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.