THE POWER OF PLAGUES

Irwin W. Sherman

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Second Edition

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Preface to the Second Edition

Plagues, the historian Asa Briggs observed, "are a dramatic unfolding of events; they are stories of discovery, reaction, conflict, illness and resolution." They test "the efficiency and resilience of local and administrative structures" and "expose the relentlessly political, social and moral shortcomings…rumors, suspicions, and at times violent…conflicts." This book was written to make the science of epidemic diseases—plagues—accessible and understandable. It is a guide through the maze of contagious diseases, their past importance, the means by which we came to understand them, the methods and practices for control and eradication, and failing this how they may affect our future.

My objective in writing the *Power of Plagues* has been to provide an understanding of epidemic diseases and their impact on lives past, present and future. As a biologist I wanted to examine infectious diseases that have been and continue to afflict humankind. In this 2nd edition I describe the nature and evolution of a selected group of diseases and then aim to show how past experiences can prepare us for future encounters with them. It is also a status report of where we are today with infectious diseases that are emerging and re-emerging to inflict harm not only to the individual but to larger segments of the world's populations. This edition covers modern disease outbreaks, such as anthrax, cholera, Ebola disease, HIV, influenza, Lyme disease, malaria, tuberculosis, and Zika disease, as well as the threat of antimicrobial resistance.

For decades it has been a commonly held belief that all epidemic diseases in the developed world could be eliminated by vaccines, as was the case with smallpox. If not, then we deluded ourselves that new and more powerful chemotherapeutic agents and antibiotics would be developed and these could be relied on to cure an emerging new disease. Some of us were convinced that our water was safe to drink and our food could be eaten with little fear of contracting a disease and that the transmitters of disease—mosquitoes, flies, lice, ticks and fleas—could easily be eliminated by the spraying of deadly insecticides. If by chance a few of our neighbors became infected, some held the illusion that the infected individuals would be treated quickly and effectively so that a severe disease outbreak could be averted.

These views, however, have come to be challenged: drug-resistant tuberculosis emerged as a worldwide threat, and there were outbreaks of hantavirus and SARS (severe acute respiratory syndrome) in 2012 and 2003, respectively. In the summer of 1999 an outbreak of West Nile virus (WNV) caused illness in 62 people and 7

died. This took place in New York City, not Africa. Then in 2001 there was a terrorist attack of anthrax that killed 5 and sickened 17 in New York City, Florida, and Washington, DC. A particularly lethal bird influenza—one that killed millions of animals in a dozen Asian countries—caused alarm in 2004. This virus, which rarely infects humans, spread rapidly in the population and killed 42 people. If this "new" flu had been able to be transmitted from person-to-person by coughing, sneezing, or even a handshake, then a natural bioterrorist attack would have occurred. An outbreak of Ebola disease in Africa in 2014 and an outbreak of Zika disease in Brazil and the Caribbean in 2015 caused public health authorities to sound alarms that these might be forerunners of a pandemic. Luckily, the doomsday scenarios were not realized. But in the future, might a pandemic occur? And if there is such a catastrophe, how will we deal with it?

This book has been conceived as a conversation about how we came to understand the nature of severe outbreaks of epidemic disease—plagues. It tells about the microbe hunters who were able to identify and characterize the infectious disease agent, its mode of transmission, and how control was effected and health restored. It tells of the ways in which plagues and culture interact to shape values, traditions, and the institutions of Western civilization.

As with the previous edition, I have not taken a chronological approach in the examination of the plagues that have afflicted humans. Chapters have been written so that they are more-or-less independent and as a result they need not be read in a proscribed sequence. However, in some instances readers may attain a somewhat better understanding when the chapters on principles and protection (Chapters 1, 10, and 11) as well as the Appendix on Cells and Viruses are read early on. Some readers will be disappointed that their "favorite" plague has not been included in these pages. To have added many more epidemic diseases would have made the book much longer and encyclopedic—something I wanted to avoid. Rather, the particular plagues included have been selected for their value in teaching us important lessons. The style of the *Power of Plagues* is such that readers without any background in the sciences should easily be able to understand its message. This book is intended to promote an understanding of infectious disease agents by a sober and scientific analysis and is not a collection of horror stories to provoke fear and loathing. Learning about how infectious diseases have shaped our past has proven to be an exciting and enlightening experience for me. My hope is that readers of this book will also find that to be true.

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1 The Nature of Plagues

Disease can be a personal affair. Peter Turner, a World War II veteran, was a commander of the Pennsylvania Division of the American Legion. In the summer of 1976, Turner, a tall, well-built 65-year-old, decked out in full military regalia, attended the American Legion convention in Philadelphia. As a commander, Turner stayed at the Bellevue-Stratford Hotel, headquarters for the meeting. Two days after the convention Turner fell ill with a high fever, chills, headache, and muscle aches and pains. He dismissed the symptoms as nothing more serious than a "summer cold." His diagnosis proved to be wrong. A few days later he had a dry cough, chest pains, shortness of breath, vomiting, and diarrhea. Within a week his lungs filled with fluid and pus, and he experienced confusion, disorientation, hallucinations, and loss of memory. Of 221 fellow Legionnaires who became ill, Commander Turner and 33 others died from pneumonia. The size and severity of the outbreak, called Legionnaires' disease, quickly gained public attention, and federal, state, and local health authorities launched an extensive investigation to determine the cause of this "new" disease. There was widespread fear that Legionnaires' disease was an early warning of an epidemic. Though no person-to-person spread could be documented, few people attended the funerals or visited with the families of the deceased veterans.

Statistical studies of Legionnaires' disease revealed that all who had become ill spent a significantly longer period of time in the lobby of the Bellevue-Stratford Hotel than those who remained healthy. Air was implicated as the probable pathway of spread of the disease, and the most popular theory was that infection resulted from aspiration of bacteria (called *Legionella*) in aerosolized water either from cooling towers or evaporative condensers. Unlike infections caused by inhalation, in aspiration secretions in the mouth get past the choking reflex and, instead of going into the esophagus and stomach, mistakenly enter the lungs. Protective mechanisms that normally prevent aspiration are defective in individuals who are older, in smokers,

Figure 1.1 (Left) *Woman with Dead Child*. Kathe Kollwitz etching. 1903. National Gallery of Art, Washington, D.C.

and in those who have lung disease. The Legionnaires were near-perfect candidates for contracting the disease.

After the outbreak, the hotel, which had been the choice of conventions such as that held by the Legionnaires as well as those of Hollywood stars such as John Wayne, Grace Kelly, and Elvis Presley, was shunned by guests. The hotel closed down and was empty for almost 3 years, during which time there was talk of tearing the building down. After tens of millions of dollars in renovation, however, there was a new owner, and after reopening in 1989, today it is the Hyatt at The Bellevue.

Since the Philadelphia outbreak, there have been numerous reports of Legionnaires' disease. For example, in 1985 in Stafford District Hospital in Stafford, England, there were 175 cases and 28 deaths; in 1999 in Bovekarspel, Holland, a hot tub was responsible for 318 cases and 32 deaths; in 2001, a hospital in Murcia, Spain, reported 800 cases; in 2005 at the Seven Oaks Home for the Aged in Toronto, Canada, 127 were sickened and 21 died; and in 2015 in a housing development in the South Bronx, NY, 128 were infected with *Legionella* and 13 died. It is estimated that in the United States there are 8,000 to 18,000 cases of legionellosis a year that require hospitalization, and worldwide the numbers are even greater.

A few years after the outbreak of Legionnaires' disease in Philadelphia, another "new" disease appeared. Mary Benton, a graduate student and English composition teaching assistant at UCLA, knew something was amiss as she prepared for Monday's class. She had spent the previous day happily celebrating her 24th birthday, but by evening she was doubling over in pain every time she went to the bathroom. Mary figured she probably had an infection or was suffering from overeating. Mary, who was previously healthy and active, became concerned as her symptoms worsened. By the time she saw her physician, she had nausea, chills, diarrhea, headache, and a sore throat. Her temperature was 104.7°F, her heart rate 178 beats/min, and she had a red rash, initially on her thighs, but it had become diffuse over her face, abdomen, and arms. Her blood pressure had fallen to 84/50 mm Hg, she had conjunctivitis in both eyes, and her chest X-ray was normal, but a pelvic examination revealed a brownish discharge. Though her doctors administered antibiotics, oxygen, and intravenous fluids, her condition deteriorated over the next 48 h. She died of multiorgan failure: low blood pressure, hepatitis, renal insufficiency, and internal blood clots. Laboratory tests provided clues to the cause of death. Cultures made from her blood, urine, and stools were negative, but the vaginal sample contained the bacterium *Staphylococcus aureus*. The "new" disease that felled Mary Benton was named toxic shock syndrome, or TSS. The source of Mary's infection, and whether it might be spread through the population as a sexually transmitted disease (STD), raised many concerns. TSS continued to appear for the next 10 years among previously healthy

young women residing in several states. As with Mary Benton, each case began with vomiting and high fever, followed by light-headedness and fainting; the throat felt sore, and the muscles ached. A day later there appeared a sunburn-like rash, and the eyes became bloodshot. Within 3 to 4 days the victims suffered confusion, fatigue, weakness, thirst, and a rapid pulse; the skin became cool and moist; and breathing became rapid. These symptoms were followed by a sudden drop in blood pressure; if it remained low enough for a long enough period, circulatory collapse produced shock.

TSS was a gender-specific disease. From 1979 to 1996, it affected 5,296 women, median age 22, with a peak death rate of 4%. TSS, however, was not an STD. Ultimately it was linked to the use of certain types of tampons, especially those containing cross-linked carboxymethyl cellulose with polyester foam, which provided a favorable environment for the toxin-producing *S. aureus*. Elevated vaginal temperature and neutral pH, both of which occur during menses, were enhanced by the use of these super-absorbent tampons. In addition, tampons obstruct the flow of menstrual blood and may cause reflux of blood and bacteria into the vagina. By the late 1980s, when these tampon brands were removed from the market, the number of deaths from TSS declined dramatically.

The effects of disease at the personal level can be tragic (Fig. 1.1), but when illness occurs in many people, it may produce another emotion—fear—for now that disease might spread rapidly, causing death, as well as inflaming the popular imagination. The 2003 outbreak of SARS (severe acute respiratory syndrome) had all the scary elements of a plague—panic, curtailed travel and commerce, and economic collapse. It began in February 2003 when a 64-year-old Chinese physician who was working in a hospital in Guandong Province in southern China traveled to Hong Kong to attend a wedding and became ill. He had a fever, a dry cough, a sore throat, and a headache. Unconcerned, he felt well enough to go sightseeing and to shop with his brother-in-law in Hong Kong; during that day, however, his condition worsened and he found that he had difficulty breathing. Seeking medical attention at a nearby hospital, he was taken immediately to the ICU (intensive care unit) and given antibiotics, anti-inflammatory drugs, and oxygen. These were to no avail, and several hours later he suffered respiratory failure and died. The brother-in-law, who was in contact with him for only 10 h, suffered from the same symptoms 3 days later and was hospitalized. Again, all measures failed, and he died 3 weeks after being hospitalized.

