CHAPTER ONE

EARLY HISTORY OF INFECTIOUS DISEASE

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Epidemics of infectious diseases have been documented throughout history. In ancient Greece and Egypt accounts describe epidemics of smallpox, leprosy, tuberculosis, meningococcal infections, and diphtheria.[1] The morbidity and mortality of infectious diseases profoundly shaped politics, commerce, and culture. In epidemics, none were spared. Smallpox likely disfigured and killed Ramses V in 1157 BCE, although his mummy has a significant head wound as well.[2] At times political upheavals exasperated the spread of disease. The Spartan wars caused massive dislocation of Greeks into Athens triggering the Athens epidemic of 430–427 BCE that killed up to one half of the population of ancient Athens.[3] Thucydides' vivid descriptions of this epidemic make clear its political and cultural impact, as well as the clinical details of the epidemic.[4] Several modern epidemiologists have hypothesized on the causative agent. Langmuir et al.,[5] favor a combined influenza and toxin-producing staphylococcus epidemic, while Morrens and Chu suggest Rift Valley Fever.[6] A third researcher, Holladay believes the agent no longer exists.[7]

From the earliest times, man has sought to understand the natural forces and risk factors affecting the patterns of illness and death in society. These theories have evolved as our understanding of the natural world has advanced, sometimes slowly, sometimes, when there are profound breakthroughs, with incredible speed. Remarkably, advances in knowledge and changes in theory have not always proceeded in synchrony. Although wrong theories or knowledge have hindered advances in understanding, there are also examples of great creativity when scientists have successfully pursued their theories beyond the knowledge of the time.

The Era of Plagues

The sheer magnitude and mortality of early epidemics is difficult to imagine. Medicine and religion both strove to console the sick and dying. However, before advances in the underlying science of health, medicine lacked effective tools, and religious explanations for disease dominated. As early communities consolidated people more closely, severe epidemics of plague, smallpox, and syphilis occurred.

The bubonic plague and its coinfections, measles and smallpox, were the most devastating of the epidemic diseases. In 160 CE plague contributed to the collapse of the Han Empire,[8] and six years later the Roman Empire was ravaged by the Antonine Plague (165–180 CE), which likely killed both coemperors Lucius Verus (130–169 CE) and Marcus Aurelius (121–180 CE) along with 5 million others.[9,10] Plague and other communicable diseases flourished in the cities of the Roman Empire and surely contributed to its final demise.[11] Four centuries later (1104–1110 CE) nearly 90% of Europeans were killed by plague.[8] The plague, or *Black Death* as it was then called, struck again in 1345 and swept across Europe. Starting in the lower Volga it spread to Italy and Egypt in 1347 on merchant ships carrying rats and fleas infected with the plague bacillus, *Yesinia pestis*.[1] During the next five years (1347–1351), the Black Death killed 3 Europeans out of 10, leaving 24 million Europeans dead with a total of 40 million deaths worldwide.[1,12,13,14] These waves of bubonic plague fundamentally affected the development of civilizations as well as imposed a genetic bottleneck on those populations exposed. Europeans may be able to attribute their lower susceptibility to leprosy and HIV to the selective pressure of bubonic plague.[15] To survive in an ancient city was no small immunologic feat—and populations that had the immunologic fortitude had an advantage over others when exploration and colonization brought them and their pathogens together.[11]

The first recorded epidemic of smallpox was in 1350 BCE, during the Egyptian–Hittite war.[1] In addition to Ramses V, typical smallpox scars have been seen on the faces of mummies from the time of the 18th and 20th Egyptian dynasties (1570–1085 BCE) Smallpox was disseminated during the Arabian expansion, the Crusades, the discovery of the West Indies, and the colonization of the Americas. Mortality ranged from 10–50% in many epidemics. The disease apparently was unknown in the New World prior to the appearance of the Spanish and Portuguese conquistadors. Cortez was routed in battle in 1520 but was ultimately victorious as smallpox killed more than 25% of the Aztecs over the next year.[8] Mortality rates of 60–90% were described by the Spanish priest Fray Toribio Motolinia. He reported that 1000 persons per day died in Tlaxcala, with ultimately 150,000 total dead.[16] Smallpox then traveled north across the Americas, devastating the previously unexposed American populations.[11]

