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Microbes

An Introduction

There was a time, a little more than a hundred years ago, when people didn't believe in germs. Nineteenth-century doctors knew a lot about disease—they could diagnose your illness correctly and tell you quite accurately how much time would pass before you would either get better or drop dead. But because knowledge of the causes of illness was primitive and knowledge of germs was nonexistent, doctors at the time couldn't do much to cure disease or affect its course. Then, in the latter half of the nineteenth century, it became clear that microscopic or invisible organisms caused disease—we've all heard about Louis Pasteur and the other pioneers of microbiology—and that you could prevent disease if you could somehow eliminate the organism that caused it. Remove the handle from the pump in the public square, and you get cholera under control. Heat up the milk to a certain temperature before you drink it, and you can kill the organisms in it that cause illness.

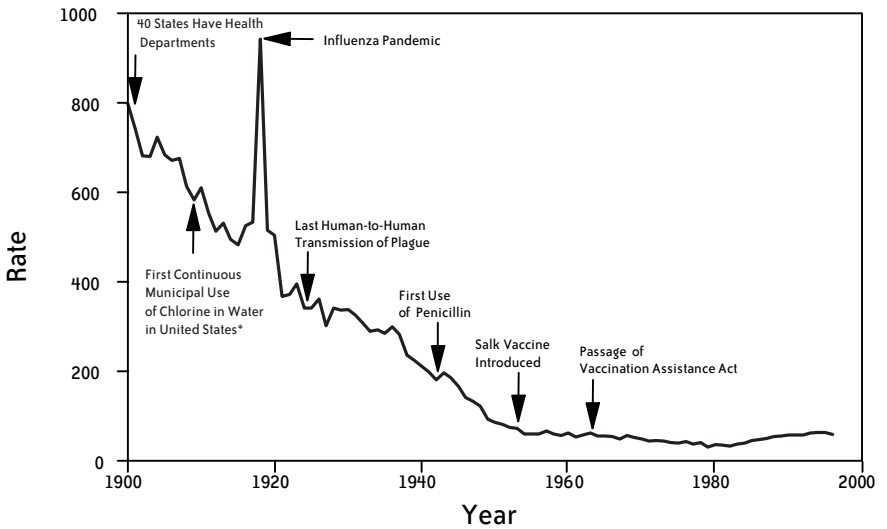
In 1900, the three leading causes of death in the United States were all infectious illnesses: pneumonia, tuberculosis, and enteritis. Along with diphtheria (the tenth most common cause), these diseases caused more than one-third of all deaths. Of these deaths, 40 percent were children under five years old. In 1997, infectious disease accounted for only 4.5 percent of deaths in the United States. The two leading causes of death in 1997 were heart disease and cancer, accounting for more than half of all deaths. Stroke and chronic lung disease were the third- and fourth-ranked killers.

You might conclude from these promising statistics that infectious disease has been gradually conquered by human ingenuity, but you would be only partly right. In fact, in the midst of this hundred-year record of increasing control of infection occurred the worst infectious outbreak in history: the influenza pandemic of 1918 that killed 20 million people worldwide and 500,000 in the United States in the course of less than one year. This is more people than have ever died in so short a period in any war, famine, or natural disaster in the history of the world. Human immunodeficiency virus (HIV) infection, first recognized in 1981, now affects 33 million people worldwide and has caused an estimated 13.9 million deaths. Infectious disease, in other words, is always a lurking threat, however great our scientific progress in battling it.*

The effectiveness of antibiotics against bacteria and of vaccines against scourges such as smallpox, polio, measles, and influenza is well-known. And of course these medicines have been immensely powerful, sometimes seemingly miraculous, in curing illness and preventing its spread. But it is less widely known that most of the progress against infectious disease in the United States in the twentieth century was realized before there were any effective antimicrobial drugs at all. Nineteenth-century industrialization caused the U.S. population to shift from rural areas to cities. The result was overcrowding, poor housing, inadequate water supply, and poor waste disposal, which led to vast increases in infectious illness—particularly tuberculosis, cholera, typhoid fever, yellow fever, and malaria. But by 1900, the incidence of many of these