Laboratory tests for the physician (patient 1) and his brother-in-law (patient 2) were negative for Legionnaires' disease, tuberculosis, and influenza. A third case of this severe respiratory syndrome occurred in a female nurse who had seen the physician in the ICU, and the fourth case was a 72-year-old Chinese-Canadian businessman who had returned to Hong Kong for a family reunion. He stayed

overnight in the same hotel and on the same floor as the physician. (He would ultimately carry SARS to Canada when he returned home.) Patient 5 was the nurse who attended the brother-in-law, and patients 6, 7, 8, and 9 were either visitors to the hospital or nurses who had attended patient 4. Patient 10 shared the same hospital room with patient 4 for 5 days. In less than a month 10 patients had SARS, with 6 (patients 3, 4, 6, 8, 9, and 10) surviving and 4 (patients 1, 2, 5, and 7) dying. Over the next 4 months the SARS survivors sowed the seeds of infection that led to more than 8,000 cases and 800 deaths in 27 countries, representing every continent except Antarctica.

On February 1, 2016, the World Health Organization (WHO), after recording a surge in the number of babies born with microcephaly—an abnormally small head—sounded the alarm that Zika virus was a threat to pregnant women and could cause serious harm to their fetuses. Six months later, on August 1, 2016, the *Los Angeles Times* reported that there were 1,638 confirmed cases of microcephaly and other neurological defects in Brazil as a consequence of the Zika virus. Worldwide, 64 countries and territories have reported to the WHO evidence of mosquito-borne transmission of Zika. There has been a steady march of the Zika virus across the Americas—an epidemic—and that is because the vector, the thoroughly "domesticated" *Aedes* mosquito, stays close to people and is present primarily in the Southwest and Southeast United States, as well as the Caribbean, Central and South America, and Europe. Indeed, by October 2016, according to the CDC, there were 3,936 cases in the continental U.S. and 25,955 cases in the U.S. territories of Puerto Rico, the U.S. Virgin Islands, and American Samoa. The number of cases of microcephaly may reach hundreds. The CDC director, Thomas Frieden, in an understatement, warned that without a vaccine "this is an emergency that we need to address."

Despite the recognition that disease, such as SARS, Legionnaires' disease, TSS, and Zika, may appear suddenly and with disastrous consequences, more often than not little notice has been given to the ways in which disease can and has shaped history. The influence of disease on history was often neglected because there appeared to be few hard-and-fast lessons to be learned from a reading of the past; sickness seemed to have no apparent impact except for catastrophic epidemics such as the bubonic plague, or it was outside our experience. We tend to live in an age in which diseases appear to have minimal effects—we are immunized as children, we treat illness with effective drugs and antibiotics, and we are well nourished. And so our impressions of how diseases can affect human affairs have been blunted. But this is an illusion: the sudden appearance of SARS, Legionnaires' disease, TSS, AIDS, and Zika are simply the most recent examples of how disease can affect society. Our world is much more vulnerable than it was in the past.

New and old diseases can erupt and spread throughout the world more quickly because of the increased and rapid movements of people and goods. Efficiencies in transportation allow people to travel to many more places, and almost nowhere is inaccessible. Today, few habitats are truly isolated or untouched by humans or our domesticated animals. We can move far and wide across the globe, and the vectors of disease can also travel great distances, and, aided by fast-moving ships, trains, and planes, they introduce previously remote diseases into our midst (such as West Nile virus and SARS, influenza and Zika). New diseases may be related to advances in technology: TSS resulted from the introduction of "improved" menstrual tampons that favored the growth of a lethal microbe, and Legionnaires' disease was the result of the growth and spread of another deadly "germ" through the hotel's air conditioning system.

This book chronicles the recurrent eruptions of plagues that marked the past (Fig. 1.2), influence the present, and surely threaten our future. The particular occurrence of a severe and debilitating outbreak of disease may be unanticipated and unforeseen, but despite the lack of predictability, there is a certainty: dangerous "new" diseases will occur.

Living Off Others

The "germs" that caused SARS, Legionnaires' disease, and TSS are parasites. To appreciate more fully the nature of these diseases as well as others and how they may be controlled, it helps to know a little more about parasites. No one likes to be called a parasite. The word suggests, at least to some, a repugnant alien creature that insinuates itself into us and cannot be shaken loose. Nothing could be further from the truth. Within the range of all that lives, some are unable to survive on their own, and they require another living being for their nourishment. These life-dependent entities are called parasites, from the Greek *parasitos*, meaning "one who eats at the table of another. "The business they practice, parasitism, is neither disgusting nor unusual. It is simply a means to an end: obtaining the resources needed for their growth and reproduction. We do the same—eating and breathing—in order to survive.

Parasitism is the intimate association of two different kinds of organisms (species) in which one benefits (the parasite) at the expense of the other (the host), and as a consequence of this, parasites often harm their hosts. The harm inflicted, with observable consequences, such as those seen in Commander Peter Turner and Mary Benton and those patients afflicted with SARS and Zika virus, is called "disease," literally "without comfort." Though parasites can be described by the one thing they are best known for—causing harm—they come in many different guises. Some may be composed of a fragment of genetic material wrapped in protein

Figure 1.2 *The Plague of Ashod* by Nicolas Poussin (1594-1665).
The painting probably represents bubonic plague since rats are shown on the plinth

(virus).* Others consist of a single cell* (bacteria, fungi, and protozoa), and some are made up of many cells (roundworms, flatworms, mosquitoes, flies, and ticks). Some parasites, such as tapeworms, hookworms, malaria, and HIV, as well as the Zika and Ebola virus, live inside the body, whereas others (ticks and chiggers) live on the surface. Parasites are invariably smaller in mass than their host. Consider the size of malaria, a microparasite, and hookworm, a macroparasite. Both produce anemia, or, as one advertisement for an iron supplement called the condition, "tired blood."

A malaria parasite lives within a red blood cell that is 1/5,000 of an inch in diameter. If only 10% of your blood cells were infected, the total mass of the malaria parasites would not occupy a thimble, and yet in a few days they could destroy enough of your red blood cells that the acute effects of blood loss could lead to death. In effect, you could die from an internal hemorrhage. Although the "vampire of the American South," the bloodsucking, thread-like hookworm, is only 0.5 in. in length and 0.05 in. in girth, if your intestine harbored 50 worms, you would lose a cupful of blood a day. Yet the entire mass of worms would weigh less than 5 hairs on your head.

Some parasites have complex life cycles and may have several hosts. In malaria the hosts are mosquitoes and humans; in blood fluke disease, the "curse of the pharaohs," the hosts are humans and snails; and in sleeping sickness the hosts are tsetse flies, game animals, and humans. All parasites—whether they are large or small—cause harm to their host, though not all kill their host outright. This is because resistance may develop in any population of hosts and not every potential host will be infected—some individuals may be immune or not susceptible due to a genetic abnormality or the absence of some critical dietary factor (vitamin deficiency).

To succeed in a hostile world where individual hosts are distinct and separate from one another, parasites need to disperse their offspring or infective stages to reach new hosts. To meet this requirement they produce lots of offspring, thereby increasing the odds that some of these will reach new hosts. It is a matter of numbers: more offspring will have a greater probability of reaching a host and setting up an infection. In this way the parasite enhances its chances for survival. Three cases will illustrate this: the red blood cell-destroying hookworms, malaria, and the white blood cell killer HIV.

When a malaria-infected mosquito feeds, it injects with its saliva perhaps a dozen of the thousands of parasites that are present in its salivary glands. Each malaria parasite invades a liver cell, and after a week each produces up to 10,000 offspring; in turn, every one of these infects a red blood cell. Within the infected red blood cell, a malaria parasite produces 10 to 20 additional infective forms to continue the destructive process. In little more than 2 weeks a person infected by a single malaria parasite will have produced >100,000 parasites, and 2 days later the blood will contain millions of malaria parasites.

Hookworms live attached to the lining of the small intestine, which they pierce with their razor-sharp teeth, allowing them to suck blood, as would a leech. Each female hookworm—no bigger than an eyelash—can live within the intestine for >10 years, producing each day >10,000 eggs. In her lifetime, this "Countess Dracula" can produce >36 million microscopic eggs.

The AIDS-causing virus, HIV, is a spherical particle so small that if 250,000 were lined up they would hardly be 1 in. in length. Each virus, however, has an incredible capacity to reproduce itself. After it invades a specific kind of white blood cell (the T-helper lymphocyte), where it replicates, a million viruses will be produced in a few short days. To gain some appreciation of the high reproductive capacity of this virus, we might think of the infecting HIV as a person standing on a barren stretch of beach; if we were to return to this beach a few days later, we would find it jammed and overcrowded with millions—a population explosion.

Any environment other than a living host is inimical to the health and welfare of the parasite. Some parasites have gotten around this with resistant stages such as spores, eggs, or cysts that enable them to move from one host to another in a fashion akin to "island hopping." Hookworms, tapeworms, blood flukes, and pinworms have eggs that are able to survive outside the body; the microscopic cysts of the roundworm *Trichinella* are able to resist the ordinarily lethal effects of the acids in our stomach to cause trichinosis, and now we are all too familiar with the possibility of a bioterrorist attack from anthrax (p. 416), which has resistant spores that allow it to spread by inhalation of "anthrax dust." The movement of a parasite from host to host—whether by direct or indirect means—is called transmission. When the transmission of parasites involves a living organism such as a fly, mosquito, tick, flea, louse, or snail, these "animate intermediaries" are called vectors. Transmission by a vector may be mechanical (e.g., the bite wound of a mosquito or fly) or developmental (e.g., parasites that grow and reproduce in snails in blood fluke disease, or in mosquitoes, as in malaria and yellow fever). Transmission of a parasite may also occur through contamination of eating utensils, drinking cups, food, needles, bedclothes, towels, or clothing, or in droplet secretions. In the 1976 outbreak of Legionnaires' disease in Philadelphia, transmission was not from person to person but through a fine mist of water in the air conditioning system, whereas in the case of SARS (and influenza), transmission is from person to person via droplet secretions from the nose and mouth.

Parasites and their free-living relatives come in a variety of sizes, shapes, and kinds (species). Bacteria, 1 to 5 micrometers (μm) in size, are prokaryotes* that can be free-living or parasitic. They may assume several body forms: rods (bacilli),

spheres (cocci), or spiral. Protozoa, 5 to 15 μm in size, are one-celled eukaryotes* that can lead an independent existence (such as the freshwater *Amoeba* sp.) or be parasitic (such as the *Entamoeba* sp. that causes amebic dysentery or the corkscrew-shaped trypanosomes that cause African sleeping sickness). Bacteria and protozoa are too small to be seen with the unaided eye. The technological advance—the microscope—perfected in the 1600s allowed for their discovery, and so they are called microparasites. The ultimate microparasite is a virus—a small piece of nucleic acid (RNA or DNA) enclosed within a protein coat. A virus has no cell membrane, no cytoplasm, and no organelles; and because it has no metabolic machinery of its own, it requires a living cell to make more virus. Viruses are <0.1 μm in size; they cannot be seen even with the light microscope, but only with the electron microscope, which can magnify objects >10,000 times. Viruses, such as the agents of SARS, AIDS, Zika, Ebola, yellow fever, and the flu, are neither cells nor organisms.