At that time, there was a reasonable understanding of the epidemiology of smallpox transmission. At the least, it was appreciated that the skin lesions and scabs could transmit the disease. It was known that survivors of the infection were immune to reinfection after further exposure. The practice of inoculation, or variolation, whereby people were intentionally exposed to smallpox was practiced in China, Africa, and India centuries before the practice would be adopted in Europe and the Americas.[17]

Syphilis is another epidemic infectious disease of great historical importance. Syphilis became epidemic in the 1490s as a highly contagious venereal disease in Spain, Italy, and France. By the 1530s, the venereal spread of syphilis was widely recognized in Europe.[18] The name *syphilis* originated from the popular, and extremely long, poem by Girolamo Fracastoro "Syphilis sive morbus Gallicus." Written in 1546, the poem recounts the causes of disease and the origin and treatment of syphilis.[12,18] Fracastoro describes the legend of a handsome young shepherd named Syphilis, who because of an insult to the god Apollo, was punished with a terrible disease, "the French Disease"—or syphilis. The origins of venereal syphilis are debated. One theory proposes that it began as a tropical disease transmitted by direct (nonsexual) contact.[18] In support of this theory, the organism, *Treponema pallidum*, was isolated from patients with endemic (nonvenereal) syphilis (bejel) and yaws. After the first accounts of syphilis, it was reported to spread rapidly through Europe and then North America. In keeping with the hypothesis that syphilis was a recently emerged disease, mortality from syphilis was high in these early epidemics.[11]

Early Epidemiology

In Western medicine, Hippocrates (460–377 BCE) was among the first to record his theories on the occurrence of disease. In his treatise *Airs, Water and Places*, Hippocrates dismissed supernatural explanations of disease and instead attributed illness to characteristics of the climate, soil, water, mode of life, and nutrition surrounding the patient.[2,19–21] It is Hippocrates who coined the terms *endemic* and *epidemic disease* to differentiate those diseases that are always present in a population, endemic, from those that are not always present but sometimes occurred in large numbers, epidemic. It was Claudius Galen (131–201 CE) however, who codified the Hippocratic theories in his writings. Galen combined his practical experience caring for gladiators with experiments, including vivisections of animals, to study the anatomy and physiology of man.[22] His voluminous writings carried both his correct and incorrect views into the Middle Ages. It was over a thousand years before Andreas Vesalius (1514–1564), who based his work on dissections of humans, was able to correct Galen's errors in anatomy.[22]

That infectious diseases were contagious was recognized in early epidemics, but because knowledge of the true epidemiology of diseases was lacking, efforts to control the spread of such diseases were flawed. Plague was recognized to be contagious; however, the control measures focused primarily on quarantine and disposal of the bodies and the possessions (presumably contaminated) of the victims. Although it was observed that large numbers of rats appeared during an epidemic of plague, the role of rats and their fleas was not appreciated.

As far back as biblical times, leprosy was believed to be highly contagious. Afflicted patients were treated with fear and stigmatization. Given that leprosy progresses slowly, quarantine of cases late in disease likely had little effect on the epidemic spread. In the Middle Ages lepers were literally stricken from society as leprosy became increasingly equated with sin. Some even required lepers to stand in a dug grave and receive the "Mass of Sepa-

ration" from a priest after which they were considered "dead." One example of a Mass of Separation reads as follows:

> I forbid you to ever enter a church, a monastery, a fair, a mill, a market or an assembly of people. I forbid you to leave your house unless dressed in your recognizable garb and also shod. I forbid you to wash your hands or to launder anything or to drink at any stream or fountain, unless using your own barrel or dipper. I forbid you to touch anything you buy or barter for, until it becomes your own. I forbid you to enter any tavern; and if you wish for wine, whether you buy it or it is given to you, have it funneled into your keg. I forbid you to share house with any woman but your wife. I command you, if accosted by anyone while traveling on a road, to set yourself downwind of them before you answer. I forbid you to enter any narrow passage, lest a passerby bump into you. I forbid you, wherever you go, to touch the rim or the rope of a well without donning your gloves. I forbid you to touch any child or give them anything. I forbid you to drink or eat from any vessel but your own.[23]

Persons with leprosy, or suspected leprosy, were forced to carry a bell to warn others that they were coming (see Figure 1-1).