*There has been a lot of press about the vast increases in infectious disease over the last decade, but the statistics cited (e.g., a startling report in the *Journal of the American Medical Association* that between 1980 and 1992 the rate of death from infectious disease had increased 58 percent) need some explication. First, those years were the time when HIV rates vastly increased. If you take HIV out of the equation, the increase is only 22 percent. After AIDS, respiratory infections are the next leading cause of infectious disease death during this period, but these deaths are mainly in older people—that is, people who thanks to modern medicine have not died of heart disease, stroke, or cancer, and have lived long enough to die of something else. Death rates in the United States from other infectious diseases—tuberculosis, for example—actually declined during this period, and new AIDS cases have been declining in the United States since 1995. While there is of course reason to be concerned, as is amply demonstrated in this book, there is no reason to engage in fear mongering.

diseases had begun to decline as local, state, and federal governments instituted vast improvements in water supply, sewage facilities, pest control, food safety, and public education. All but five of the 45 states had established public health departments by the turn of the twentieth century. The idea of public health as a governmental responsibility had taken hold, and its success was spectacular. In 1900, 194 out of every 100,000 Americans died of tuberculosis. By 1940 the rate had dropped by more than 75 percent to 46 per 100,000. Malaria had been reduced to insignificant levels thanks to mosquito-control programs. Rat-control measures had made plague all but disappear. Chlorination, begun in the early 1900s, had vastly reduced the incidence of waterborne diseases such as dysentery and cholera. And all this had been accomplished without the use of any effective antimicrobial medicines, because there were none.



*American Water Works Association. "Water chlorination principles and practices." *AWWA* annual M20. Denver: American Water Works Association, 1973.

Figure 1 Crude death rate, per 100,000 population per year, for infectious diseases—United States, 1900–1996. Adapted from G.L. Armstrong, L.A. Conn, R.W. Pinner. "Trends in infectious disease mortality in the United States during the 20th century." *JAMA* 1999:202:61–6. *U.S. Department of Health & Human Services.*

When antibiotics were developed, they of course were helpful in reducing disease even further, and especially in treating it once it occurred, even though much of the work of controlling infectious illness had already been done. Importantly, antibiotics reduced the occurrence of infectious epidemics. As you can see from the figure on page 3, between 1900 and 1940, every time an infectious disease outbreak occurred, deaths rose, sometimes dramatically. Toward the end of World War II, there was a plateau. Since that time, fewer outbreaks have occurred—but they have not been eliminated.

While an arsenic treatment for syphilis had been discovered in 1909 (Ehrlich's famous "magic bullet") and the sulfonamide drugs in use in the 1930s and early 1940s were to some extent useful in treating infections, the introduction of penicillin during World War II provided the first truly effective chemotherapeutic agent—that is, a medicine that can efficiently kill microbes without also killing the person who takes the medicine. And after the war, along with the discovery of new antibiotics, came the rapid development of vaccines against diphtheria, tetanus, pertussis (whooping cough), and polio. Vaccination programs in the United States and around the world were so successful that the idea of "disease eradication" was born, and in 1977 smallpox became the first (and so far the only) disease ever to be completely eliminated. The World Health Organization (WHO) is hopeful that polio, guinea worm disease, and leprosy can be eliminated within the next few years. But the emergence of previously unknown diseases such as HIV, Ebola, and Marburg and the appearance of new drug-resistant strains of familiar germs means that despite the availability of a wide range of drugs that treat disease, prevention is just as important today as it was in 1900.

Our bodies are filled with microorganisms—they live on our skin, in our guts, in our mouths, and in our bodily organs no matter how sanitary our living conditions, but for the most part we live healthily with them. In fact, we couldn't live without some of them, such as the ones that help us digest food. Much of the protection we have against harmful germs comes naturally, from our own immune systems. What makes a given microbe "harmless"? Only the fact that we have natural defenses that prevent such germs from overwhelming us. One way in which we naturally fight disease is with the phagocytes, macrophages, and more than a half dozen different types of leukocytes (white blood cells) in our

blood. These are cells that ingest bacteria and other foreign particles that find their way into the bloodstream. But we are also protected by a different mechanism in areas of our bodies that have little blood flow. The conjunctivae of our eyes and the membranes of our nasal passages and respiratory systems, for example, are constantly exposed to the thousands of microscopic organisms that are always in the air, yet most of the time we suffer no infection from them. Why not? Because we (like many other animals and plants) produce substances that are natural anti-infectives.