Microparasites reproduce within their hosts and are sometimes referred to as infectious microbes, or, more commonly, "germs." Larger parasites, ones that can be seen without the use of a microscope, are referred to as macroparasites; they are composed of many cells. Those that most often cause diseases of humans or domestic animals are roundworms, such as the hookworm; flatworms, such as the blood fluke; blood-sucking insects, such as mosquitoes, flies, and lice; or arachnids, such as ticks. Macroparasites do not multiply within an infected individual (except in the case of larval stages in the intermediate hosts) but instead produce infective stages that usually pass out of the body of one host before transmission to another host.

"What's in a name? That which we call a rose by any other name would smell as sweet." When William Shakespeare penned these lines in *Romeo and Juliet*, he gave value to substance over name-calling. But being able to tell one microbe from another is more than having a proper name for a germ—it can have practical value. Imagine you have just returned from a trip and now suffer with a fever, headache, and joint pains, and worst of all you have a severe case of diarrhea. What a mess you are! When you see your physician, she tells you that the cause of your distress could be due to an infection with *Salmonella* or *Giardia* or *Entamoeba* or the influenza or SARS virus. Prescribing an antibiotic for diseases caused by a virus would do you no good, but for "food poisoning" caused by *Salmonella*, a bacterium, a course of antibiotic therapy might restore you to health. On the other hand, if your clinical symptoms were due to the presence of protozoan parasites such as *Giardia* or *Entamoeba*, they would not respond to antibiotics either, and other drugs would have to be prescribed to cure you. Determining the kind of parasite (or parasites) you harbor, therefore, will do more than provide the name of the offender; it will allow for the selective treatment of your illness.

*See: Cells and Their Structure in the Appendix

Plagues and Parasites

In antiquity, all disease outbreaks, irrespective of their cause, were called plagues; the word "plague" comes from the Latin *plaga*, meaning "to strike a blow that wounds." When a parasite invades a host, it establishes an infection and wounds the body (Fig. 1.2). Individuals who are infected and can spread the disease to others (such as SARS patient 4) are said to be contagious or infectious. Initially, Legionnaires' disease and TSS were thought to be contagious. Despite the obvious clinical signs of coughing, nausea, vomiting, and diarrhea, however, a person-to-person-transmissible agent was not found. In short, the victims of TSS and Legionnaires' disease were not infectious, in contrast to what we know in cases of influenza, SARS, and the common cold with a similar array of symptoms. Influenza and SARS are different kinds of diseases of the upper respiratory system: the flu is contagious 24 h before symptoms appear, has a short (2-to-4-day) incubation period, and requires hospitalization infrequently; whereas SARS has a longer (3-to-10-day) incubation period, the patient is infectious only after symptoms appear, and the infection requires that the victim be hospitalized.

Infectiousness, however, may persist even after disease symptoms have disappeared; such infectious but asymptomatic individuals are called carriers. The most famous of these carriers was the woman called "Typhoid Mary," an Irish immigrant to the United States whose real name was Mary Mallon. In 1883 she began working as a cook for a wealthy New York banker, Charles Henry Warren, and his family. The Warren family rented their large house in Oyster Bay, Long Island, from a George Thompson. That summer, six of eleven people in the house came down with typhoid fever (caused by the "germ" *Salmonella typhi*), including Mrs. Warren, two daughters, two maids, and a gardener. Mr. Thompson, fearing he would be unable to rent his "diseased house" to others, hired George Soper, a sanitary engineer, to find the source of the epidemic. Soper's investigation soon led him to Mary Mallon, who had been hired as a cook just 3 weeks before the outbreak of typhoid in the Warren household. Mary had remained with the Warrens for only a month and had already taken another position when Soper found her. On June 15, 1907, Soper published his findings in the *Journal of the American Medical Association*: Mary was a healthy carrier of typhoid germs. Although she was unaffected by the disease (which causes headache, loss of energy, diarrhea, high fever, and, in a tenth of cases, death), she still could spread it. When Soper confronted Mary and told her she was spreading death and disease through her cooking, she responded by seizing a carving fork, rushing at him, and driving Soper off. Soper, however, was undaunted and convinced the New York City Health Department that Mary was a threat to the public's health. She was forcibly carried off to an isolation cottage at Riverside Hospital on Rikers Island in the Bronx. There, her feces were examined and found to contain the ty-

phoid bacteria. Mary remained at the hospital, without her consent, for 3 years and then was allowed to go free as long as she remained in contact with the Health Department and did not engage in food preparation. She disappeared from the Health Department's view for a time but then took employment as a cook at the Sloane Maternity Hospital under an assumed name, Mrs. Brown.

During this time she spread typhoid to 25 doctors, nurses, and staff, 2 of whom died. She was sent again to Rikers Island, where she lived the rest of her life, 23 years, alone in a one-room cottage. During her career as a cook, "Typhoid Mary" probably infected many more than the 50 documented cases, and she surely caused more than 3 deaths. Mary Mallon was not the only human carrier of typhoid. In 1938 when she died, the New York City Health Department noted that there were 237 others living under their observation. She was the only one kept isolated for years, however, and one historian has ascribed this to prejudice toward the Irish and a noncompliant woman who could not accept that unseen and unfelt "bugs" could infect others. Mary Mallon told a newspaper: "I have never had typhoid in my life and have always been healthy. Why should I be banished like a leper and compelled to live in solitary confinement … ?"

Predicting Plagues

Recognizing the elements required for a parasite to spread in a population allows for better forecasting of the course a disease may take. Three factors are required for a parasite to spread from host to host: there must be infectious individuals, there must be susceptible individuals, and there must be a means for transmission between the two. Transmission may be by indirect contact involving vectors such as mosquitoes (in malaria and yellow fever) or flies (in sleeping sickness and river blindness) or ticks (in Lyme disease), or it may be by direct contact as it is with measles, influenza, SARS, and tuberculosis, where it is influenced by population density.

In the past, the sudden increase in the number of individuals in a population affected by a disease was called a plague. Today we frequently refer to such a disease outbreak as an epidemic, a word that comes from the Greek *epi*, meaning "among," and *demos*, "the people." Epidemiologists are disease forecasters who study the occurrence, spread, and control of a disease in a population, using statistical data and mathematical modeling to identify the causes and modes of disease transmission and to predict the likelihood of an epidemic, to identify the risk factors, and to help plan control programs such as quarantine and vaccination. When TSS broke out, epidemiologic studies linked the syndrome to the use of tampons, principally Rely tampons, and the recommendation was that the illness could be controlled in menstruating women by the removal of such tampons from the market. Acting on this advice, Procter & Gam-

ble stopped marketing Rely tampons and the number of cases virtually disappeared.

For an infection to persist in a population, each infected individual on average must transmit the infection to at least one other individual. The number of individuals each infected person infects at the beginning of an epidemic is given by the notation R_0; this is the basic reproductive ratio of the disease, or, more simply, the multiplier of the disease. The multiplier helps to predict how fast a disease will spread through the population.

The value for R_0 can be visualized by considering the children's playground game of touch tag. In this game one person is chosen to be "it," and the objective of the game is for that player to touch another, who in turn also becomes "it." From then on each person touched helps to tag others. If no other player is tagged, the game is over, but if more than one other player becomes "it," then the number of touch taggers multiplies. Thus, if the infected individual (it) successfully transmits the disease (touches another), then the number of diseased individuals (touch taggers) multiplies. In this example the value for R_0 is the number of touch taggers that result from being in contact with "it."

The longer a person is infectious and the greater the number of contacts that the infectious individual has with those who are uninfected, the greater the value of R_0 and the faster the disease will spread. An increase in the population size or in the rate of transmission increases R_0, whereas an increase in parasite mortality or a decrease in transmission will reduce the spread of disease in a population. Thus, a change that increases the value of R_0 tends to increase the proportion of hosts infected (prevalence) as well as the burden (incidence) of a disease. Usually, as the size of the host population increases, so do disease prevalence and incidence.

If the value for R_0 is >1, then the "seeds" of the infection (i.e., the transmission stages) will lead to an ever-expanding spread of the disease—an epidemic or a plague—but in time, as the pool of susceptible individuals is consumed (like fuel in a fire), the epidemic may eventually burn itself out, leaving the population to await a slow replenishment of new susceptible hosts (providing additional fuel) through birth or immigration. Then a new epidemic may be triggered by the introduction of a new parasite or mutation, or there may be a slow oscillation in the number of infections, eventually leading to a persistent low level of disease. If R_0 is <1, though, then each infection produces <1 transmission stage and the parasite cannot establish itself.

The economic costs of the outbreak of SARS in 2003 were nearly $100 billion as a result of decreased travel and decreased investment in Southeast Asia. The University of California at Berkeley was so concerned about this epidemic that it put a ban on Asian students planning to enroll for the summer session. The question raised at the outset was: How long will the SARS outbreak last? Calculating the value of R_0 provid-

ed an answer. Analysis of ~200 cases during the first 10 weeks of the epidemic gave an R_0 value of 3.0, meaning that a single infectious case of SARS would infect about three others if control measures were not instituted. This value suggested a low to moderate rate of transmissibility and that hospitalization would block the spread of SARS. The prediction was borne out: transmission rates fell as a result of reductions in population contact rates and improved hospital infection control as well as more rapid hospitalization of suspected (but asymptomatic) individuals. By July of 2003 the R_0 value was much smaller than 1, and the ban on Asian students enrolling at the Berkeley campus of the University of California was lifted.

Epidemiologists know that host population density is critical in determining whether a parasite can become established and persist. The threshold value for disease establishment can be obtained by finding the population density for which $R_0 = 1$. In general, the size of the population needed to maintain an infection varies inversely with the transmission efficiency and directly with the death rate (virulence). Thus, virulent parasites, that is, those causing an increased number of deaths, require larger populations to be sustained, whereas parasites with reduced virulence may persist in smaller populations.

Measles, caused by a virus, provides an almost ideal pattern for studying the spread of a disease in a community. The virus is transmitted through the air as a fine mist released through coughing, sneezing, and talking. The virus-laden droplets reach the cells of the upper respiratory tract (nose and throat) and the eyes and then move on to the lower respiratory tract (lungs and bronchi). After infection, the virus multiplies for 2 to 4 days at these sites and then spreads to the lymph nodes, where another round of multiplication occurs. The released viruses invade white blood cells and are carried to all parts of the body using the bloodstream as a waterway. During this time the infected individual shows no signs of disease. But after an incubation period (8 to 12 days), there is fever, weakness, loss of appetite, coughing, a runny nose, and a tearing of the eyes. Virus replication is now in high gear. Up to this point the individual probably believes his or her suffering is a result of a cold or influenza, but when a telltale rash appears—first on the ears and forehead and then spreading over the face, neck, trunk, and to the feet—it is clearly neither influenza nor a common cold. Once a measles infection has begun, there is no treatment to halt the spread of the virus in the body.

