer from the autoimmune diseases that may have been produced as a side effect. Some researchers are using the hygiene hypothesis to figure out ways to treat these diseases of modernity. Some doctors have dispensed parasitic worms to people suffering from Crohn's disease, and they've found that the parasites tend to reduce the symptoms. These experiments are just a proof of principle, however. Ideally, doctors would be able to prescribe drugs that would trigger the same response as the worms and bacteria, without the harm that they can cause. (*H. pylori*, for example, may protect children from asthma, but it also increases the chance of developing stomach cancer.) It's possible that someday people will swallow pills containing surface proteins from parasitic worms or bacteria to teach their immune systems how to behave themselves.

Modern medicine is not the only sudden change our bodies face. Animals, plants, and many other organisms have evolved an internal clock that controls how their bodies function at different times of day. The human body clock controls the expression of many genes and the release of hormones. It creates 24-hour fluctuations in our appetite, our body temperature, and our wakefulness. When sunlight enters our eyes each day, it resets the clock. Today, however, we are confusing our bodies. We keep lights on well past dark, for example,



A satellite image captures the vast expanses of artificial light at night. Researchers have found that exposure to light at night increases the risk of cancer and other diseases.

and we sometimes fly from one time zone to another. Lights at night and long-distance plane travel have both been linked to an increased risk of cancer, possibly because they disrupt our hormone cycles.

The sudden mismatches between our bodies and modern life have changed the fitness of our alleles. As we've seen in previous chapters, the fitness of a mutation is not some absolute value. It depends on the other genes with which a mutant gene shares its genome, and it also depends on the environment in which its owner lives. This perspective changes the way we think about genetic disorders. What is healthy in one century may not be healthy in another century.

Evolutionary Medicine: Gloom and Hope

Evolutionary medicine is a sobering science. It reveals the many obstacles we face in fighting diseases, from the rapid evolution of antibiotic resistance to the deep vulnerabilities that make us susceptible to illnesses. But evolutionary medicine can also offer researchers inspiration and guidance in the struggle to improve our health. Models of evolution can show which antibiotic treatments will lead to more resistance, and which treatments will lower it. Scientists are also building similar models to help avoid the evolution of tumors that are resistant to chemotherapy and the evolution of HIV strains that resist antiviral drugs.

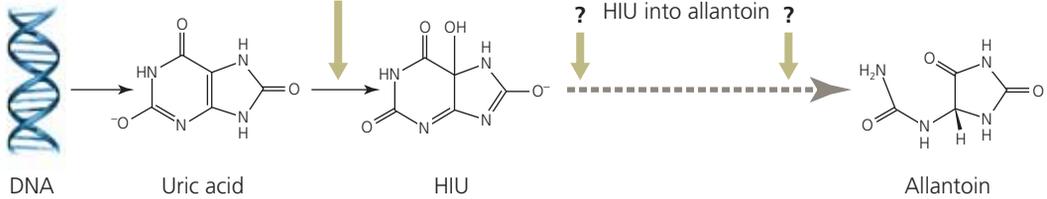
Evolutionary biology also points the way to potential new treatments. We humans are particularly vulnerable to a form of blood poisoning called hyperuricemia—an excess of a chemical called uric acid. All organisms, from bacteria to humans, break down DNA in their food with a set of proteins so that they can use its fragments to build new molecules. Most species break it down until all that's left is a relatively harmless waste product called allantoin (**Figure 13.11**). But humans can't reach the end of this pathway. Instead, we stop with an intermediate molecule called uric acid. We excrete the uric acid out of our kidneys in our urine.

Stopping with uric acid brings special risks for us. If we can't flush it out of our bodies fast enough, it can cause all kinds of damage. Uric acid can crystallize into painful kidney stones, or it can cause gout, a disease caused by sand-like grains of uric acid that build up in the extremities, such as the joints of the toes. Uric acid can also contribute to hypertension and cardiovascular disease. When cancer treatments kill off tumor cells, they dump their DNA into the bloodstream. If patients can't handle the surge of uric acid that follows, they may suffer kidney failure.

Exactly how other animals turn uric acid into allantoin has long been a mystery. The first step requires a protein called urate oxidase, which turns uric acid into an intermediate called HIU. But until recently scientists didn't know how HIU turns into allantoin.