One day in 1921, an English bacteriologist happened to have a cold, so he added a bit of his own nasal mucus to a petri dish just to see what might be cultured out of it. A few weeks later, he noticed that the bacteria growing in the dish—a harmless type of coccus—had failed to grow in the area near the mucus. Something in the mucus was dissolving and killing the bacteria. The bacteriologist called that something "lysozyme," and over the ensuing years of intensive investigation of the substance, he found it in tears; sweat; saliva; the mucus linings of the cheeks; fingernail parings; hair; sperm; mother's milk; the leukocytes and phagocytes of blood; the fibrin that forms scabs over wounds; the slime of earthworms; the leaves and stalks of numerous plants including buttercups, peonies, nettles, tulips, and turnips; and in very high concentrations in egg whites. He had stumbled upon the first natural anti-infective, an enzyme later given the chemical name "mucopeptide glucohydrolase." This scientist would, eight years later, accidentally find something else in one of his petri dishes, a substance that would change the life of almost everyone on the planet. The bacteriologist's name was Alexander Fleming, and he would name this new discovery "penicillin."

Of course, the discovery of penicillin and the many other antibiotics (more than a hundred are in use today) was not the end of the story. Microbes did not succumb so easily to human ingenuity. The slight rise detectable in figure 1 on page 3 over on the far right side represents a resurgence of infectious disease beginning about 1980 that continues to this day. Germs, in other words, are still very much to be feared. In fact, infectious disease is back—in a big and dangerous way. The death rate from infectious disease in the United States today has risen back to approximately where it was 40 years ago. What happened to cause what is apparently the reversal of a nearly century-long downward trend?

Germs reproduce quickly, creating many generations within hours. With such rapid reproduction comes ample opportunity for genetic mutation. And one of the ways germs fight back is by producing genetic mutations that give them resistance to the antibiotics we use to try to eradicate them. Every time we take an antibiotic, we are killing the weakest germs and allowing the strongest—the resistant ones—to survive and reproduce. Eventually, only resistant germs survive, and the antibiotic that was once effective against them becomes less effective or even useless. This phenomenon was noticed very early on in the development of antibiotics. In 1945, it took a total of about 40,000 units of penicillin to cure a case of pneumococcal pneumonia. Today, because the germ is now resistant to low doses, as many as 24 million units a day are given to effect a cure in severe cases. Some diseases for which penicillin was once effective are now completely resistant to it, even in large doses. As new antibiotics are developed, more resistant strains of bacteria almost immediately follow. Vancomycin was until recently the antibiotic used when nothing else would work, but vancomycin-resistant *Staphylococcus aureus* was found in Japan in 1996 and in the United States in 1997. Streptomycin, discovered in 1944, was highly effective against tuberculosis, reducing its incidence from 39.9 deaths per 100,000 in 1945 to 9.1 in 1955. But its usefulness is now limited by the emergence of resistant strains of *Mycobacterium tuberculosis*, and today the disease must be treated with a combination of therapeutic agents. And even these combinations, which can involve more than a half dozen different drugs, fail to work in some particularly bad cases called multidrug-resistant TB.

Yet antibiotic resistance (about which we will have more to say in the course of our narrative), while it is an important reason for the resurgence of infectious disease, is not the only one. Advances in technology, which have obvious great benefits, have their dark side as well. Legionnaire's Disease could not have spread so easily without the presence of modern heating and air conditioning systems. HIV and hepatitis C have both been spread through blood transfusions. Centrally processed food infected with salmonellosis or *E. coli* is efficiently passed around the country, and even around the world, with modern distribution techniques. Tourist trade and economic development in parts of the world that harbor animals infected with human-transmissible diseases have given the human population "new" and potentially devastating germs. Lyme disease, caused by infected ticks carried by deer, is now a problem because what was once agricultural land has become

secondary-growth forest, increasing the population of deer, and suburbs have expanded into such areas, bringing people into closer contact with these animals. Airplanes are quick and efficient international transporters of infection. And people whose immune systems have been impaired by modern medical treatment (e.g., organ and bone marrow transplants, kidney dialysis, or chemotherapy) are more likely to acquire "opportunistic" infections—that is, infections that are only troublesome when the immune system is in some way compromised.

