Figure 1.1 *Woman with Child*, by Pablo Picasso, 1903. © 2005 Estate of Pablo Picasso/Artists Rights Society (ARS), New York.

Chapter 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 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. Although 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 became ill had 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 from either cooling towers or evaporative condensers. Unlike infections caused by inhalation, aspiration is produced by choking. 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 older people, smokers, and those with lung disease. The Legionnaires were near-perfect candidates

for contracting the disease. Since the Philadelphia outbreak, there have been numerous reports of Legionnaires' disease in the general population: 11,000 documented cases annually in the United States and estimates as high as 100,000, with a fatality rate of 15%. These outbreaks have been traced to water heaters, whirlpool baths, respiratory therapy equipment, and ultrasonic misters used in grocery stores.

A few years later, 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, who was previously healthy and active, figured she had an infection or was suffering from overeating; she 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 was 178 beats/minute, and she had a red rash, initially on her thighs but becoming diffuse over her face, abdomen, and arms. Her blood pressure had fallen to 84/50, she had conjunctivitis in both eyes, and her chest X ray was normal, but a pelvic examination revealed a brownish discharge. Despite administration of antibiotics, oxygen, and intravenous fluids, her condition deteriorated over the next 48 hours. 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 had felled Mary Benton was named "toxic shock syndrome," or TSS. The source of Mary's infection, and the possibility that it might be spread through the population as a sexually transmitted disease (STD), raised many concerns. For the next 10 years, TSS continued to appear among previously healthy young women residing in several states. As with Mary Benton, each case began with vomiting and high fever followed by lightheadedness and fainting, the throat felt sore, and the muscles ached. A day later, a sunburn-like rash appeared, and the eyes became bloodshot. Within 3 to 4 days, victims suffered confusion, fatigue, weakness, thirst, and a rapid pulse; the skin became cool and moist; and breathing became rapid. This was followed by a sudden drop in blood pressure; if it remained low enough for a long enough period, circulatory collapse produced shock.

TSS is a gender-specific disease. From 1979 to 1996, it affected 5,296 women, median age 22, with a peak death rate of 4%. However, TSS 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 superabsorbent 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, these tampon brands were removed from the market, and 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 the 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 sightsee and shop with his brother-in-law in Hong Kong; however, during that day his condition worsened, and he had difficulty in breathing. Seeking medical attention at a nearby hospital, he was taken immediately to the intensive care unit and given antibiotics, anti-inflammatory drugs, and oxygen. This was 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 hours, 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 SARS case occurred in a female nurse who had seen the physician in the intensive care unit, 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, six of whom (3, 4, 6, 8, 9, and 10) survived and four of whom (1, 2, 5 and 7) died. 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.

Despite the recognition that sickness, such as SARS, Legionnaires' disease, and TSS, may appear suddenly and with disastrous consequences, more often than not, little notice has been taken of the ways that disease can shape history. The influence of disease on history has often been 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

live in an age when diseases appear to have minimal effects—we are immunized as children, we treat illness with effective drugs and antibiotics, and we are well nourished. Thus, our impressions of how disease can affect human affairs have been blunted. This, however, is an illusion: the sudden appearances of SARS, Legionnaires' disease, TSS, and acquired immunodeficiency syndrome (AIDS) 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. Aided by fast-moving ships, trains, and planes, they introduce previously remote diseases into our midst (such as West Nile virus infection, SARS, influenza, and mad cow disease). 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.

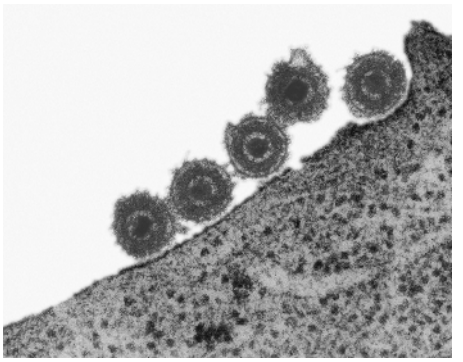
This book chronicles the recurrent eruptions of plagues that marked the past, influence the present, and surely threaten our future. The particular occurrence of a severe and debilitating outbreak of disease may be unanticipated and unforeseen, but despite the lack of predictability, there is a certainty: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