Fracastoro (1478–1553) was much more than just an author of the popular poem on syphilis. As a true Renaissance man, Fracastoro was also an astronomer and doctor. In his book published in 1546, *De contajione, ontagiosis morbis et curatine* (On Contagion, Contagious Diseases, and their

FIGURE 1-1 The leper was required to dress in recognizable clothing and to carry a bell.

Treatment), he proposed the revolutionary theory that infectious diseases were transmitted from person to person by minute invisible particles.[12,24] Fracastoro conceived of the idea that infections were spread from person to person by minute invisible seeds, or *seminaria*, that were specific for individual diseases, were self-replicating, and acted on the humors of the body to create disease. Although revolutionary, Fracastoro did not realize that the seeds of a disease were microbes, and he held to ancient beliefs that they were influenced by planetary conjugation particularly "*nostra trium superiorum, Saturni, Iovis et Martis*" (our three most distant bodies: Saturn, Jupiter, and Mars). He postulated that the environment became polluted with seminaria and that epidemics occurred in association with certain atmospheric and astrologic conditions.[12,24] Fracastoro proposed three modes of transmission of contagious disease: by direct contact from one person to another, through contact with fomites (a term for contaminated articles still used today), and through the air. His theories were respected and certainly far ahead of their time. He was able to persuade Pope Paul III to transfer the Council of Trent to Bologna because of the prevalence of contagious disease in Trent and the risk of contact with contaminated fomites.[1] But it would take the discovery of the microscope 200 years later to prove his theories.

The Observation and Care of Patients

Medical practice was gradually transformed by the introduction of disease-specific treatments during the Renaissance era. Peruvian bark, or cinchona, was imported into Europe for the treatment of malaria around 1630.[25] Its active ingredient, quinine, was the first specific treatment for the disease. Based on the observation that smallpox disease conferred immunity in those who survived, intentional inoculation of healthy people to induce immunity was attempted. This process was known as *variolation* and was advocated by Thomas Jefferson (1743–1826), Benjamin Franklin (1706–1790), and Cotton Mather (1663–1728). Mather learned of it from a man he enslaved, Onesimus, who was innoculated with smallpox in a cut as a child in Africa.[17] In 1796, Edward Jenner (1749–1823), based on the observation that milkmaids were immune to smallpox, greatly improved the process by substituting cowpox in place of the human pathogen. He performed the first vaccine clinical trial by inoculating 8-year-old James Phipps (1788–1853) with lesions containing cowpox (vaccinia virus) and later showed that the boy was immune to variolation, or challenge with variola virus.[26] Thus was born the science of vaccination, which led eventually (180 years later) to the eradication of smallpox.[26] Napoleon (1769–1821) showed his support by vaccinating his army declaring that "anything Jenner wants shall be granted. He has been my most faithful servant in the European campaigns."[27] It is worthy of mention that other empiric attempts were proposed during the 1700s to induce protection by intentional inoculation, such as for measles (called morbillication) and syphilis. Neither of these efforts were successful.

Changes in the practice of clinical medicine in the 1600s began to differentiate diseases from one another. One of the earliest advocates of careful observation of patients' symptoms and their disease course was the London doctor Thomas Sydenham (1624–1689). He classified different febrile illnesses

plaguing London in the 1660s and 1670s in a book entitled *Observations Medicae*. His approach departed from Galen and Hippocrates, who focused on the individual and their illness rather than on trying to differentiate specific diseases. After Sydenham, the Italian physician Giovanni Morgagni (1682–1771) inaugurated the method of clinicopathologic correlation. His book *De sedibus et causis morborum per anatomen indagatis (On the Seats and Causes of Diseases, Investigated by Anatomy)*, based on over 700 autopsies, attributed particular signs and symptoms to pathologic changes in the tissues and organs. The influence of Sydenham and Morgagni on medicine can be seen in Benjamin Rush's (1745–1813) description of dengue among patients afflicted in the 1780 Philadelphia epidemic.[28]

> The pains which accompanied this fever were exquisitely severe in the head, back, and limbs. The pains in the head were sometimes in the back parts of it, and at other times they occupied only the eyeballs. In some people, the pains were so acute in their backs and hips that they could not lie in bed. . . . A few complained of their flesh being sore to the touch, in every part of the body. From these circumstances, the disease was sometimes believed to be a rheumatism. But its more general name among all classes of people was the Break-bone fever.