Sometimes you read of the "age of dinosaurs" or the "age of reptiles" or hear people speak of the time we live in now as the "age of mammals." But in fact we are in—and always have been in since the beginning of life on earth—the age of microbes. Microbes were the first kind of life, and they remain the most common by far. Bacteria existed more than three and a half billion years ago, and we have the fossils to prove it.

No other species, plant or animal, has been as successful. Microbes live in air and in water, and even where there is no air and no water. Some bacteria, like the ones that cause food poisoning and those that live deep under the ocean in sedimentary rock, are called "anaerobic"—they can't survive if exposed to gaseous oxygen. Others, called "aerobic," require oxygen to survive. And then there are some, the facultative anaerobics, whose attitude toward oxygen is that they can take it or leave it. They feed on a vast variety of substances—decaying organic matter, oil, rocks, you name it—and some even make their own food by transforming carbon dioxide into nourishment with the aid of sunlight. They live in the ice of Antarctica and in the hottest deserts of Africa. They live in the ocean from its surface to its greatest depths. There are microbes called archaea (quite different biologically from bacteria or viruses) that live deep in the ocean under tremendous pressure and near volcanic vents at temperatures well above boiling. There are microbes that invade your body and then, once inside, take up permanent residence. The *Varicella* virus that causes chicken pox is one; the herpes virus is another. The specialization of their habitats can be remarkable: there is one species of bacteria, in a genus called *Cristispira*, that lives only in a certain section of the digestive tract of certain mollusks, and apparently nowhere else. Various species of bacteria living inside them give cattle their unhuman ability to use grass as food. Microbes live in your house, in your bed, in your clothing. They live in every orifice of your body, in

your bloodstream, and inside your bodily organs. They live in vast numbers, far more than any other kind of animal or plant, and there is no place on Earth you can live without them.

When a baby is born, its mouth and digestive tract are sterile. But the first time it feeds, whether on breast milk or cow's milk, bacteria invade the infant, and they will live and thrive inside it for the rest of its life. The human mouth is home to a veritable zoological garden of bacteria. Almost two dozen different species live there—and we're talking about people who are perfectly healthy. Right now—swallow hard—you've got as many as eight different species of *Streptococcus* in there, including, quite possibly, the ones that cause scarlet fever (group A *Streptococcus*), middle ear infections (*Pneumococcus*), and meningitis (*neisseria*), and *Streptococcus fecalis*, which, as its revolting name suggests, also lives in the solid waste matter contained in the intestinal tract. If *Streptococcus fecalis* gets into the bloodstream, it can cause endocarditis (an inflammation of the lining of the heart) in susceptible people. Other oral bacteria, relatively harmless in your mouth, can get into other tissues where they can cause bone, lung, or brain abscesses. Dental procedures can sometimes allow this movement of bacteria from the mouth to other tissue. Dental plaque is the result of an accumulation of various bacteria up to 500 cells thick on the surface of the teeth. Most of these are S*treptococcus sanguis* and *Streptococcus mutans*. The latter produce the lactic acid that causes tooth decay; once lesions are formed, other bacteria help in the process of tooth destruction. The higher the concentration of these bacteria in your saliva, the more cavities you are likely to have. Gingivitis, the kind of serious gum disease that causes destruction of the bones that hold the teeth, is caused by a complex population of many organisms, including *Streptococci* and *Actinomyces*. The actual mechanism by which these bacteria destroy bone is not well understood.

Some of these oral bacteria are probably helpful—they prevent more harmful species from inhabiting the mouth by inducing low levels of antibodies, and some actually contribute to good nutrition by helping to synthesize vitamins.

Staphylococcus lives happily on your skin, up your nose, and in your pharynx. Nontypable *Haemophilus influenzae*, the bacterium that causes ear infections in children, finds a comfortable home in your nose and pharynx as well. *Proteus mirabilis*, a species often found in rotting

meat that probably causes enteritis, can sometimes live in your respiratory system, and so can corynebacteria, which cause diphtheria. The normal vagina usually has about 14 different species of bacteria living in it at any given moment; the normal intestine about 17.