Living Off Others

The "germs" that caused SARS, Legionnaires' disease, and TSS are parasites. To more fully appreciate the nature of these and other diseases 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 entities are unable to survive on their own and require another living being for their nourishment. These life-dependent entities that "feed at the table of the rich" are called parasites, from the Latin word *parasitus*, meaning "food." 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) wherein 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, 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 (Fig. 1.2 and 1.3). Some may be composed of



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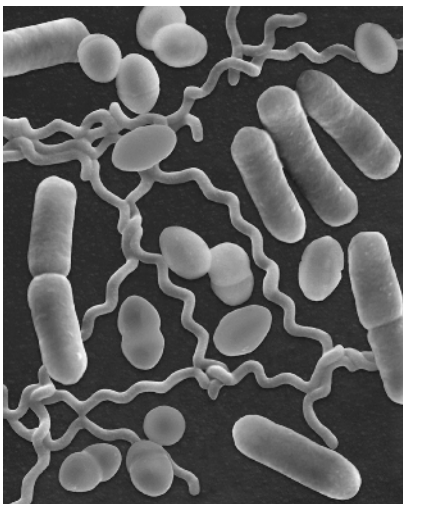

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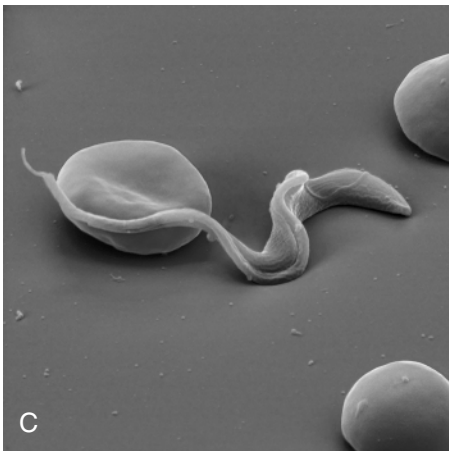

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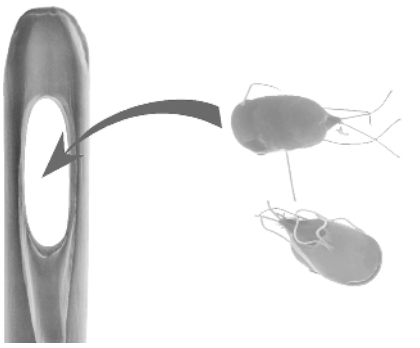

D

Figure 1.2 A catalog of microparasites. (A) Cold sore virus, as seen with the transmission electron microscope. (B) Three kinds of bacteria—spherical (coccus), rod shaped (bacillus), and corkscrew (spirillum or spirochete)—as seen with the scanning electron microscope. (C) Trypanosome (ribbon-like organism) among red blood cells, as seen by the scanning electron microscope. (D) Using a scanning electron microscope it can be seen that *Giardia* easily fits through the eye of a needle. (Panels A, B, and D courtesy of Dennis Kunkel Microscopy, Inc. Panel C courtesy of Eye of Science/Photo Researchers, Inc. © 2005 Photo Researchers, Inc.)