This new way of thinking about diseases, requiring careful clinical observation, differentiation, and specific diagnosis, led naturally to the search for specific, as opposed to general, causes of illness.

Expanding on the concept of careful clinical observation of individuals, epidemiologists in the 1800s observed unusual epidemics and performed controlled studies of exposed persons. Epidemiologic theories about the means of transmission of various infectious diseases often preceded the laboratory and clinical studies of the causative organisms. Peter Panum (1820–1885) recorded his observation of an epidemic of measles on the Faroe Islands in 1846.[29] Measles had not occurred on these remote Scandinavian islands for 65 years. Remarkably, the attack rates among those under 65 years old was near 97%, but older persons were completely spared. This demonstrated that immunity after an attack of natural measles persists for a lifetime. Further, Panum described the mean 14-day incubation period between cases.[29] Outbreaks of mumps and other contagious diseases in isolated populations also have contributed to the early understanding of the epidemiology of these diseases.[30,31]

The epidemiology of bacterial diseases also progressed at this time. John Snow (1813–1858) performed classic epidemiology of the transmission of cholera in the mid-1850s, nearly 30 years prior to the identification of the causative organism.[32] William Budd (1868–1953) demonstrated the means of transmission of typhoid fever and the importance of the human carrier in transmission 35 years prior to the isolation of *Salmonella typhi*.[33] Ignatz Semmelweiss (1818–1865) demonstrated with a retrospective record review that an epidemic of puerperal fever, or childbed fever, in 1847 at the Vienna lying in hospital was due to transmission of infection on the hands of medical students and physicians who went from the autopsy room to the delivery room without washing their hands. In contrast, the women who were delivered by midwives, who used aseptic techniques (by immersing their hands in antiseptic solution prior to contact with the patient), had

much lower rates of puerperal sepsis (Figure 1-2).[34] Unfortunately, while Semmelweiss was correct, bacteria were not yet identified. His theories were not welcomed by the medical profession, and this, combined with his more liberal political views, resulted in his leaving the hospital in 1849.[27] These early epidemiologic theories would have to wait for scientific knowledge to catch up.

The Development of Statistics and Surveillance

Meanwhile, the fields of probability and *political arithmetic*, a term coined by William Petty (1623–1687) to describe vital statistics on morbidity and mortality,[27] were advancing. Gerolamo Cardana (1501–1576) introduced the concept of probability and described that the probability of any roll of the dice was equal so long as the die was fair.[35] Jacques Bernoulli (1654–1705) carried this concept further with the central limit theorem which states that the observed probability approached the theoretical probability as the number of observations increased.[35] One of the early leaders in the use of statistics to help understand the natural occurrence and epidemiology of infectious diseases was John Graunt (1620–1674), a wealthy haberdasher; he became interested in bills of mortality and published the *Natural and Political Observations—The Bills of Mortality* in 1662.[27,36] Here he detailed the number and causes of deaths in London during the preceding third of a century. He used inductive reasoning to interpret the mortality trends and noted the ratio of male to female births and deaths, mortality by season, and mortality in persons living in rural versus urban locations. He examined several causes of deaths over time and constructed the first life tables.[36] Subsequently, other