Measles passes from one host to another without any intermediary; recovery from a single exposure produces lifelong immunity. As a consequence, measles commonly afflicts children, and for that reason it is called a "childhood disease." Although measles has been eradicated in the United States because of childhood immunization, it can be responsible for a death rate of ~30% in lesser-developed countries. It is one of the ten most frequent causes of death in the world today. One of the

reasons that measles may disappear from a community is immunity that may be the result of natural recovery from an infection or immunization.

The spread of infection from an infected individual through the community can be thought of as a process of diffusion, in which the motions of the individuals are random and movement is from a higher concentration to a lower one. Therefore, factors affecting its spread include the size of the population, those communal activities that serve to bring the susceptible individuals in contact with infectious individuals, the countermeasures used (e.g., quarantine, hospitalization, and immunization), and seasonal patterns. For example, in northern temperate zones, measles spreads most frequently in the winter months because people tend to be confined indoors, while in Iceland, when the spring thaw is followed by a harvest, there are also summer peaks because of communal activities on the farm.

Epidemiologists have as one of their goals the formulation of a testable theory to project the course of future epidemics. It is possible to calculate the critical rate of sexual partner exchange that will allow an STD to spread through a population, i.e., when R_0 is >1. For HIV, with a duration of infectiousness of 0.5 year and a transmission probability of 0.2, the partner exchange value is 10 new partners per year. For other STDs, such as untreated syphilis and gonorrhea, with somewhat higher transmission probabilities, the values are 7 and 3, respectively. Despite the development of mathematical equations, predicting the spread of an epidemic can be as uncertain as forecasting when a hurricane, blizzard, or tornado will occur. Indeed, making predictions early in a disease outbreak by fitting simple curves can be misleading because it generally ignores interventions to reduce the contact rate and the probability of transmission. For SARS, fitting an exponential curve to data from Hong Kong obtained between February 21 and April 3, 2003, predicted 71,583 cases 60 days later, but using a linear plot, 2,410 cases were predicted. In fact, by May 30, 2003, according to the WHO, there were >8,200 cases worldwide and >800 deaths. By July 5, 2003, a headline in the *New York Times* declared "SARS contained, with no more cases in the last 20 days."

Other uncertainties in predictability may involve changes in travel patterns with contact and risk increased. Sociological changes may also affect the spread of disease—children in school may influence the spread of measles, as occurred in Iceland when villages grew into towns and cities. Quarantine of infected individuals has also been used as a control measure. Generally speaking, quarantine is ineffective, and more often than not it is put in place to reassure the concerned citizens that steps at control are being taken. As is noted above, though, there are other interventions that do affect the spread of disease by reducing the number of susceptible individuals. One of the more effective measures is immunization.

A Measles Outbreak

In the year 2015, for some, Disneyland wasn't the happiest place on Earth. It was in January of that year that a single measles-infected individual was able to spread the disease to 145 people in the United States and a dozen others in Canada and Mexico. Patient zero in the 3-month-old Disneyland outbreak was probably exposed to measles overseas and while contagious unknowingly visited the park. (The measles strain in the Disneyland outbreak was found to be identical to one that spread through the Philippines in 2014, where it sickened ~50,000 and killed 110. It is likely that patient zero acquired the virus there.)

Measles spreads from person to person by sneezing and coughing; the virus particles are hardy and can survive as long as 2 h on doorknobs, handrails, elevator buttons, and even in air. For the first 10 to 14 days after infection, there are no signs or symptoms. A mild to moderate fever, often accompanied by a persistent cough, runny nose, inflamed eyes (conjunctivitis), and sore throat, follows. This relatively mild illness may last 2 or 3 days. Over the next few days, the rash spreads down the arms and trunk, then over the thighs, lower legs, and feet. At the same time, fever rises sharply, often as high as 104 to 105.8°F (40 to 41°C). The rash gradually recedes, and usually lifelong immunity follows recovery. Complications, which may include diarrhea, blindness, inflammation of the brain, and pneumonia, occur in ~30% of cases. Between 1912 and 1916 there were 5,300 measles deaths per year in the United States. Yet all that changed in 1968 with the introduction of the measles vaccine; in the United States, measles was declared eliminated in 2000.

What, then, underlies the Disneyland outbreak?

On average, every measles-infected person is able to spread the disease to ten other people, i.e., its R_0 value is 10. With this multiplier, measles will spread explosively; indeed, with multiplication every 2 weeks and without any effective control (such as immunization), millions could become infected in a few months. It has been estimated that to eliminate measles (and whooping cough) ~95% of children under the age of 2 must be immunized. For disease elimination not everyone in the population need be immunized, but it is necessary to reduce the number of susceptible individuals below a critical point (called herd immunity).

An analysis of the Disneyland outbreak of measles shows that that those infected were unvaccinated. The researchers have calculated that the number of vaccinated individuals might have been as low as 50%. The outbreak that began in California was a reflection of the anti-vaccination movement, which had led some parents to believe the false claim that the vaccine for measles caused an increase in autism. (The "evidence" for this was based on just 12 children and has been thoroughly discredited by massive studies involving half a million children in Denmark

and 2 million children in Sweden.) Then, too, some parents believe their children are being immunized too often and with too much vaccine because pharmaceutical companies are recklessly promoting vaccination in pursuit of profit. Other parents contend that the vaccine is in itself dangerous. It is not, as is evidenced in Orange County, where Disneyland is located: the outbreak sickened 35 people, including 14 children. And although a measles vaccine has been available worldwide for decades, according to the WHO, about 400 people a day died in 2013.

The response to the outbreak at Disneyland prompted the California Senate to pass a bill, SB 277, which required almost all California schoolchildren to be fully vaccinated in order to attend public or private school, regardless of their parents' personal or religious beliefs. In signing the bill, Governor Edmund G. (Jerry) Brown wrote: "While it is true that no medical intervention is without risk, the evidence shows that immunization powerfully benefits and protects the community."

The Evolution of Plagues

"A recurrent problem for all parasites … is how to get from one host to another in a world in which such hosts are never contiguous entities," wrote the historian William McNeill. He went on: "Prolonged interaction between human host and infectious organisms, carried on across many generations and among suitably numerous populations on each side, creates a pattern of mutual adaptation to survive. A disease organism that kills its host quickly creates a crisis for itself since a new host must somehow be found often enough and soon enough, to keep its chain of generations going." Based on this view, it would seem obvious that the longer the host lives, the greater the possibility for the parasite to grow, reproduce, and disperse its infective stages to new hosts. The conventional wisdom, therefore, is that the most successful parasites are those that cause the least harm to the host, and over time virulent parasites would tend to become benign.

At first glance, it would appear that the progress of the disease myxomatosis in Australia supports this evolutionary perspective. The story of myxomatosis begins in 1839, when the Austin family migrated from England to Australia. Over time they became rich from sheep farming. To reestablish their English environment, the Austins imported furniture, goods, and a variety of animals. In 1859 a ship came from England to Australia with rabbits. Since the rabbits had no natural predators, they multiplied rapidly, destroying plants and the native animals. The Austins began to wage war on the rabbits. By 1865, >20,000 rabbits were killed on the Austin estate. And still the rabbits continued to spread, traveling as much as 70 miles per year. Control measures such as fences, barbed wire, ditches, and the like did not work. A viral disease of wild rabbits from South America, called myxomatosis and lethal

to domestic rabbits, was introduced into Australia in the 1950s to act as a biological control agent. The vector for the myxoma virus is a mosquito. In 1950, 99% of the rabbits died of myxomatosis. Several years later the virus killed only 90%, and it declined in lethality with subsequent outbreaks. It was also found that the viruses from the later epidemics were less virulent than the earlier forms and that these less virulent forms were much better at being transmitted by mosquitoes—the rabbits lived longer and the number of infected rabbits was higher with milder disease. One may conclude that the virus had evolved toward benign coexistence with the rabbit host. McNeill, impressed by the results of the introduction of the myxoma virus into Australia, wrote: "from an ecological point of view … many of the most lethal disease-causing organisms are poorly adjusted to their role as parasites … and are in the early stages of biological adaptation to their human host; though one must not assume that prolonged co-existence necessarily leads toward mutual harmlessness. Through a process of mutual accommodation between host and parasite … they arrive at a mutually tolerable arrangement … (and based on myxomatosis) … some 120-150 years are needed for a human population to stabilize their response to drastic new infections." There is, however, reason to question McNeill's conclusions.

A recent reexamination of myxomatosis in Australia shows that the mortality of the rabbits, after the decrease in the virulence of the virus and the increase in rabbit resistance, was comparable to the mortality of most vector-borne diseases of humans, such as malaria. In other words, the virus was hardly becoming benign. Further, the decrease in virulence observed over the first 10 years of the study did not continue, but reversed. It appears that myxomatosis is not an example of benign evolution.

An alternative to the contention that parasites evolve toward a harmless state is that natural selection favors an intermediate level of virulence. This intermediate level is the result of a trade-off between parasite transmission and parasite-induced death. Since the value for R_0 increases with the transmission rate as well as the duration of the host's infectiousness, an increase in transmission would reduce the duration of infection, and then selection may favor intermediate virulence. And because R_0 depends directly on the density of susceptible hosts, if the number of susceptible individuals is great, then a parasite may benefit from an increased rate of transmission even if this kills the host sooner and prevents transmission at a later time. If susceptible hosts are not abundant, however, then the parasite that causes less harm to the host (i.e., is less virulent) may be favored since that would allow the host to live longer, thereby providing more time for the production of transmission stages. The hypothesis that virulence is always favored when hosts are plentiful and is reduced when there are fewer hosts neglects the fact that a feedback exists in the host-parasite interaction: a change in parasite virulence impacts the density of

the host population, and this in turn alters the pressures of natural selection on the parasite population, and so on. Thus, although parasite virulence generally tends to decline over evolutionary time, it never becomes entirely benign, and in the process the parasite population becomes more efficient in regulating the size of the susceptible host population.

The view that parasites evolve toward becoming benign suggests that parasites are inefficient if they reproduce so extensively that they leave behind millions of progeny in an ill or dead host. Indeed, some biologists have contended that enhanced virulence is the mark of an ill-adapted parasite or of one recently acquired by the host. This is not true. The number of parasite progeny lost is not of evolutionary significance; rather, it is the number of offspring that pass on their genes to succeeding generations that determines evolutionary success. Natural selection does not favor the best outcome for the greatest number of individuals over the greatest amount of time, but instead favors those characteristics that increase the passing-on of a specific set of genes. Consider a particular species of weed that is growing in your garden. The production of 1,000 seeds that yields only 100 new weed plants might be considered wasteful in terms of seed death and the amount of energy the weed put into seed production, but if the surviving seeds ultimately yield more weed plants in succeeding generations, then that weed species is more efficient in terms of evolutionary success. Parasites are like weeds. They have a high biotic potential, and those that leave the greatest number of offspring in succeeding generations are the winners, evolutionarily speaking. Evolutionary fitness, be it for a parasite, human, bird, or bee, is a measure of the success of the individual in passing on its genes into future generations through survival and reproduction. When the fitness of the host is reduced by a parasite, there is harm, illness, and an increased tendency toward death. Host resistance is the counterbalance to virulence or the degree of harm imposed on the host by the presence of the parasite. If host resistance is lowered, a disease may be more pathogenic although the parasite's inherent virulence may be unchanged. How negatively a host will be affected, i.e., how severe or how pathogenic is the disease, is thus determined by two components: virulence and host resistance. In addition, virulence is not so much a matter of a particular mutation but rather how that mutation is filtered through the process of natural selection; it is through natural selection that the final outcome may be a lethal outbreak or a mild disease, and, of course, when a new pathogen emerges, R_0 must be a number >1.