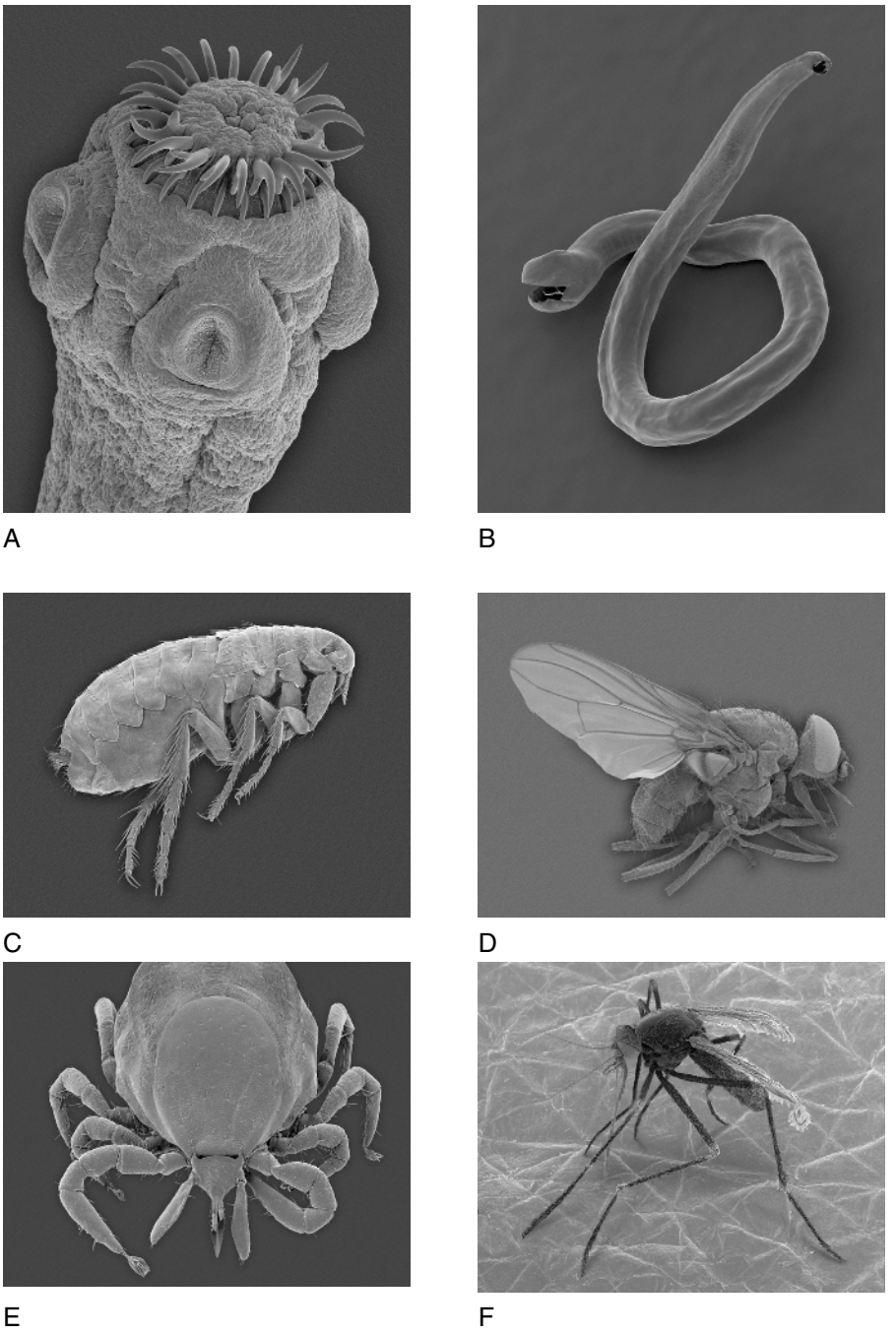

Figure 1.3 A catalog of macroparasites. (A) The head of a tapeworm (a flatworm); (B) the hookworm (a roundworm); (C) flea; (D) fly; (E) tick; and (F) mosquito. All seen through the scanning electron microscope. (Courtesy of Dennis Kunkel Microscopy, Inc.)

a fragment of genetic material wrapped in protein, such as a virus. Others (bacteria, fungi, protozoa) consist of a single cell (see "Cells and Viruses" in the Appendix), and some are made up of many cells (roundworms, flatworms, mosquitoes, flies, ticks). Some parasites, such as tapeworms, hookworms, the malaria parasite (*Plasmodium falciparum*), and the human immunodeficiency virus (HIV), live inside the body, whereas others (ticks and chiggers) live on the surface. Parasites are invariably smaller in mass than their host. Consider the sizes of the malaria parasite (a microparasite) and hookworm (a macroparasite). Both produce anemia or, as one advertisement for an iron supplement called it, "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, 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 blood-sucking, threadlike hookworm, is only 0.5 inches in length and 0.05 inches 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 because of a genetic abnormality or the absence of some critical dietary factor (e.g., 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 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 malaria parasite, the red blood cell-destroying hookworms, 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 offspring 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 be infected

with more than 100,000 parasites, and 2 days later the blood will contain millions of malaria parasites.