The surface of your eyes—the conjunctivae—are in constant contact with air, and therefore with germs. Fortunately, tears contain lysozymes, those natural anti-infectives, and the constant mechanical washing of the eyes by blinking helps keep them clean. Still, some bacteria are found in the conjunctivae, including *Staphylococcus epidermidis* and some cornyneforms, but usually in very small numbers. The urinary tract enjoys a similar cleansing process because it is flushed with sterile urine every few hours. Yet even here, small numbers of bacteria can be found, probably contaminants from the skin, vulva, or rectum.

If you're beginning to think that there aren't enough antibiotics in the world to clean up this mess, you're probably right. Fortunately, there isn't any reason to clean it up, because in healthy people most of these bacteria are either mildly annoying, completely harmless, or somewhat helpful.

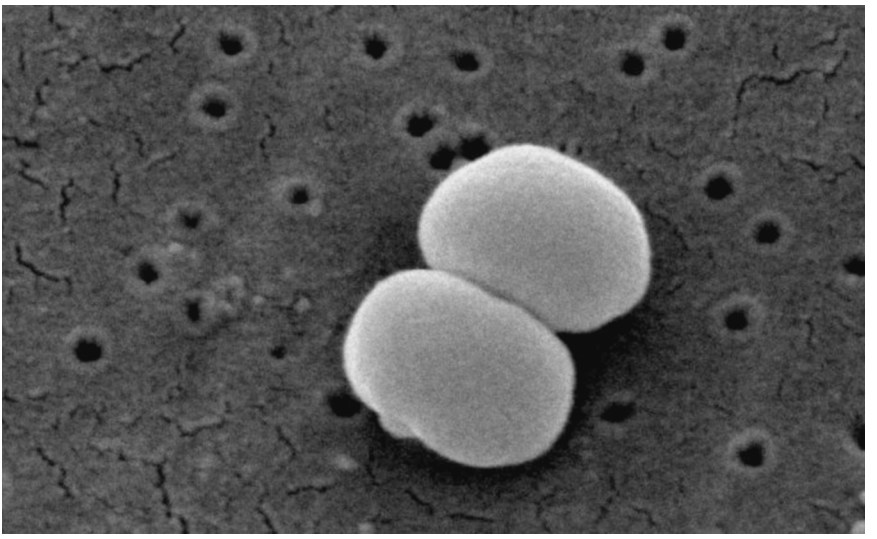


Figure 2 A scanning electron micrograph of *Staphylococcus epidermis*. You can't see them, but you're covered with them and shedding them everywhere you go. They can also commonly be found in human eyes. *CDC. Photograph by Segrid McAllister.*

Bacteria are helpful in the wider world as well. They are at the bottom of the food chain, for one thing. There are bacteria that are essential in breaking down dead organic matter. Scientists have recently discovered that bacteria play a role in species differentiation among certain insects. Different species of wasps, for example, are apparently infected with bacteria that make mating with uninfected species impossible. When the wasps are treated with antibiotics, otherwise incompatible species can interbreed and produce fertile offspring.

Researchers are always finding new ways in which bacteria can be helpful. In December 2000, the journal *Science* published an article written by researchers at the University of Wisconsin and other institutions that showed that certain sulfate-reducing anaerobic bacteria remove the zinc from the waste water produced by mines. These germs are surrounded by beads of zinc sulfide crystals. As they reduce sulfate, freed sulfide ions combine with zinc ions, which then precipitate out of the water. Scientists have known for some time that there are bacteria that can dechlorinate chlorobenzenes, a common industrial compound that can accumulate in the food chain. German scientists, according to a report in the journal *Nature*, have now identified the specific strain. This discovery offers the possibility that the bacteria could be cultured and prove useful in industrial waste cleanup.

Some bacteria are positively delightful, like the ones that make grapes into wine, give yogurt its tang, assure cheeses their multitude of flavors, and lend sourdough bread its pleasant sour taste. Some are normally harmless—our own bodies protect us from them unless we are for some reason susceptible (the very young, the very old, the unhealthy, or those with weakened immune systems). Others are harmful and cause disease even in healthy people. And still others would be harmful if we didn't have drugs to counter their effects.