Since parasite survival requires reaching and infecting new hosts, effective dispersal mechanisms may require that the host become sick: sneezing, coughing, and diarrhea may assist in parasite transmission. The conventional wisdom is that it takes a prolonged period of time for virulence to evolve; the evolution of parasite

virulence, however, may be quite rapid (on the order of months) and need not take years, as was the case with the myxoma virus. The basis for this is that a parasite may go through hundreds of generations during the single lifetime of its host. Then, too, because of competition between different parasites living in a single host, it might be advantageous for one kind of parasite to multiply as rapidly as it can before the host dies from the other infectious species. Succinctly, the victorious parasite is the one that most ruthlessly exploits the pool of resources (food) provided by the host and produces more offspring, thus increasing its chances to reach and infect new hosts.

If parasite dispersal depends on the mobility of the host as well as host survival, then severe damage inflicted on the host by enhanced virulence could endanger the life of the parasite.

Consider, for example, the common cold. It would be very much in the interest of the cold virus to avoid making you very sick, since the sicker you become, the more likely you are to stay at home and in bed; this would reduce the number of contacts you would have with other potential hosts, thereby reducing the possibilities for virus transmission by direct contact. Similarly, the development of diarrhea in a person with the disease cholera or *Salmonella* infection (which causes "food poisoning") facilitates the dispersal of these intestinal microbes via fecally contaminated water and food, and in the absence of diarrhea parasite transmission would be reduced.

AIDS is a consequence of an increase in the virulence of HIV. The enhancement in HIV virulence is believed to have resulted from accelerated transmission rates due to changes in human sexual behavior: the increased numbers of sexual partners was so effective in spreading the virus that human survival became less important than survival of the parasite. As the various kinds of plagues are considered in greater detail in subsequent chapters, recognition of the evolutionary basis for virulence may suggest strategies for public health programs. Clean water may thus favor a reduction in the virulence of waterborne intestinal parasites (such as cholera), and clean needle exchange and condom use would both reduce transmission and lessen HIV virulence. But some contend that this indirect mechanism may be too weak and too slow to reduce virulence substantially, and that a better approach could be direct selection by targeting the virulence factor itself. For example, immunization that produces immunity against the toxin produced by the diphtheria microbe also results in a decline in virulence. Future efforts will determine which strategy is the better means for effective "germ" control to improve the public's health.

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2
Plagues, the Price of Being Sedentary

In Stanley Kubrick's classic film *2001: A Space Odyssey*, Richard Strauss's music ("Thus Spake Zarathustra") provides a haunting and frightening background to the sequence of scenes that represent the dawn of humanity. The sun rises on a barren African savannah. A band of squat, hairy ape-men appear; they eat grass. Though herds of tapirs graze close by, the ape-men ignore them, since the means and the tools necessary to attack or kill the tapirs have not yet been developed. These ape-men are vegetarians who forage for roots and edible plants. On the dawn of the second day, the ape-men are seen huddled around a water hole; the landscape is littered with bones. One, the leader of the group, picks up a bone, smashes the skeleton of an antelope, and then the bone is used to kill a tapir (Fig. 2.1). Shortly thereafter, the raw pieces of tapir flesh are eaten and shared by other hairy apelike creatures, members of the clan. At the dawn of the third day, the meat-eating, tool-using man-apes drive off a neighboring band of apelike creatures. Bone tools used for killing animal prey are now used to threaten and drive off rival tribes. In slow motion, accompanied by the slowly building tones of Strauss's music, the leader of the man-apes flings his weapon, a fragmented piece of bone, into the air. It spins upward, twisting and turning, end over end. There is a jump cut of 4 million years into the future, and the bone dissolves into a white, orbiting space satellite. Kubrick's science fiction film has been described as a countdown to tomorrow, a visual masterpiece and a compelling drama of human evolution. Absent from the film is an examination of how the enlightened roving bands of early apelike humans settled down and become increasingly disease-ridden. Here is that part of the story.

Figure 2.1 (Left) Hollywood's view of A*ustralopithecus* as seen in the movie *2001: A Space Odyssey*. Turner Entertainment Co. Licensed by Warner Bros Entertainment Inc. All rights reserved, Alamy Stock Photo

Becoming Human, Becoming Parasitized

It is now generally accepted that Africa was the cradle of humanity. The earliest evidence of hominids, that is, animals ancestral to modern humans and not closely related to other monkeys and apes, is found in Africa. The evidence for this comes from unearthed bones and teeth (fossils). The fossil record shows that one of our oldest ancestors—called *Australopithecus*—lived in Africa about 4.2 million to 3.8 million years ago. These early hominids, which split from the ape lineage (and were discovered in Kenya in1994), are named *A. anamensis*, and to judge from the structure of the teeth and the position of the opening where the spinal cord enters the skull, one can conclude that they were apelike humans, not apes. Our ancestor *Australopithecus* spent time in trees and basically behaved similarly to chimpanzees, or so we believe, since fossils provide no record of behavior. Whether *A. anamensis* walked on two feet is uncertain, but evidence for erect, upright posture in *Australopithecus* comes from bones discovered in Ethiopia and Tanzania that are 3.8 million to 3.0 million years old, from a species named *A. afarensis*. One of these finds, a small female, was discovered and named Lucy by Donald C. Johanson of the University of California at Berkeley. The limb structure and the way the hip joint and pelvis articulate make it clear that Lucy walked on two legs (Fig. 2.2). This was dramatically shown by Mary Leakey and her team, who discovered three sets of fossilized footprints left in wet volcanic ash some 3.2 million years ago. *A. afarensis* weighed about 75 lb and was not very "brainy," its brain being no larger than the brains of living African great apes. When *A. afarensis* descended from the trees and stood upright with two feet firmly planted on the ground, not only did it affect posture, but it dramatically changed lifestyles and diets, and disease patterns began to be altered.

Descent from the trees to the ground placed the australopithecines into a new environment, an ecological niche that was very different from the forest canopy. This freed them from some diseases but allowed for the acquisition of new ones. For example, in the treetops australopithecines would have been bitten by mosquitoes that carried parasites acquired from other animals living in the canopy, but at ground level they would be exposed to other airborne bloodsuckers such as ticks and flies, or they would come in contact with different food sources and contaminated water. Their teeth were small and underdeveloped, as in modern human beings, and the canines, highly developed in existing ape species, were small like ours. We can infer from their teeth that these australopithecines probably chewed fruits, seeds, pods, roots, and tubers. Since no stone tools have been found associated with the fossils, it is believed that *A. afarensis* did not make or use durable tools or understand the use of fire. They were opportunistic scavengers or vegetarians. The life span of an australopithecine has been estimated to have been between 18 and 23 years.

Figure 2.2 *Australopithecus* reconstruction of Mr. and Mrs. Lucy.
Courtesy of Ken Mowbry, American Museum of Natural History

Beginning about 3 million years ago, the climate in Africa changed from tropical warm and wet to a more temperate cool and dry one, and as a consequence, the dense woodlands were replaced by more open grassy habitats, a savannah. This climate change presented a challenging environment for the woodland-dwelling australopithecines. Although we do not know whether the climate change triggered it, at about this same time, ~2.5 million to 1.8 million years ago, there appear in the fossil record several different kinds (species) of hominids, with two or three coexisting species in eastern and southern Africa. One of these species was *A. boisei*, a small-brained vegetarian, and the other was *Homo habilis* (Fig. 2.3b). The name *Homo habilis*, or "handy man," is based on the fact that altered stones and animal remains have been found with the fossil bones. *H. habilis* was more than a scavenger and a gatherer. *H. habilis* was also a hunter who made and used stone tools: simple stone flakes, scrapers and "choppers" that were chipped from larger stones (Fig. 2.3a). (These stone tools, first found in Africa's Olduvai Gorge, are called Oldowan tools.) The fashioning of tools suggests a great leap in human intelligence and begins the technological changes that would forever mark *Homo* as a tool maker and a tool user. *H. habilis* used the flake tools to cut up the carcasses of the animals that were killed; these were

Figure 2.3a Oldowan tools used by *Homo habilis,* Courtesy Didier Descouens, CC-BY-SA 4.0

transported to a home base where the meat was fed upon. *H. habilis*, with a somewhat larger brain, was "smarter" than *A. afarensis*, but the fossil finds tell us nothing of the numbers of individuals, whether there was division of labor among males and females, or anything about their behavior. We speculate, however, that there were 50 to 60 individuals in a group living in an area of 200 to 600 square miles. We imagine that *H. habilis* lived at the edge of shallow lakes and in crude rock shelters.

There is no fossil record of the parasites that afflicted *H. habilis* since their soft bodies have disintegrated over time, but we do know that with meat eating came an increase in parasitism. As these nomadic hunters encountered new prey, they met new parasites and new vectors of parasites. The result was zoonosis; that is, animal infections were transmitted to humans. What were these zoonotic infections? We surmise that the parasites of *H. habilis* were those acquired from the wild animals that were killed and scavenged. The butchered meat might have had parasites such as the bacteria anthrax and tetanus, the roundworm that causes trichinosis, and a variety of intestinal tapeworms. *H. habilis* would probably have been bitten by mosquitoes, ticks, mites, and tsetse flies, and probably also had head lice. *H. habilis* also may have suffered from viral diseases such as the mosquito-transmitted yellow fever, as well as non-vector-borne viruses that cause hepatitis, herpes, and colds, and he may have had spirochete infections such as yaws. It is doubtful, but *H. habilis* could also have been infected with the parasites that cause sleeping sickness, malaria, and leprosy. They certainly must have been infected with filaria, pinworms, and blood flukes,