Hookworms (Fig. 1.3B) 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 more than 10 years, producing each day more than 10,000 eggs. In her lifetime, this "Countess Dracula" can produce more than 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 an inch in length. However, each virus 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 got 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 we are all too familiar with the possibility of a bioterrorist attack from anthrax spores, which 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 living organisms such as flies, mosquitoes, ticks, fleas, lice, or snails, 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, as 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 μm in size, are prokaryotes (see "Cells and Viruses" in the Appendix) that can be free living or parasitic. They may assume several body forms—rods (bacilli), spheres (cocci), or spiral. Proto-

zoa, 5 to 15 μm in size, are one-celled eukaryotes (see "Cells and Viruses" in the Appendix) 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 (Fig. 1.2 illustrates some parasites that cannot be seen without the aid of a microscope). The ultimate microparasite is a virus. Viruses are smaller than bacteria and cannot be seen with the light microscope but only with the electron microscope, which can magnify objects more than 10,000 times. Although a virus's genetic code (in the form of either RNA or DNA) contains all the information needed for assembling a new virus, it lacks that which is necessary for reproduction. Therefore, for a virus to reproduce, it must enter a living cell and use the cellular machinery to replicate itself. Because viruses are not completely independent, they are not alive, and yet they can be killed if their DNA or RNA is destroyed. Viruses—the agents of SARS, AIDS, 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 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 disease in humans or domestic animals are the roundworms, such as the hookworm; the flatworms, such as the tapeworm and the blood fluke; the blood-sucking insects, such as mosquitoes, flies, and lice; or the arachnids, such as ticks (Fig. 1.3 illustrates parasites that can be seen with the human eye). Macroparasites do not multiply within an infected individual (except in the case of larval stages in the intermediate hosts); instead, they produce infective stages that usually pass out of the body of one host before transmission to another.

"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. However, 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; worst of all, you have a severe case of diarrhea. What a mess you are! When you see your physician, she tells you that your distress could be due to an infection with *Salmonella*, *Giardia*, *Entamoeba*, or the influenza or SARS virus. Prescribing an antibiotic for a disease caused by a virus would do you no good, but in the case of "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 are due to the presence of protozoan parasites such as *Giardia* or *Entamoeba*, they would not respond to antibiotics; other drugs would have to be

prescribed to cure you. Therefore, determining the kind of parasite (or parasites) you harbor will do more than provide the name of the offender; it will allow for selective treatment of your illness.

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. 1.4). 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. However, despite the obvious clinical signs of coughing, nausea, vomiting, and diarrhea, a person-to-person transmissible agent was not found. In short, the victims of TSS and Legionnaires' disease were not infectious, in contrast to patients with influenza, SARS, and the common cold, who display a similar array of symptoms. Influenza and SARS are different kinds of upper respiratory diseases: the flu is contagious 24 hours before

Figure 1.4 *The Plague of Ashod* by Nicolas Poussin (1594–1665). Poussin's painting is probably that of bubonic plague since rats are shown on the plinth. (Courtesy of Corbis.)

symptoms appear, has a short (2- to 4-day) incubation period, and infrequently requires hospitalization, whereas with SARS there is a longer (3- to 10-day) incubation period, the individual is infectious only after symptoms appear, and hospitalization is required.

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 1906 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 Mr. George Thompson. That summer, 6 of 11 people in the house came down with typhoid fever (caused by the "germ" *Salmonella enterica* serovar 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 10% 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 he 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 North Brother Island in the Bronx. There, her feces were examined and found to contain the typhoid bacteria. Mary remained at the hospital, without her consent, for 3 years and was then 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 Health Department 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, two of whom died. She was sent again to North Brother 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 caused many more than the well-documented cases, and she surely caused more than three 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. However, she was the only one kept isolated for years, and one his-

torian 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 . . .?"