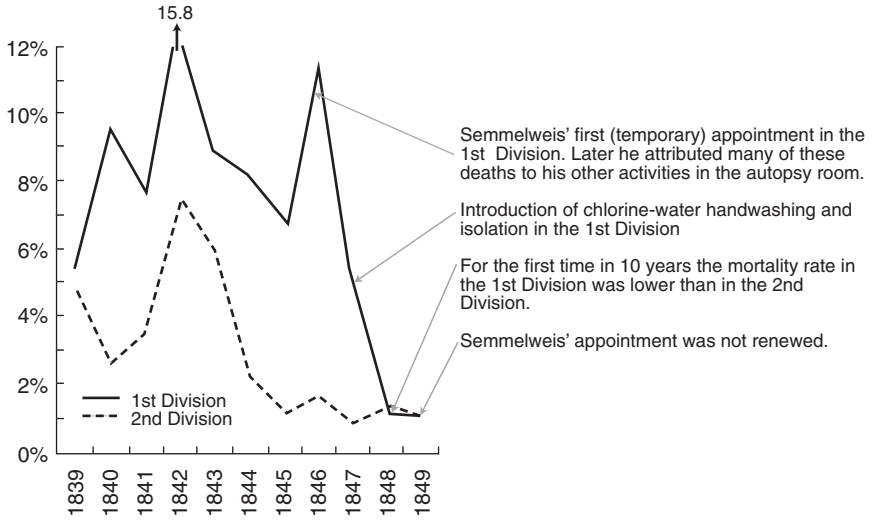

FIGURE 1-2 Mortality rates in first and second divisions of the Department of Obstetrics in the Vienna Lying-In Hospital between 1839 and 1849.

observers used public health data for the study of epidemics of infectious diseases. Daniel Bernoulli (1700–1782), the son of Jacques Bernoulli, analyzed smallpox mortality to estimate the risk-benefit ratio of variolation.[12] His calculations determined that the fatality rate of variolation exceeded the benefit in population survival.[37] In England, numerous improvements in public health sanitation and vital registries were made in the 1800s. Edwin Chadwick (1800–1890), an arrogant zealot, managed to institute numerous sanitary reforms when he wasn't annoying his peers.[27] Chadwick used health statistics to effectively change public policy. His 1842 report "to the Poor Law Commission" outlined the cost effectiveness of public health. His report emphasized the understanding that hygiene was closely related to health, but he also linked morality to hygiene and health. He made the following pronouncements:

- That the formation of all habits of cleanliness is obstructed by defective supplies of water.
- That the younger population, bred up under noxious physical agencies, is inferior in physical organization and general health to a population preserved from the presence of such agencies.
- That the population so exposed is less susceptible of moral influences, and the effects of education are more transient than with a healthy population.
- That these adverse circumstances tend to produce an adult population short-lived, improvident, reckless, and intemperate, and with habitual avidity for sensual gratifications.
- That defective town cleansing fosters habits of the most abject degradation and tends to the demoralization of large numbers of human beings, who subsist by means of what they find amidst the noxious filth accumulated in neglected streets and bye-places.
- That the expense of public drainage, of supplies of water laid on in houses, and of means of improved cleansing would be a pecuniary gain, by diminishing the existing charges attendant on sickness and premature mortality.[38]

His countryman William Farr (1807–1883) made important contributions to the improvement and analytical use of public health statistical data. His careful documentation of deaths was used by John Snow to investigate the 1849–1953 London cholera epidemics. Farr initially disagreed with Snow's hypothesis that cholera was transmitted by water. He preferred the miasma theory. However, he was eventually convinced, and his book based on the 1866 epidemic demonstrated that contaminated water was a risk for cholera.[39]

The Discovery of Microorganisms

A significant leap forward in scientific understanding came with the visualization of microorganisms. Anton van Leeuwenhoek (1632–1723) invented the microscope, and in 1683 he described how materials such as rainwater and human excretions had cocci, bacilli, and spirochetes.[8] But he did not evaluate these organisms as agents of disease. Considerable controversy arose over the

origin of these minute forms. Because they were often present in decaying or fermenting materials, some people maintained that they were spontaneously generated from inanimate material. However, Leeuwenhoek believed that they were derived from animate life.[27]