Figure 2.3b Diorama in the Nairobi National Museum of *Homo habilis*,

Figure 2.3c *Acheulean tools used by Homo erectus,* Courtesy Didier Descouens

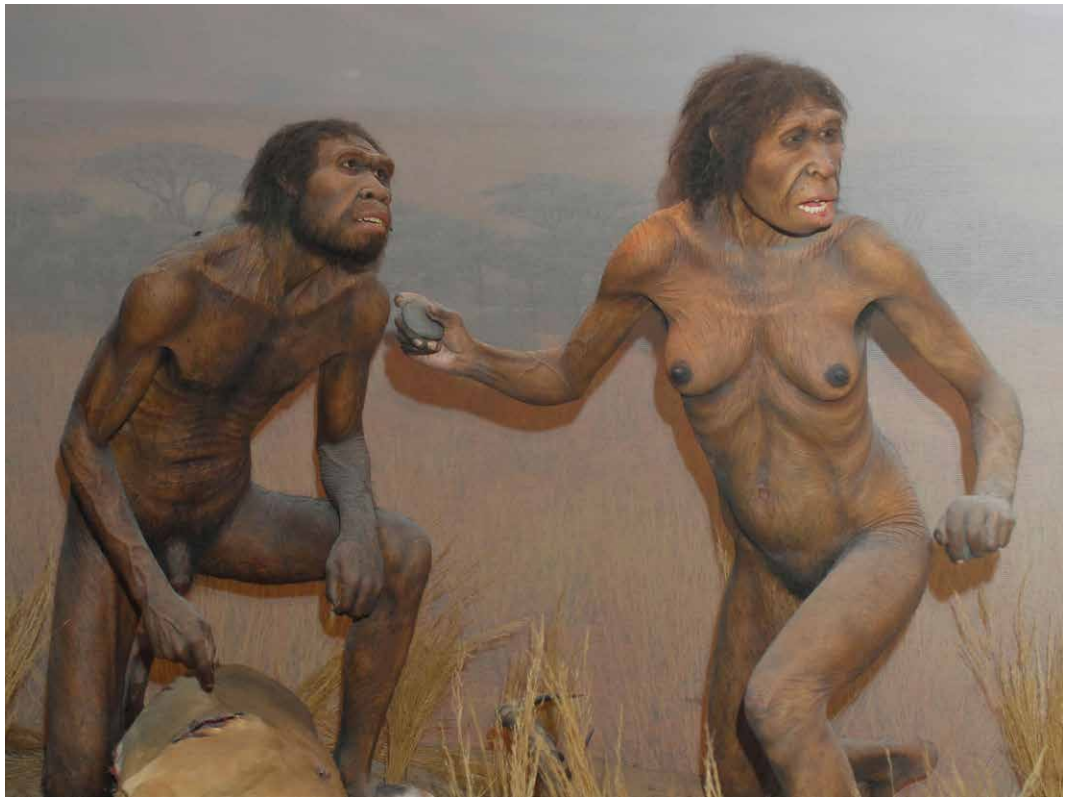

Figure 2.3d Diorama of *H. ergaster* the "African equivalent" to fossils of *H. erectus*. Alamy Stock Photo.

but probably did not have typhus, mumps, measles, influenza, tuberculosis, cholera, chickenpox, diphtheria, or gonorrhea. At the time when *H. habilis* roamed the African savannah, the human population was quite small, consisting of about 100,000 individuals, and we expect that rates of human-to-human transmission of parasites were low.

Roughly 1.6 million years ago (or ~1.8 million years ago in Africa), *H. habilis* was replaced by *H. erectus* (meaning "erect man") (Fig. 2.3d). (In Africa, *H. erectus* is equivalent to fossils that have been named *H. ergaster*.) *H. erectus* was close to modern humans in body size, and its skull capacity suggests that it was somewhat larger-brained than *H. habilis*—but still with barely half the capacity of modern humans. *H. erectus* had smaller cheek teeth, suggesting that they were omnivores; they were smaller-faced; they developed a culture characterized by living in caves; and they hunted game animals using bifaced flake stone tools fashioned into "hand axes." This stone tool technology (called Acheulean tools) (Fig. 2.3c) allowed *H. erectus* to process more completely the harder parts of animals and plants by grinding, crushing, splitting, and cutting up these before eating. As such, these stone tools represented a technological advance and served as extensions of the hands and teeth to break down food before digestion. *H. erectus* was able to start fires and made use of fire to cook the food. The *H. erectus* population was now somewhat less than a million. According to the "long journey" hypothesis, about 2 million years ago the *H. erectus* populations began to move out of Africa via the Middle East, but climate and geography prevented them from turning west, and so they took a more southerly route into present-day China and Indonesia. Then they turned north and moved west again across the more central parts of Europe and Asia. The earliest fossil remains of *H. erectus* were found in Indonesia (Java) by Eugene Dubois in 1891 and so were named Java Man; 2 decades later, when Davidson Black found similar fossils in caves in China, they became known as Peking Man. The cave sites in China are ~500,000 years old, and the last of these were abandoned ~230,000 years ago.

When the populations of *H. erectus* left Africa, some of their parasites went with them, but only those that could be transmitted directly from person to person. Those vectors that remained restricted to Africa, such as the species of mosquito, snail, and fly that transmit diseases such as filariasis, blood fluke disease, and sleeping sickness, respectively, did not follow the migratory path. Indeed, even today they remain diseases that are characteristic of Africa. But as *H. erectus* encountered new environments with new kinds of animals, they were subjected to sources of new parasites; with an increase in the number of humans living in more-restricted geographic environments, the probability for large-scale infections was enhanced.

Tool making and tool use, as well as human cooperation, made hunting possible. Together they contributed to further increases in the size of the human population,

and over time *H. erectus* evolved into humans closely resembling us. A half-million years ago the human populations of Africa and those in Europe and Asia began to diverge from one another. Some 200,000 years ago the fossil record shows individuals who were larger-brained; those with a more graceful face, found in southwestern Europe and dated to 40,000 years ago, were called Cro-Magnon man. In a fit of hubris, Carolus Linnaeus gave them the scientific name *Homo sapiens*, literally "wise man." *H. sapiens* not only used the stone technology of *H. erectus* but also made tools from bone and antlers. They made artistic carvings and cave paintings, kept records on bone and stone, played music on simple wind instruments, adorned themselves with jewelry, and buried their dead in ritual ceremonies; their living sites were highly organized and stratified, and they hunted and fished in groups. The intermittent technological advances in tool making seen with *H. habilis* and *H. erectus* were constantly refined. Clearly, they were our immediate ancestors. At this time the human population numbered about a million individuals.

In western Europe, human skeletons were found first in the Neander Valley of Germany in 1856; they were called Neanderthals. Subsequently, Neanderthal fossils were found in the Middle East and parts of western Asia. They date from between 190,000 and 29,000 years ago. Some archeologists have classified them as a separate species,

Figure 2.4a Neanderthal man in profile; Neanderthal woman cleaning a reindeer skin, (both) Wellcome Library, London (CC-BY 4.0)

Homo neanderthalensis. The Neanderthals, who previously have been depicted as brutish cavemen (Fig. 2.4a and b), have been "modernized" on the basis of a brain size slightly greater than our own, and they left evidence showing that they cared for the sick and performed ritual burials (Fig. 2.4c). Their stone tools, however, were cruder than those of Cro-Magnon man. Within a few thousand years the Cro-Magnons, with their superior weapons and other advanced cultural practices, had completely displaced the Neanderthals. In Africa there are skeletal remains that are more modern than those of Neanderthals, dating back 200,000 years. Thus, nearly a quarter of a million years ago, populations of *H. sapiens* lived in Africa, Asia, and Europe. Their migration into the Americas took place ~35,000 to 12,000 years ago when they crossed the land bridge at the Bering Strait from Asia into the Americas. Forty thousand years ago humans moved into Australia. Thus, over the past 5 million years, new hominid species have emerged, coexisted, competed, and colonized new environments, in some instances succeeding, in others becoming extinct. The fossil record is of necessity incomplete, and much will be learned from future anthropological digs, but what is certain is that

Figure 2.4b A 1953 B- grade movie poster representing a monster-like Neanderthal man. Courtesy of Popcorn Posters.

Figure 2.4c Neanderthal Family, Reconstruction. Ian Tattersall, American Museum of Natural History

we did not arrive by a straight-line descent from the apes; we are not the single topmost limb in the hominid evolutionary tree, but simply one of its many branches.

Hunter-gatherers, unable to preserve and store fruits, vegetables, and meat, were forced to roam over large distances in search of wild edible plants and to hunt down game animals and find sources of drinking water. Moving from place to place, these nomadic bands were not surrounded by heaps of rotting meat or feces, and exposure to parasite-infested waters was limited. Though the hunter-gatherers did come together in groups, the size of their populations was small, and so diseases of crowds requiring human-to-human transmission were absent. Based on what we know about modern hunter-gatherer societies like those in present-day New Guinea, the Australian aborigines, and the Kalahari bushmen, we believe our hunter-gatherer ancestors were a relatively healthy lot. Gradually, however, conditions would change as the size of human populations increased and people adopted sedentary habits—living for extended periods of time in permanent or semipermanent settlements. This would, over time, dramatically increase the incidence of human disease.

The Road to Plagues: More Humans, More Disease

Today we speak of the problems associated with the population bomb—the unbridled growth of humans—that threatens our very existence. This growth in human populations cannot be calculated with any certainty until the middle of the 18th century, but we can make some educated guesses. Three hundred thousand years ago there were 1 million; 25,000 years ago that number had grown to 3 million; and 10,000 years ago the estimated human population was 5 million. By A.D. 1 it was 300 million. The phenomenal growth spurt in the human population coincides with the initiation of agriculture and the domestication of animals, which is generally dated to 8000 B.C. Between 8000 B.C. and A.D. 750, the population of the world increased 160 times to 800 million. Not only was the human population increasing, so too was overcrowding. For example, in 8000 B.C. human density was 0.2 people per square mile, but by 4000 B.C. it was 4 people per square mile.

What is the basis for this growth in the human population? The English clergyman Thomas Malthus (1766-1834) wrote *An Essay on the Principle of Population* in 1798, in which he stated that a population that is unchecked increases in geometric fashion. Malthus assumed that there would be a uniform rate of doubling, and this is of course naive, because it leads to impossibly large numbers. (By way of example, if you doubled a penny every day over a month, the final amount would be >$20 million.) It has been said that explosions are not made by force alone, but by a force that exceeds restraint. As Malthus correctly observed, there are factors that will eventually bring population growth to a halt; for example, restraint could result from the fact that the food supply increases only arithmetically. The consequences of unrestrained population growth, in Malthus's words, would lead to "misery and vice," or, in today's vernacular, to starvation, disease, and war. These would tend to act as "natural restraints" on population growth. Thus, the Malthusian model suggested that a natural population has an optimal density.