A

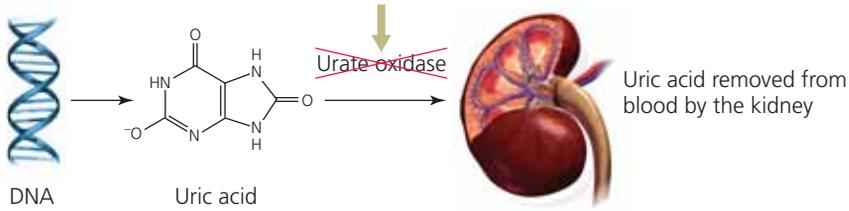
FROG



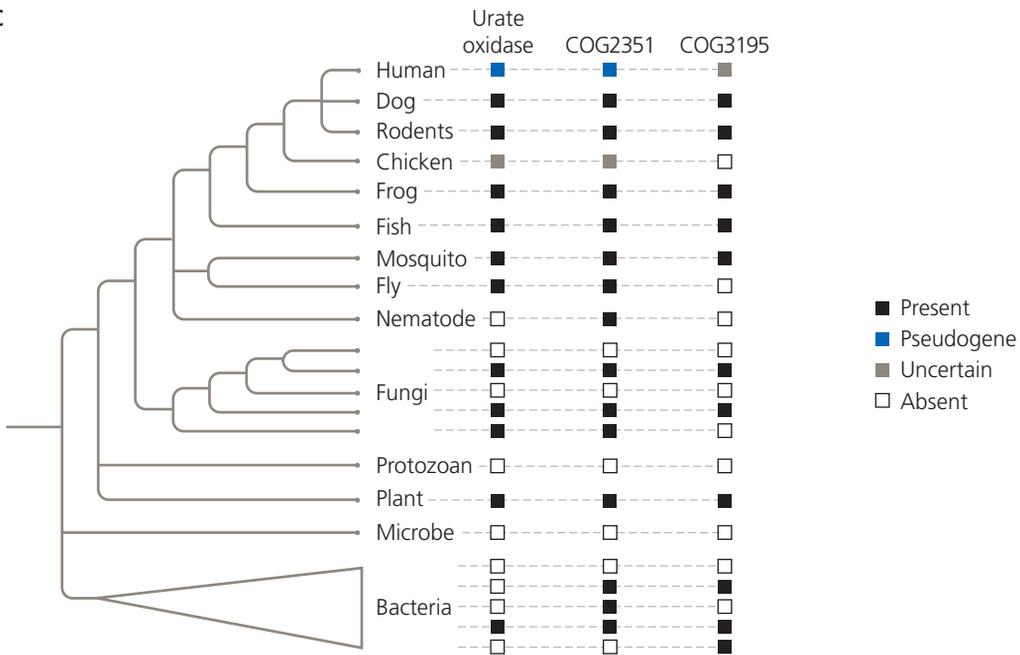
B

HUMAN

Mutation produces pseudogene for urate oxidase in apes and humans

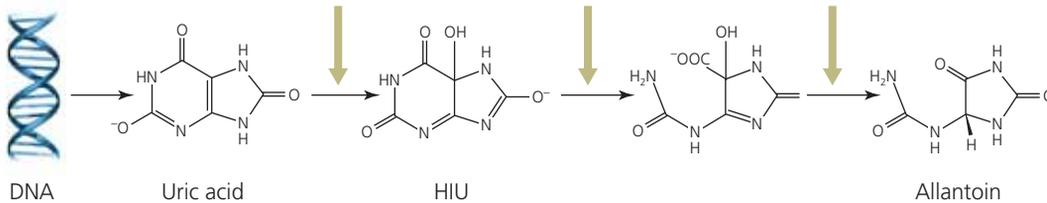


C



D

FROG



Our ancestors lost the ability to make allantoin a long time ago—about 20 million years ago, in fact. In 2002, Naoyuki Takahata and colleagues at Kyoto University showed that chimpanzees, gorillas, orangutans and humans all share the same pseudogene for urate oxidase. That protein must have been disabled in the common ancestor of humans and other great apes. Losing urate oxidase raised levels of uric acid in the blood of primates. It's possible that change had some benefit—researchers have suggested that it may have helped to protect primates from dangerously low levels of salt. Whatever the advantage, however, primates also became vulnerable to dangerously high levels of uric acid, a danger we still face today.

Doctors have tried treating gout and other uric-acid-triggered diseases by giving patients urate oxidase, in the hopes of breaking uric acid down into a less dangerous form, but this treatment has not been very successful. Some researchers suspect its failure is due to the fact that urate oxidase is just the first of a series of proteins that turn uric acid into harmless allantoin. To treat high levels of uric acid, some scientists suggest, we must re-create the lost chemical reactions of our ancestors.