What is a germ? The question may seem trivial—after all, a germ is obviously a bad microscopic thing that gets in you and makes you sick. Well, yes and no. As we've seen, there are plenty of "germs"—that is, microscopic organisms—that are in you and don't make you sick. And there are organisms that get in you, make you sick for a while, and then, after you get better, just stay in you, sometimes taking up residence in very odd places, as you will see later in this book. For convenience, and so as not to bore everyone to death, I use the term "germ" in this book

rather loosely to describe lots of different kinds of organisms that live in and on us, some of which make us sick, some of which make us sick for a while and then live on without bothering us, and some of which never do any harm at all. The first person who saw a microscopic organism, Antonie van Leeuwenhoek, called them "animalcules." Our term "germs" is no more specific than that term assigned in 1674. The glossary makes some fine distinctions among organisms, but nevertheless we need to clarify a bit here at the outset.

There are somewhere between a half million and a million species of bacteria, and roughly five thousand different viruses. Only a small fraction of these bacteria have been scientifically studied and categorized. Then there is the group of disease-causing one-celled organisms mentioned previously, the archaea, which includes the blue-green algae that constitutes pond scum (and which, confusingly, are not algae at all). There are other organisms that are neither viruses nor bacteria nor archaea that nevertheless infect us and cause disease—some of these we call "parasites," although one could as easily call bacteria and viruses parasites as well. Malaria, for example, is caused by a protozoan called *Plasmodium*. A protozoan is a germ, if you want, but it is a one-celled organism that is a member of the phylum Protozoa, neither a virus nor a bacterium in the classification scheme. Even fungi, which are species of plants, cause disease. *Candida*, for example, is a yeastlike fungus whose various species cause thrush, vaginitis, and some systemic infections. To make things even more complicated, virologists have discovered yet another infectious organism called a "prion," which contains neither DNA nor RNA and is probably composed entirely of a single protein. This doesn't discourage anyone from calling these organisms germs, and it won't discourage us from discussing such bugs in this book.

Bacteria, viruses, archaea, protozoa, fungi, and prions can all be harmful, but they work their mischief in different ways. The distinctions are important because they determine how the diseases they cause can be prevented or treated.

Of the thousands of species of bacteria, most live their lives either with beneficial effects or with no effect at all on humans. But there are a number of them that can make you sick, and some that can kill you. Bacteria are one-celled organisms that reproduce by dividing. There are four groups of bacteria, classified by shape: the *bacilli* (rod-shaped),

the *cocci* (spherical), the *spirilla* (spiral), and the *vibros* (shaped like commas). You may have heard the terms "gram-negative" and "gram-positive." These terms refer to whether or not a given organism can be stained with a certain substance that makes them visible under an electron or phase contrast microscope. (Despite the fact that it is normally styled with a small "g," Hans Christian Gram is the name of the Danish bacteriologist who developed the staining technique in 1844 and has nothing to do with the gram that is a measure of weight.) Gram-negative and gram-positive are one way of classifying bacteria. Penicillin is useful against gram-positive bacteria like *Streptococcus*. It doesn't work against gram-negative bacteria like the one that causes salmonella food poisoning. And these groups are classified further according to the way they live in colonies and their metabolic actions. The taxonomy of bacteria is no less complex than that of any other species—they are divided into kingdom, division, class, order, family, genus, species, and subspecies just like other animals and plants.

In general, all the species of bacteria that make you sick do so in pretty much the same way: they invade your cells, making the body's immune system react in some way, usually by causing tissue inflammation. How they get into your cells varies from one kind of bacterium to another. Campylobacter, for example, a gram-negative genus of which there are several species, can cause infectious diarrhea, appendicitis, and an acute inflammatory nerve disease called Guillain-Barré syndrome, which causes (usually temporary) paralysis. A relatively small number of these cells can cause very serious illness. Campylobacter produces a kind of glue, a protein called adesin, which sticks the germ to the wall of the intestinal mucosa, making invasion of the tissue possible. It then produces toxins that destroy the cells. The group of *E. coli* species that probably produces most cases of "traveler's diarrhea" invades the cell with the help of fibrils, tiny filaments that penetrate parts of the cell's genetic material to gain entrance. Chlamydia, another gram-negative bacterium that causes various symptoms and disorders depending on the species, can reproduce only by invading the tiny empty spaces called vacuoles in the plasma of the cell. There they produce a form called "reticular corpuscles," which are released to invade, cause inflammation, and reproduce in other cells.