Louis Pasteur (1822–1895) demonstrated the dependence of fermentation on microorganisms in 1857 and showed that these organisms came from similar organisms present in the air.[40] Subsequently, Robert Koch (1843–1910) demonstrated in 1876 that he could reproducibly transmit anthrax to mice by inoculating them with blood from sick cattle and that he could then recover the same rodlike bacteria from the sick mice as came from the cattle. Further, he could pass the disease from one mouse to another by inoculating them with these microorganisms.[12] Based on these experiments he proposed the "Henle-Koch postulates" for proof that a microorganism was the cause of an infectious disease. In the subsequent 50 years, numerous microorganisms were identified as the causative agents of important human diseases (Table 1-1) and their epidemiology elucidated. Among these was the causative agent of plague, identified in 1894 by Alexander Yersin (1863–1943) and Shibasaburo Kitasato (1852–1931). They discovered the organism in both rats and humans who had died of plague during an epidemic in Hong Kong.[12,13] Two years later in Bombay, Paul-Louis Simond (1858–1947) of France established that the link between rats and humans was the rat flea, *Xenopsylla cheopis*. Once a rat flea becomes infected with *Yersinia pestis*, the plague bacillus, it cannot digest its food—rat blood. Starving, it looks aggressively for another animal to feed on and, in so doing, passes the organism on to humans. After it is infected, the rat flea can hibernate for up to 50 days in grain, cloth, or other items and spread the disease to humans coming into contact with these items of commerce.[12]

3 **TABLE 1-1 The Scientist Credited with the Discovery of Important Human Pathogens and the Year of That Discovery**

Year	Disease or Organism	Scientist
1874	Leprosy	Hansen
1880	Malaria typhoid (organism seen in tissues)	Laveran and Eberth
1882	Tuberculosis glanders	Koch, Loeffler, and Schutz
1883	Cholera streptococcus (erysipelas)	Koch and Fehleisen
1884	Diphtheria	Klebs and Loeffler
4	Typhoid (bacillia isolate)	Gaffky
5	Staphylococcus	Rosenbach
	Streptococcus	Rosenbach
	Tetanus	Nicolaier
1885	*Escherichia coli*	Escherich
1886	Pneumococcus	Fraenkel
1887	Malta fever,	Bruce
	Soft chancre	Ducrey
1892	Gas gangrene	Welch and Nuttall
6 1894	Plague	Yersin and Kitasato
	Botulism	Van Ermengen
1898	Dysentery bacillus	Shiga
1896	*Hemophilus influenzae*	Pfeiffer

To study disease in a controlled setting, some researchers resorted to self-experimentation. Sometimes with great success, other times not. The first specific published account of human hookworm disease was in 1843 by Angelo Dubini (1813–1902) from Milan.[41] He had found hookworms in the intestines of nearly 20% of autopsies. However, the means of spread was commonly believed to be by the fecal–oral route until the observation of Arthur Looss in Cairo, Egypt, in 1898.[42] Looss was studying *Stronglyloides stercoralis* and swallowed several larvae of this organism to infect himself but, when he examined his stools, he found only hookworm eggs. Then he recalled that he had accidentally spilled a fecal inoculum on his hands that caused a transitory itchy red rash. He then intentionally exposed his skin to another hookworm inoculum and, after a few minutes, was unable to find the organisms on his exposed skin. After several additional careful experiments, he reported the entrance of hookworms into humans by skin penetration of the parasites, rather than by ingestion. One self-experimenter who succumbed was Daniel Carrion (1858–1885), a medical student in Lima, Peru. Carrion injected himself with the material from a chronic skin lesion called *Verraga peruana*. This self-experiment was designed to determine whether the same organism (later identified to be *Bartonella bacilliformis*) could also cause another disease, known as Oroya fever. Oroya fever was a more serious disease, involving the red blood cells. When Carrion developed Oroya fever, he proved that the two diseases were caused by the same infectious organism but the experiment cost him his life.[43]

In the subsequent decades numerous scientists began to focus their investigations on vector-borne disease. The explosive epidemic nature of yellow fever and malaria when they occurred in Europe and the United States, not to mention the military and commercial interests in their control, spurred researchers and their governments to support studies. The first proof that an animal disease was spread by an arthropod was the report in 1893 by Smith and Kilbourne on the transmission of Texas cattle fever by a *Borrelia* sp. tick.[44] Another group of landmark studies was organized in Cuba, which led to an understanding of the biology and epidemiology of yellow fever.[45] Although epidemics of yellow fever had been reported as far north as Philadelphia in the 1700s and 1800s, the means of transmission of the disease were unclear. Some believed that the disease was spread directly from person to person. However, Stubbins Firth (1784–1820) in 1804 observed that secondary cases among nurses or doctors caring for patients with the disease were unheard of. To prove that person-to-person transmission wasn't a risk, he undertook a remarkable series of self-experiments, in which he exposed himself orally and parenterally to the hemorrhagic vomitus, other excretions, and blood of patients dying of yellow fever. He was unable to transmit the infection in these experiments, and he concluded that yellow fever wasn't directly transmitted from person to person.[12]