Forecasting Storms, Predicting Plagues

In October 1991, meteorologists predicted "the perfect storm." As a result, the public was warned of an impending storm of epic proportions that would send high winds and Atlantic Ocean waves crashing on the East Coast of the United States, from Boston, Mass., to Cape Hatteras, S.C. The storm was created by three factors: a collision between a high-pressure system, a low-pressure system, and the remnants of a dying hurricane. Understanding weather factors allows for better tracking and predicting of storms; similarly, 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), flies (in sleeping sickness and river blindness), or ticks (in Lyme disease and Nantucket fever), or it may be by direct contact, as it is with measles, influenza, SARS, and tuberculosis, whereby 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 words *epi* ("among") and *demos* ("the people"). Weather forecasters use satellites, Doppler radar, and measures of barometric pressure, wind velocity and direction, water and land surface temperatures, humidity, and cloud formations to produce statistical models that predict "the perfect storm" and lesser weather disturbances. The predictions of meteorologists are heard daily: there's a 20% chance of rain; the snow level will be down to 4,000 feet; road conditions will be hazardous; or tomorrow will be sunny and mild. Epidemiologists are disease forecasters who study the occurrence, spread, and control of a disease in a population by using statistical data and mathematical modeling to identify the causes and modes of disease transmission, 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, epidemiological studies linked the syndrome to the use of tampons, principally Rely Tampons, in menstruating women. The recommendation was that the illness could be controlled by removal of such tampons from

the market. Acting on this advice, Procter and Gamble stopped marketing Rely Tampons, and cases of TSS 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 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 object 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 touches another (transmits), then the number of diseased individuals (touch taggers) multiplies. In this example, the value for R_0 is the number of touch taggers that results from their 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 larger than 1, 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. However, if R_0 is less than 1, each infection produces fewer than one 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 provided 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 that there was 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 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 of 8 to 12 days, there is fever, weakness, loss of appetite, coughing, a runny nose, and tearing of the eyes. Virus replication is now in high gear. Up to this point, the individual probably believes that 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 (along with mumps, whooping cough, smallpox, and chicken pox) passes from one host to another without any intermediary; recovery from a single exposure produces lifelong immunity. As a consequence, measles and the other diseases commonly afflict children and are therefore called "childhood diseases." Although measles has been eradicated in the United States because of childhood immunization, it can be responsible for a death rate of about 30% in less developed countries. It is one of the 10 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.

Hurricanes are areas of low pressure that form over oceans in the tropics. (Over the Pacific Ocean and north of the equator, such storms are called typhoons, and in the South Pacific and Indian Oceans they are referred to as tropical cyclones.) Meteorologists classify these storms into five categories depending on the wind speed, barometric pressure, storm surge height, and potential for damage. A category 1 hurricane has winds of 74 to 95 mph and may cause damage to shrubbery and mobile homes, whereas a category 5 hurricane has winds of greater than 155 mph and has the potential to do extensive damage to roofs on buildings; massive evacuation of residents may be recommended. This classification informs us of the strength of these tropical storms and helps predict their development. However, as valuable as this classification can be, it is not a precise indicator of all the possible aspects, e.g., the location of landfall, extent of damage to property, number of deaths, economic losses, and when it will decline in force. Like hurricanes, epidemics or plagues can be classified into three types with their own stages of development (Fig. 1.5), and each may produce a very different set of outcomes.

Measles is highly infectious and moves rapidly through a population in epidemic waves, coming at regular intervals. Let us consider the pattern of measles in a population. The persistence of measles depends on the critical community size and is defined as the smallest population without any temporary absence of disease. This type I epidemic pattern for measles is found in a population of about 300,000 to 500,000 people, with about 7,000 to 10,000 cases of measles per year. In a type I epidemic, the population is large and the pattern shows a regular series of outbreaks (peaks), but the disease never completely disappears—that is, it is endemic—and cases persist. This is because the number of susceptible individuals is large enough for the chain of transmission of infection to remain unbroken, and so R_0 is greater than 1.

In a type II epidemic, the peaks of infection are discontinuous, but there is a regular pattern of occurrence of cases. But there is no endemicity; there are temporary absences of the disease, and the value of R_0 is less than 1. This pattern occurs because there are not enough susceptible individuals to maintain the chain of virus transmission. Measles shows this pattern in a population of about 10,000 to 100,000. Finally, a type III epidemic occurs in even smaller communities, those with less than 10,000 people. Here, the pattern of an increased number of cases occurs at irregular intervals, and there are long periods when there is no disease. Because of the small size and/or the remoteness of these communities, the chain of transmission of infection is interrupted, infections have to be reintroduced, and R_0 is a number much smaller than 1. In contrast, when an infectious disease becomes worldwide or widespread (and R_0 is a large number), then the epidemic is called a pandemic. Examples of pandemic diseases include SARS, influenza, bubonic plague, cholera, and AIDS.