Protozoa, responsible for malaria and many other diseases, reproduce and infect in a variety of ways. Cryptosporidium is a common waterborne parasite that is usually harmless to humans, except those

whose immune systems are for some reason compromised. Under the right circumstances, however, the parasite flourishes, and some of them convert into a form called an oocyst, which is very resistant to ordinary water treatment procedures. If this oocyst is ingested by an animal (including humans), it can release sporozoites, which attach to the surface of the intestines to initiate a new cycle of infection that causes abdominal cramping and explosive watery diarrhea. No one knows for sure, but the nature of the diarrhea suggests that the cause is a toxin that poisons the cells of the intestines.

The protozoan that causes malaria has a life cycle that begins when a mosquito of the species *anopheles* feeds on the blood of an infected person. The protozoan (which comes in four different species called *Plasmodium falciparum*, *P. vivax*, *P. malariae*, and *P. ovale*) then undergoes sexual development inside the mosquito, leaving sporozoites in the insect's salivary glands. When the insect bites another human, these sporozoites are released into that person's blood. They reproduce asexually in the cells of the liver. After two to four weeks, they are released into the bloodstream in a form called merozoites, which invade and destroy red blood cells. The parasites can persist in the liver (in the case of *P. vivax* and *P. ovale*) or in the blood (in the case of *P. falciparum* and *P. malariae*), where they cause recurrent malaise, fever, headaches, chills, and bodily pain that may persist for months or even years. People who are otherwise in good health usually recover from malaria even without treatment, although early treatment with quinine drugs is very effective. The exception is falciparum malaria, which if left untreated can kill by destroying the cells of the liver, spleen, and brain.

Viruses, unlike bacteria and protozoa, can live and reproduce only inside cells, and they are much smaller than either of those types of organisms. They consist of an outer protein or lipid shell that surrounds a nucleic acid core, which may be either RNA or DNA. And they can infect not only the cells of animals and plants, but the cells of bacteria as well. There are about a hundred of them that infect humans, and they cause diseases as mild as head colds and as deadly as AIDS. Some have long incubation periods and can cause one disease upon initial infection and another after years producing no symptoms at all. Varicella zoster, for example, the virus that causes chicken pox, can be contracted in childhood and then live in your body permanently, causing shingles, a painful nerve disorder, much later in life. And there are many viruses that infect humans without causing any symptoms at all—the only way

you can tell that you're infected is by laboratory tests that reveal antibodies to the virus in your blood.

Viruses have reactive sites on their outer shells that interact with receptor sites on the cells they are attacking. These "key-in-lock" reactions are quite specific—a given virus is limited to infecting certain kinds of cells in certain species of animals. Once the virus finds the right receptor site, it can either fuse with the host cell membrane or move inside the cell. Either way, it can then insert its nucleic acid into the cell and then reproduce—that is, messenger RNA is "transcribed" from viral DNA or RNA. This process can take place in the nucleus of the cell (as it does with the herpes virus, for example), in the cell's cytoplasm (like the polio virus), or at the cell's surface (the flu virus does it this way). The final step is the release of new infectious material from the cell, which can then go on to infect other cells. This happens in various ways depending on the virus, including by the disintegration of the host cell wall. Because viruses replicate in such an intimate way with the cell itself, it is very hard to develop a medicine that will kill the virus without poisoning the host as well. This is why there are so few effective treatments for viral illnesses.

If bacteria, protozoa, and viruses aren't enough to worry about, you can always think about the recently discovered infectious agent called a prion. Bacteria, viruses, and protozoa are clearly living things. With prions, it isn't so clear. They apparently have no nucleic acid, and consist of a protein alone. That a protein can by itself transmit disease was quite surprising to microbiologists, but this nevertheless appears to be the case. Prions produce various diseases in animals and humans that are often referred to as "spongiform encephalopathies." "Spongiform" means just what it looks like it means—having a form that resembles a sponge. "Encephalopathy" refers to diseases of the brain. On postmortem examination, the brains of animals (including humans) infected with these diseases are marked by large empty spaces in the cortex and cerebellum, giving the organ the appearance of a sponge.