If we were to make a graph plotting the human population on an arithmetic scale from 500,000 years ago to the present, we would find that the resulting curve suggests that the population remained close to the baseline from the remote past to about 500 years ago, and then it surged abruptly as a result of the scientific-industrial revolution (Fig. 2.5). More instructive, however, would be to plot the same data for a longer time period using a logarithmic scale, since this allows for more of the data points to be placed in a smaller space. This log-log plot reveals that the human population has moved upward in a stepwise fashion, and that there were three surges: those reflecting the development of tool making or the cultural revolution, followed by the agricultural, and finally by the scientific-industrial revolution. What were the

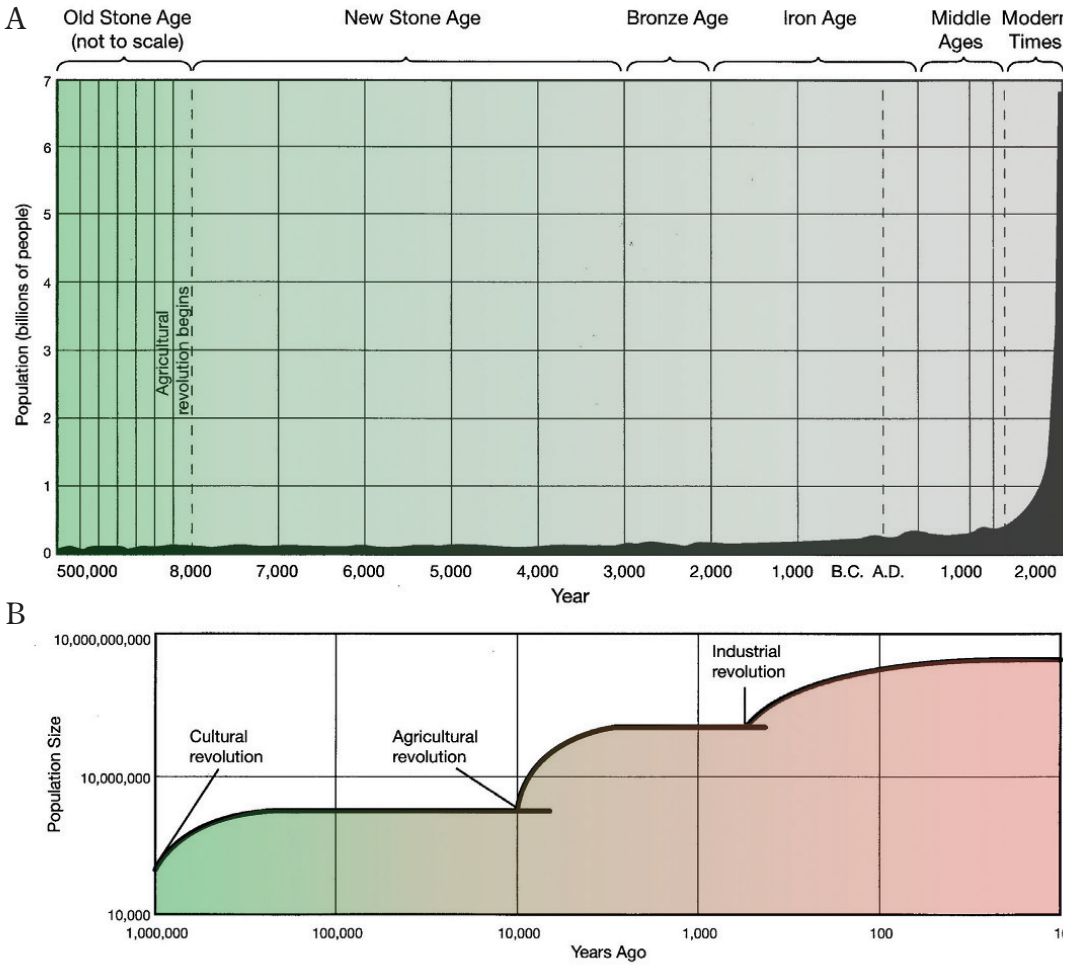

Figure 2.5 A. Growth of the human population for the last 500,000 years. If the Old Stone Age (Paleolithic) were in scale it would reach 18 feet to the left. B. Log-log plot of the human population over the last million years.

checks on human growth rates that limited population size so that at equilibrium (the flat part of the logarithmic "curve") there was a zero rate of change and the number of deaths equaled the number of births? Two kinds of checks occurred to set the upper limit (or the set point) for population growth: external or environmental factors (including limited food, space, or other resources) and self-regulating factors (such as fewer births, deliberate killing of offspring, or an increased death rate due to accidents or more-virulent parasites). For Malthus, disease and warfare as well as "moral restraint" (birth control) acted as "natural restraints"—the Four Horsemen of the Apocalypse: Disease, Famine, War, and the Pale Rider, Death. Indeed, it has been estimated that prior to the introduction of agriculture the earth could have supported

a population of between 5 million and 10 million people who were engaged in hunting and gathering. Agriculture changed the environmental restraint so that the set point, or upper limit, of population size was increased.

The Effect of Agriculture

Human history took off 50,000 years ago in what Jared Diamond, professor of geography and physiology at the University of California at Los Angeles School of Medicine, called "the Great Leap Forward." Fifty thousand years ago *H. sapiens* used standardized stone tools that could be used for cutting, scraping, and grinding, as well as pieces of bone that could be fashioned into fishhooks and spears, needles, awls, harpoons, and eventually bows and arrows. These tools could also be used as weapons, and now humans could begin to hunt down and kill their animal prey at a distance. Not only did these early humans use the meat of animals for their nourishment, but they began to clothe themselves in the skins of these animals. Through the invention of rope it was possible to make snares and nets so that birds and fishes could also become part of the diet. All this attests to the fact that between 100,000 and 50,000 years ago there was a significant change in the cognitive capacity of the human brain without a significant change in its size. Coupled with this change in brain organization was the anatomical improvement of the voice box; now humans could not only speak but also begin to develop language.

For 99% of human existence we were hunter-gatherers, so why some 10,000 years ago did we settle down to become farmers? This change from hunting and gathering to farming has been termed the agricultural revolution, the time when humans domesticated plants and animals and exerted control over food production. Although the term "revolution" would seem to indicate that it appeared suddenly and dramatically, this was certainly not the case. The human control of food production was not discovered or invented, nor was it a conscious choice made by our ancestors "to farm" or "not to farm," since at the time there would have been no farmers to serve as role models. No, domestication of plants and animals evolved as a consequence of human choice made without any awareness of its future long-term consequences.

Development of techniques and practices for agriculture and animal husbandry progressed step by step in sequential fashion. They were not developed over a short time, and not all the wild animals and wild plants that would eventually be domesticated in a particular region would be domesticated at the same time. Indeed, it probably took thousands of years to shift the human diet from wild foods alone to foods both cultivated and wild. The reason for this time lag is that food production evolved as a result of the accumulation of many separate choices, and there were trade-offs, especially in the allocation of time and effort.

Consider for the moment that you are a hunter-gatherer who has accumulated enough wisdom and technology to set up a small garden. Some of the choices you would be faced with are: Which plants should I grow? How much time should I spend planting instead of hunting or scavenging? What are the benefits of tending the garden over going out to hunt and gather wild plants? Perhaps your most important consideration might be which of the two, hunting or gardening, will save you from starvation in the future. It has been speculated by Jared Diamond that "all other things being equal, people seek to maximize their return of calories, protein or other specific food categories by foraging in a way that yields the most return with the greatest certainty in the least time for the least effort. Simultaneously they seek to minimize the risk of starving. … One suggested function of the first gardeners 11,000 years ago was to provide a reliable reserve larder as insurance in case wild food supplies failed." Although the factors that contributed to the shift from hunting and gathering to farming still remain controversial with regard to their relative importance, one thing is certain: once there was a shift from nomadic hunting and gathering to more-sedentary food production, there could be no turning back.

At the end of the Pleistocene era (~11,000 years ago), the climate began to change: the glaciers had receded; the climate became milder and drier; and many large mammals had become extinct in Europe, Asia, and Africa. This led to a decline in the abundance of wild game, and hence the life of the hunter-gatherer became more precarious: to obtain the same amount of food as in the past would require the expenditure of greater amounts of time and energy. The reduction in the number and kind of game animals was coupled with a change in climate that favored plants with the potential for domestication, particularly the cereal grains. Now there were larger and larger areas with wild cereals, and these could be harvested with little difficulty, using stone and bone tools fashioned into sickles with flint blades. In addition to the technologies for harvesting cereals such as wild barley and wheat, the technologies needed for processing and storing these grains came into being. These technologies, which appear crude and simple by today's standards, allowed for the first unconscious steps of plant domestication to take place. Tools included baskets to carry the grain from the field to the home base; mortars and pestles to remove the husks and to pulverize the grain; a technique of heating the grain to allow storage without sprouting; and the construction of underground storage pits, some of which were made waterproof by plastering. Coincident with farming, the density of the human population increased. It is not clear whether the rise in density of human populations led to the domestication of plants and animals or vice versa, but it is certainly true that with the availability of more and more calories it was possible to feed more and more people. Diamond, in his book *Guns, Germs, and Steel*, has observed that the adoption of food production

is an autocatalytic process, a positive feedback, in which a gradual rise in population densities required that people obtain more food, and in turn those who took the steps to produce it were rewarded. Once "farming" began, people could become more and more sedentary—they settled down. In turn, birth spacing could be shortened, resulting in more births and larger families, who required still more food, and so on.

Farming populations became better nourished thanks to an increase in the availability of the number of edible calories per square mile, and eventually farmers replaced the nomadic groups of hunter-gatherers by converting them to engage in the practice of farming or by displacing them by the sheer force of greater numbers.

The life of nomadic hunter-gatherers was such that population levels were well below the maximum limit that would be imposed by their reproductive biology and the availability of food. What then limited their increase? The inability of the hunter-gatherer mother to carry more than a single child along with her normal baggage, coupled with her inability to nurse more than one child at a time, limited the practical interval between births to four years. It is likely that hunter-gatherers effectively spaced their children by means of lactation amenorrhea, sexual abstinence, infanticide, and spontaneous abortion. In contrast, once humans settled down, they were freed from the encumbrances imposed on the hunters and gatherers who had to carry their children around, so that now they could have as many children as they could bear and raise. Consequently, the birth interval for the "farmer" was reduced to two years. Agriculture also encouraged higher birth rates because additional children provided cheap labor. Further, farming had another advantage over hunting and gathering: more calories could be produced per unit land area and time expended. While 200 square miles could support 50 to 60 hunter-gatherers, more than 10,000 "farmers" could be supported on this same land area. The higher birth rate of the food producers, together with their ability to feed more people per square mile, allowed these "farmers" to achieve much higher population densities than those who were engaged in hunting and gathering.

Once agriculture and animal husbandry yielded a surplus of food that could be stored, there was a need for some members of the sedentary population to guard it. This was of course impractical for the nomadic hunter-gatherers since they would have to both hunt and gather and at the same time protect their bounty from others. But the availability of surplus stored food allowed members of the settled population to specialize: some became guards, and others were armed and served as soldiers who could group together to steal food from others. Perhaps this foreshadowed the origins of war. And when food production did not require every member of the settled community to directly work the land, then it became possible for some members of the group to engage in other activities. Once humans formed agriculturally based societies, those

who chose to participate in such group activity may have been at a competitive advantage over those who did not. The latter likely became outcasts. Hence the agricultural revolution may have provided selective advantages to those who were in a controlled group, and superstition and organized religious practices were effective means for control by promoting group cohesion. It may be not be accidental that the first known and highly organized religions arose coincident with the agricultural revolution.

Some of the surplus food could be used to feed those "who provide religious justification for wars of conquest, artisans such as metalworkers who develop swords, guns and other technologies; and scribes, who preserve far more information than can be remembered accurately." In time, political stratification would develop: heading the settled community would be the elite, consisting of hereditary chiefs (or kings) and bureaucrats. Under the appropriate circumstances these complex political units, which governed "the settled," could also be mustered into formidable armies of conquest. Stored food and the land upon which it was grown became valuable resources that could be taxed, and surpluses could be traded for other goods; commerce and banking began to emerge. Thus, with larger populations family and inheritance schemes result, class structures with elaborate religious practices emerge, and writing is invented. Through agriculture and its prospect for increased food production, there was a population expansion that favored technological advances, as well as the development of cities (urbanization) and the rise of civilizations.