Recently, Riccardo Percudani, a molecular biologist at the University of Parma in Italy, and his colleagues decided to find the missing proteins. They reasoned that they must have coevolved with urate oxidase. If the urate oxidase gene was disabled and became a pseudogene in a lineage, for example, the missing proteins were likely to have become pseudogenes as well. In other cases, all of the proteins might have been completely deleted. The scientists also took advantage of the fact that genes that function together are often located close to one another in a genome, sometimes even fused together. It was possible, they reasoned, that the genes for the missing proteins were close to the gene for urate oxidase.

The researchers searched online databases of genomes noting which ones contained working versions of uric oxidase genes or pseudogenes and which lacked any uric oxidase gene at all. They then looked for other genes that showed associations with the uric oxidase gene from one species to another. Their search yielded two genes. No one had figured out what those two genes were for. Percudani and his colleagues synthesized proteins according to the sequence of the two genes and mixed them with uric acid. The scientists discovered that each protein made a precise cut in the bonds of the uric acid, and together they could turn it into allantoin. The discovery of these two missing proteins opens the possibility of an effective treatment for hyperuracemia. In effect, doctors

Figure 13.11 Opposite: Humans are vulnerable to diseases such as gout because they cannot completely break down uric acid, a byproduct of DNA. A: Most animals, such as frogs, can transform uric acid into a harmless molecule called allantoin. They use a series of proteins to carry out the transformation, starting with urate oxidase. B: In humans, the urate oxidase gene is disabled, and so uric acid must be removed by the kidney. C: A team of Italian scientists set out to find the genes that allow frogs and other animals to break down uric acid. They searched for genes that tended to be present or absent along with urate oxidase. They discovered two such genes. D: By combining these proteins with uric acid, the researchers were able to transform it into allantoin. This discovery promises to help in the search for new treatments for diseases involving uric acid. (Adapted from Ramazzina, 2006)

may be able to cure a disease by giving patients back the proteins our ancestors lost 20 million years ago.

Most of the medical drugs in use today were not synthesized by researchers from scratch. For the most part, researchers discovered molecules that had been made by living things. The breast cancer drug taxol, for example, was originally discovered in a yew tree. Most antibiotics on the market today were discovered in fungi or bacteria. Scientists have barely begun to survey the world's diversity of biological molecules, and so there's good reason to expect that there are many valuable new compounds out there that are waiting to be discovered (page 238).

Insights from evolution are helping scientists to zero in on potential new drugs. Snake venoms, for example, have been transformed into drugs to treat blood clots, high blood pressure, and other ailments. Like any kind of drug, snake-venom molecules have some drawbacks. One is their size: snake-venom molecules are relatively large for drug compounds. The larger a drug molecule, the more easily it can be recognized by the immune system, which may then destroy it before it can have an effect.

Bryan Fry of the University of Melbourne has been tracing the evolution of snake venom through the duplication and co-option of old genes (page 160). His research led him back through time to discover when snake-venom genes first evolved. When he looked in the mouths of the lizards most closely related to snakes, he discovered proteins that he believes also function as venom. Molecule for molecule, the lizard proteins appear to be just as powerful as snake venoms. There is one important difference, however—the lizard proteins Fry has identified so far are smaller than snake-venom molecules. Their small size may make them even more promising as drugs than snake venom.

Medical researchers are like treasure hunters, wandering across a continent in search of jewels. A real treasure hunter wouldn't even start the search without a map. Evolutionary biology offers medical researchers a map of life.

TO SUM UP...

- Evolutionary medicine is the study of the evolutionary roots of health and sickness.
- Some diseases are caused by pathogens that have been infecting our ancestors for millions of years. Some have begun infecting humans in just the past few decades.
- Reconstructing the evolutionary trees of emerging pathogens allows scientists to determine their origins.
- Human pathogens are always rapidly evolving, adapting to their human hosts.
- The virulence of pathogens emerges from an evolutionary trade-off between replicating quickly and moving easily from host to host.
- Pathogens have driven the evolution of defenses in human populations.

- Pathogens evolve resistance to antibiotics.
- Genetic drift can lead to harmful mutations becoming common in a population.
- Our evolutionary history has given the human body many flaws.
- Cancer develops in an evolutionary process.
- Aging is an evolutionary byproduct of natural selection for traits that help animals survive during their reproductive years.
- Sexual conflict can lead to gene imprinting disorders.
- Our bodies are adapted to a preindustrial life. Some diseases are the result of the mismatch between our bodies and modern life.
- Evolutionary biology reveals the great obstacles to treating some diseases, but it also opens new avenues of research for potential new cures.