Prion diseases all have similar and extremely unpleasant symptoms: loss of motor control, paralysis, dementia, emaciation, and death. There are four forms of the disease in animals, affecting sheep, mink, elk, mule deer, and cows. The "mad cow disease" of recent headlines is bovine spongiform encephalopathy. In humans, this prion causes Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker

syndrome (GSS), familial fatal insomnia (FFI), and kuru. CJD in humans can be contracted by eating infected beef. Kuru, one of the first prion diseases discovered, was found among isolated tribes in New Guinea where religious ceremonies in which the brains of dead relatives were ingested were identified as the cause of transmission. Prion diseases in infants are called Alpers Syndrome. Somewhat mysteriously, these diseases appear in some cases to be genetically transmitted as well as acquired. No one knows exactly how.

Some organisms are known to release poisons that kill. Certain kinds of algae, for example, that live in seawater can poison fish and shellfish, which then store the poisons in their tissue. Eating one of these infected animals can produce dramatic effects: demoic acid produced by a species of algae called *Nitzschia pungens*, for example, can cause amnesia. Others produce toxins that can paralyze you. Some just give you diarrhea; some can kill you. Some molds and fungi also release substances that cause disease in humans.

Many animals are "vectors" of infectious disease—that is, they carry disease and transmit it to other animals or humans. Mosquitoes, as we saw previously, are a vector of malaria. Birds carry West Nile virus. Cockroaches, mice, rats, flies, and many other animals can cause disease in humans by transmitting infectious organisms. These animals are important because they are the ones with which we humans have a very close relationship—second in intimacy only to our relationship with germs themselves.

Viruses, bacteria, archaea, prions, protozoa, and fungi all exist in nature. Disease does not. Disease is a human invention, a method of characterizing and organizing symptoms, not a phenomenon that exists out there apart from us. From the point of view of humans, HIV infection is a disease, one of the most terrible there is. But from the point of view of a human immunodeficiency virus, HIV infection is merely life. From the point of view of some organisms, human beings themselves are a disease. You might say (even if the analogy is somewhat imperfect) that tigers, for example, have a bad case of "humans," so bad that it may in the end wipe them out completely. We're infested with microbes of many kinds, but we are infected with a disease only when one of those microbes causes troublesome symptoms. And of course even microbes that are ordinarily considered disease-causing don't always cause disease.

Antibiotics are not the only weapons against infectious disease. Several other important technological changes have helped considerably. Serologic testing, first used in the early years of the twentieth century, made diagnosis much more reliable. Syphilis and gonorrhea were widespread diseases at the beginning of the century, but they are difficult to diagnose during latent stages. Serologic testing revealed in 1901 that between 5 percent and 19 percent of men in New York City were infected with syphilis.

Isolating germs in order to determine whether they are disease-causing is an essential technique that first came into use in the late nineteenth century. The first method used was to strain infected material through a series of smaller and smaller screens and then inject the final product into an animal or plant to see if the disease would be produced. This technique was used in 1898 to isolate the organism that causes tobacco mosaic virus, and then in 1900 to discover the virus that causes yellow fever. By the 1930s, techniques had been developed to culture viruses, a technology that allowed large-scale production of live or killed viruses from which vaccines could be developed. Staining techniques to make viruses visible under electron microscopes were widely used by 1960.

Today, techniques for identifying infectious pathogens are even more sophisticated. Nucleic acid hybridization and sequencing (tests that examine the genetic code) have now been used to identify the organisms that cause hepatitis C, human ehrlichiosis, hantavirus pulmonary syndrome, Nipah virus disease, and AIDS. Understanding infection at the level of molecules has led to knowledge of new methods of prevention and treatment. The replication analogs and protease inhibitors used to treat HIV infection, for example, are based on a knowledge of the virus's method of replication at a molecular level, and their success depends on using that knowledge to target certain sites on the virus to limit or eliminate its ability to cause harm.

Now you have some of the basics of what scientists know about microorganisms, what germs do, and how they do it. As you might imagine, the details are much more complicated than what we've outlined here, and so much research is going on in microbiology that what I've said may soon be outdated. In the following chapters we'll try to apply some of this knowledge to the most common and most unavoidable of the germs we live with.