Another consequence of humans settling down was an increase in the amount of human disease. Agriculture by itself did not create new infections; it simply accentuated those that were already present or it converted an occasional event into a major health hazard. This was largely due to the fact that transmission of infectious agents becomes easier as individuals are crowded together; the practice of using human excrement ("night soil") or animal feces (manure) as fertilizer allows for the transmission of infective stages; and finally, the closer association with domestic animals allows for their diseases to be transmitted to humans.

The Lethal Gifts of Agriculture

Permanent settlements developed independently in several parts of the world, including the Middle East, China, and the Americas. But those that have been best studied are found in the so-called Fertile Crescent, a region bounded by the Tigris and Euphrates Rivers and curving around the Mediterranean and the Nile Valley to include present-day Syria, Lebanon, Israel, Egypt, Turkey, Jordan, Iran, and Iraq. The oldest village known, just outside present-day Jericho in Israel, may have sprung up around a shrine used by roving bands of hunters and gatherers. By 10,500 years ago it had evolved into a small farming village. At first this settlement and others like

it were simply collections of villages on the banks of natural streams, but soon they were able to spread out via networks of irrigation canals. The surplus of food and the practice of irrigation contributed to larger and larger concentrations of people, allowing some people to quit farming and to become full-time artisans, priests, or members of other professions. Meanwhile, the farmers who provided the food for these ever-enlarging villages continued to live on their outskirts. And 5,500 years ago the first undisputed city—a place where farmers do not live—Uruk in Mesopotamia (present-day Iraq), was established.

We have little precise information about the parasitic diseases that afflicted our ancestors more than 10,000 years ago. To be sure, they had their parasites, but we believe their impact may not have been quite as severe as in the period that stretches from the present back to the time of the earliest cities. The reason for this is that the pattern and the impact of disease depend on several factors: the population density, the character and quality of the water supply, food and shelter, the frequency of contact among individuals, human contact with animals, and the climate. Once human populations were concentrated into larger and larger communities and their numbers increased, however, then the enhanced potential for infectious disease organisms to be transmitted could (and did) affect the size and well-being of the population. Farming and domestication also reduce the biological variability of animals and crop plants, leading to purebred strains, making local populations of plants and animals more and more uniform. As a consequence, any upset in the balance could decimate an entire population, whether that was a crop or a flock or a herd. (A modern example of this is the 1845-1851 potato famine in Ireland.) Agriculture necessitated artificial flooding of land, which was naturally devoid of adequate amounts of water, enabling longer growing seasons; it also required tilling or plowing and replenishing the soil with fertilizer. The cheapest and most available of fertilizers is human waste or animal feces. Intensive agricultural practices, requiring crop protection from weeds and pests, demand some kind of control measures. Tilling the soil necessitates some kind of work force: animal power, human power, or machines. Disruptions in the availability of these could lead to disaster. With purebred strains (monocultures), disruption becomes that much easier. Living in villages or cities—that is, in permanent settlements—involves the risk of parasite invasion. Those infected with intestinal parasites can through their feces more easily transmit disease to others, and where the water supply becomes contaminated through the use of either night soil or fecally contaminated streams, the spread of disease can be great indeed. A single contaminated water source serving a large population can be a much greater threat than several sources supplying smaller bands of hunters and gatherers. Irrigation practices thus created a favorable environment for transmission

of parasites—moisture was abundant; there was a liquid medium in which parasites and/or their cysts and eggs could persist; and the water could also be used for drinking, bathing, washing of clothes, and waste disposal.

The disruptive effects of an epidemic disease are more than simply the loss of individual lives. Often the survivors are demoralized, they lose faith in inherited customs, and if it affects the working age group, it can lead to a material as well as a spiritual decline. As a consequence, the cohesion of the community may collapse and it may become susceptible to invasion from neighbors. Once disease is widespread in an agricultural community, it can produce a listless and debilitated peasantry, handicapped for sustained work in the fields, for digging irrigation canals, and for resisting military attack or throwing off alien political domination. All this may allow for economic exploitation.

The smaller population size of hunters and gatherers makes it seem probable that person- to-person "civilized" infectious diseases, such as measles, influenza, smallpox, and polio, could not have established themselves, because these are density-dependent diseases requiring a critical number of individuals for transmission. Although there is no hard literary or archeological evidence, it does seem reasonable to suggest, as did William McNeill, that "the major civilized regions of the Old World each developed its own peculiar mix of infectious, person-to-person diseases between the time when cities first arose (about 3000 BC) and about 500 BC. Such diseases and disease-resistant populations were biologically dangerous to neighbors unaccustomed to so formidable an array of infections. This fact made territorial expansion of civilized populations much easier than would otherwise have been the case."

The Accident That Caused Societal Differences

Imagine for a moment that you are living in the year 1492 and you have just graduated from the University of Padua in Italy with a degree in medicine. Before you are able to set up your practice, you receive a letter from an old friend, Giuseppe Diamonte, who writes from Spain that King Ferdinand and Queen Isabella are about to provide funds for the discovery of a new route to India; the expedition is to be under the command of a fellow Italian, Christopher Columbus, and he is in need of a naturalist to collect plants and animals and to act as the ship's doctor. Giuseppe writes that he has recommended you for the position. You are enthusiastic, so you board a ship in Venice, land in Barcelona, and travel by horseback to Palos, Spain. The journey across the Atlantic Ocean begins on August 3. Upon arrival in "India" (in actual fact the present-day Dominican Republic) on October 12, you are astounded to be greeted by a band of near-naked "Indians" who have paddled their canoes to greet

the ship and its crew. No iron tools or oceangoing vessels can be seen, the village consists of a scattering of huts, and there is little that could be considered a city. The natives have no writing, and what agriculture there is is on an entirely different scale from that with which you were familiar in Europe. Ten weeks earlier you left iron tools and weapons, agriculture, oceangoing ships, large cities, horses, carts and carriages, writing, money, banking, painting, sculpture, cathedrals, palaces, buildings of brick and stone, established religion and ritual, and music. You are perplexed. You ask yourself: Why has the rate of technological and political development been so much faster in Europe-Asia than in the Americas? In short, why were the Americas technologically a few thousand years behind Europe? Why were stone tools, comparable to those used by Europeans and Asians 10,000 years earlier, being used?

Fast forward to the future. In *Guns, Germs, and Steel*, Diamond argues persuasively that it was not biological differences but geography that was the decisive element. It was differences not in the braininess or genetics of the human populations but in the plant and animal resources available on a particular continent—an accident of geography—that made the difference. Diamond believes that the fortuitous accident began in the Fertile Crescent, which contained a suitable array of plants and animals, called "founders," and that these formed the basis for domestication. What were the founder plants? Those locally available in Southwest Asia/Fertile Crescent that would not serve as the basis for domestication were plants with a large amount of indigestible material such as bark or that were poisonous, low in nutritional value, or tedious to prepare and gather. The desirable attributes of plants that make them suitable for domestication include having a larger proportion of edible parts (large seeds) and a lower proportion of woody, inedible parts; being easy to harvest en masse (with a sickle); a seasonal nature; being easy to grind, easy to sow, and easily stored; and being high in yield and high in calories. Plants with these characteristics were selected for domestication. They fall into four categories: grasses (wheat, barley, oats, millet, and rice), legumes (peas and beans), fruit and nut trees (olives, figs, dates, pomegranates, grapes, apples, pears, and cherries), and fiber crops (flax, hemp, and cotton).

Of the 148 big wild terrestrial plant-eating animals (herbivores)—those suitable for domestication—only 14 were able to serve as founders. What were these founder animals that could be domesticated? In Europe and Asia in about 4000 B.C. it was the "Big Five"—sheep, goats, pigs, cows, and horses. In East Asia the cow was replaced by the yak, water buffalo, and gaur. On the other hand, although in the Americas there were mountain sheep and goats, llamas, bison, peccaries, and tapirs and in Australia there were kangaroos and in Africa zebras, buffaloes, giraffes, gazelle, antelope, elephants, and rhinoceroses, all of the latter were unsuitable for domestication. Domestication involves more than taming and requires a special suite of animal

characters: social species that occupy territories and animals that are herbivores. A potentially domesticated animal species must also have the right reflexes—it must be predictable and not panic easily, and it must not be ferocious or nasty in disposition. It must grow quickly, and it must be able to breed in captivity. The appropriate domesticated animals were the cow, goat, horse, sheep, donkey, yak, and camel. Once these animals were domesticated, what benefits did they provide? Food in the form of meat and milk, clothing and fiber from wool and hides, manure for use as a fertilizer, and animal power for land transport of goods and people, as well as for plowing fields. Indeed, before there were domesticated beasts of burden, the only means for moving goods and people across the land was on another person's back! Domesticated horses, goats, camels, and cows were hitched to wagons to move humans and their possessions, and reindeer and dogs were used to pull sleds across the snow. Horse-drawn chariots revolutionized warfare, and after the invention of saddles and stirrups, it became possible for marauding Huns on horseback to strike fear into the legions of Rome.

There was a downside to animal domestication. Domesticated animals could be the source of human disease. As human populations settled down, they created heaps of waste—middens of animal bones, garbage, and feces. These served as the breeding grounds for and a source of microparasites; they also attracted insects that could act as vectors of disease, as well as wild birds and rodents carrying their own parasites and potential new sources of human disease. With each domesticated species of animal came the possible human exposure to new disease agents—parasites. For example, the numbers of diseases acquired from domestic animals (zoonotically) has been estimated to be: dogs, 65; cattle, 45; sheep and goats, 46; pigs, 42; horses, 35; rats, 32; and poultry, 26. Specifically, the human measles virus has its counterpart in the distemper virus of dogs and rinderpest in cattle. Smallpox has its closest relatives in the virus of cows and poxviruses in pigs and fowl, and human tuberculosis is a cousin of bovine tuberculosis. More recent examples of the "jump" from one animal species to another include HIV, in which a chimpanzee virus became humanized; monkey pox transmitted to humans by the bite of pet prairie dogs; SARS from civet cats; and Ebola from bats.

With the clearing of forests, the planting of crops, and destruction of wild game animals, new ecological niches were created for insects and scavenging rodents. Mosquitoes and flies that once fed on game animals now found a new source of blood: humans. These "bloodsuckers" could act as vectors for malaria, yellow fever, and African sleeping sickness. Ditches, irrigated fields, and pottery vessels could also serve as breeding grounds for insects and snails, facilitating the transmission of blood fluke disease, yellow fever, malaria, elephantiasis, and river blindness.

The crowd diseases of humans such as smallpox, measles, pertussis (whooping cough), tuberculosis, and influenza were initially derived from very similar ancestral infections of domesticated animals. At first those who hunted, farmed, and domesticated animals fell prey to the parasites they acquired, and some died, but in time resistance to these new diseases developed. When such a partially immune people came in contact with others who had had no such experience, a devastating epidemic could occur. It was these contagious diseases (caused by a wide variety of worms and "germs") that would ultimately play a decisive role in the European conquests of native Americans, Africans, and Pacific Islanders; determine the outcomes of wars; loom large in the economic growth and prosperity of nations; and contribute to slavery and colonialism.