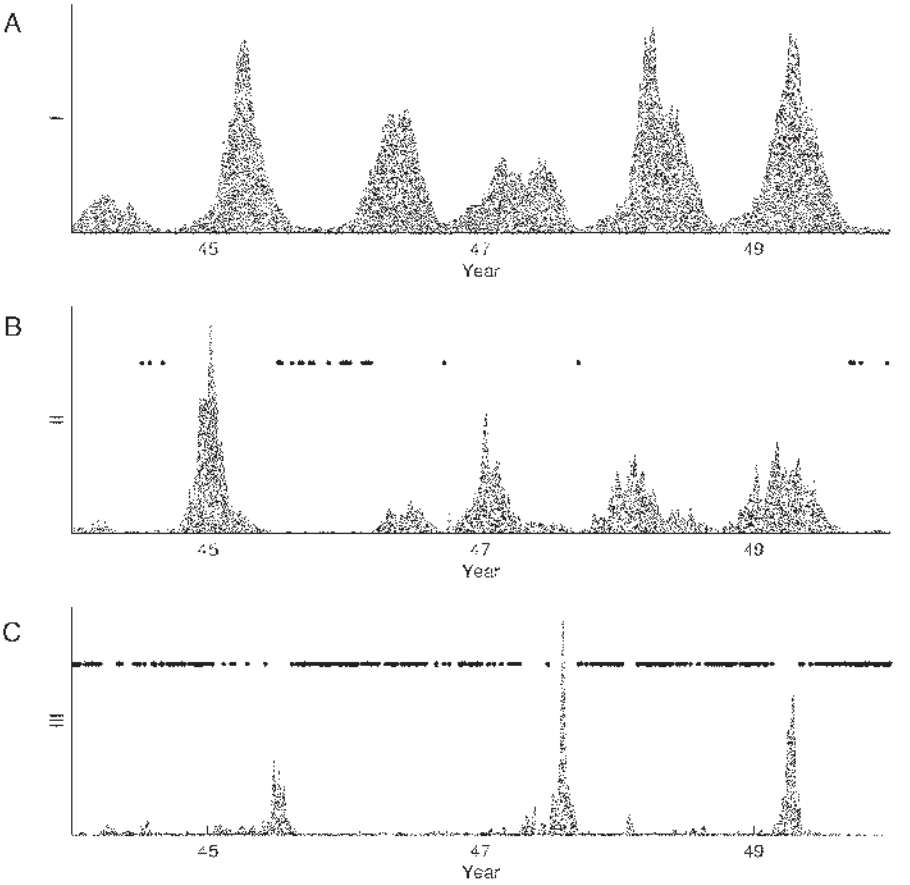

Figure 1.5 Types of epidemics. The plots show the incidence or numbers of cases of measles for three different sizes of populations from 1942 to 1952. (A) In type I, the peaks in the number of cases are regular, and there are always cases (endemicity) and no fadeouts. The population size is 3.4 million. (B) In type II, there are regular outbreaks (peaks in the number of cases), no endemicity, and fadeouts (shown by dots). This occurs with a population size of 300,000. (C) In type III, with a population size of 10,000, there are irregular outbreaks with long fadeouts occurring between the peaks. (Courtesy of Matthew Keeling.)

The spread of infection from an infected individual through the community can be thought of as a process of diffusion whereby 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 bring susceptible individuals in contact with infectious individuals, the countermeasures used (e.g., quarantine, hospitalization, immunization), and seasonal patterns. For example, in temperate northern climes, measles spreads most frequently in the winter

months because people tend to be confined indoors. However, in Iceland, where the spring thaw is followed by a harvest, there are also summer peaks because of communal activities on the farms. As noted earlier, the spread of SARS in 2003 was controlled by quarantine and hospitalization; winter flu epidemics can usually be limited by immunization.

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 greater than 1. For HIV, with a duration of infectiousness of 0.5 years 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, that have somewhat higher transmission probabilities, the values are 7 and 3, respectively. However, despite the development of mathematical equations, predicting the spread of an epidemic can be as uncertain as forecasting a hurricane, a blizzard, or a tornado. Indeed, making predictions early in a disease outbreak by fitting simple curves can be misleading, because it generally ignores interventions that reduce the contact rate and the probability of transmission. For SARS, fitting an exponential curve to data from Hong Kong that were obtained between 21 February and 3 April 2003 predicted 71,583 cases 60 days later, but using a linear plot, 2,410 cases were predicted. In fact, by 30 May 2003, according to the World Health Organization, there were more than 8,200 cases worldwide and over 800 deaths. By 5 July 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 increased contact and risk. Sociological changes may also affect the spread of disease. For example, schoolchildren 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, e.g., with SARS. 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. However, as noted above, 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.

To block parasite transmission, a sufficient number of individuals in the population must be immunized such that the value for R_0 is less than 1. For measles, R_0 is approximately 15. 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 mumps and rubella to be eliminated, the percentages are 90 and 85%, respectively. However, elimination of endemic malaria in Africa, where R_0 is 50 to 100, would require 99%

coverage with a lifelong vaccine given at 3 months of age. So if transmission is intense (i.e., R_0 is a large number), mass immunization must take place at the earliest age feasible, and the later the average age of vaccination, the less likely it is that transmission will be blocked. Thus, for disease elimination, not everyone in the population must be immunized, but it is necessary to reduce the number of susceptible individuals below a critical point (called herd immunity). When successful, immunization may convert a type I epidemic to type II, and then convert the type II epidemic to type III—as happened in the United States and Great Britain with measles, mumps, and rubella.

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 H. McNeill. He went on: "Prolonged interaction between human host and infectious organism, 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, 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. Therefore, the conventional wisdom is that the most successful parasites are those that cause the least harm to the host, and that over time there is a tendency for virulent parasites to become benign.

At first glance, it would appear that the progress of myxomatosis in Australia supports this idea. 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 in Australia, they multiplied rapidly, destroying plants and native animals. The Austins began to wage war on the rabbits. By 1865, more than 20,000 rabbits were killed on the Austin estate. 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. So myxomatosis, a viral disease of wild rabbits from South America and lethal to domestic rabbits, was introduced into Australia in the 1950s to act as a biological control agent. In 1950, 99% of the rabbits died of myxomatosis. Several years later, the virus killed only 90% of the rabbits, 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 vector for the myx-

oma virus. Therefore, the rabbits lived longer, and the number of rabbits infected with milder disease was higher. It was concluded that the virus had evolved toward benign coexistence with the rabbit host.

William 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 virulence of the virus and the increase in rabbit resistance was calculated, was comparable to the mortality of humans in most vector-borne diseases, 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 selection may favor intermediate virulence. Furthermore, because R_0 depends directly on the density of susceptible hosts in the population if the number of susceptible individuals is great, then a parasite may benefit from an increased rate of transmission even if it kills the host sooner and prevents transmission at a later time. However, if susceptible hosts are not abundant, 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 hosts are less plentiful neglects the fact that a feedback exists in the host-parasite interaction: a change in parasite virulence impacts the density of the host population, which in turn alters the pressures of natural selection on the parasite population, and so on. Thus, although parasite virulence tends to decline over evolutionary time, it never becomes entirely benign; 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 have contended that enhanced virulence is the mark of an ill-adapted parasite or 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 yield 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, a human, a bird, or a bee, is a measure of the success of the individual in passing on its genes to 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. Thus, how negatively a host will be affected, i.e., how severe or how pathogenic the disease will be, is determined by two components: virulence and host resistance. Virulence is not so much a matter of a particular mutation as it is 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 plague emerges, R_0 must be a number greater than 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; however, the evolution of parasite virulence need not take years, as in the case of the myxoma virus, but may be quite rapid, on the order of months. 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 put, 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 opportunities for virus transmission by direct contact. Similarly, the development of diarrhea in a person with cholera or *Salmonella* (which causes "food poisoning") facilitates the dispersal of intestinal microbes via feces-contaminated water and food; in the absence of diarrhea, parasite transmission would be reduced.

AIDS is a consequence of an increase in the virulence of HIV. The enhancement of 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. Thus, clean water may favor a reduction in the virulence of waterborne intestinal organisms (such as the causative agent of cholera), and clean needle exchange and condom use would both reduce transmission and lessen HIV virulence. However, some contend that this indirect mechanism may be too weak and too slow to substantially reduce virulence; 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 health.