Early in the 1800s, it had been suggested by several physicians that yellow fever might be spread by mosquitoes.[12] The theory was restated by the Cuban physician Carlos Finley (1833–1915) in 1881, but experimental proof was lacking.[12,43] When the United States occupied Cuba during the Spanish-American War, a yellow fever study commission was established and Walter Reed (1851–1902) was dispatched to Cuba in 1899 to study the question further. The commission studied the transmission of yellow fever

by *Stegomyia fasciata* mosquitoes, now named *Aedes aegypti*, using human volunteers (because there were no animal models). In the course of the investigation, one of the volunteers, who was a member of the committee, Jesse H. Lazear (1866–1900), contracted yellow fever following a mosquito bite and succumbed to the disease. After several definitive experiments, the commission was able to report that yellow fever was transmitted to humans by the bite of an infected mosquito.[45]

In 1898, Loeffler and Frosh had shown that hoof-and-mouth disease of cattle was caused by an agent small enough to pass through a filter capable of retaining the smallest bacteria.[46] Reed and colleagues demonstrated that the agent of yellow fever was present in filtered blood leading them to concluded that the causative agent of yellow fever was a virus.[45] This conclusion made yellow fever the first identified viral cause of human disease. Furthermore, their studies showed that yellow fever had an obligate insect cycle and was not transmitted directly from person to person.

Mosquitoes were also suspected in malaria, although early researchers were unsure as to whether it was a marker of poor sanitation or a necessary part of the malaria life cycle. In *De Noxiis Palodum Effloriis* (On the Noxious Emanations of Swamps), published in 1717, Giovanni Maria Lancisi (1654–1720) speculated on the manner in which swamps produced malaria epidemics.[12] Lancisi theorized that swamps produced two kinds of emanations capable of producing disease, animate and inanimate. The animate emanations were mosquitoes, and these, he thought, could carry animalcules. Over 150 years later, the microscope was the tool used to wage an intense scientific competition to identify the malaria life cycle. The malaria parasite, *Plasmodium falciparum*, was originally discovered by Alphonse Laveran (1845–1922), a French army surgeon working in Algeria. On November 5, 1880, he "was astonished to observe, [in a soldier's blood specimen] . . . a series of fine, transparent filaments that moved very actively and beyond question were alive."[47] After this discovery, researchers from England and Italy were working around the globe. The Italian research team took a wrong turn and concluded that the parasite might be an amoeba or other spore outside of the human and concentrated on collecting materials from malarious locations, including but not limited to mosquitoes. It was the tireless work of Ronald Ross (1857–1932) in India that finally uncovered the life cycle of avian malaria. Painstakingly dissecting mosquitoes he searched for malaria parasites and finally found the salivary glands packed with the germinal rods of malaria. He described the excitement of his discovery in a letter to Sir Patrick Manson (1844–1922) on July 6, 1898.

7

> I think that this, after further elaboration, will close at least one cycle of proteosoma, and I feel that I am *almost* entitled to lay down the law by direct observation and tracking the parasite step by step—Malaria is conveyed from a diseased person or bird to a healthy one by the proper species of mosquito and is inoculated by its bite. Remember however that there is virtue in the "almost". I don't announce the law yet. Even when the microscope has done its utmost, healthy birds must be infected with all due precaution. . . . In all probability it is these glands which secrete the stinging fluid which the mosquito injects into the bite. The germinal rods . . . pass into the ducts . . . and are thus poured out in vast numbers under the

> skin of the man or bird. Arrived there, numbers of them are probably instantly swept away by the circulation of the blood, in which they immediately begin to develop into malaria parasites, thus completing the cycle. No time to write more.[47]

He was able to demonstrate that birds fed upon by these mosquitoes were infected, and Patrick Manson presented these results to British Medical Association in Edinburgh at the end of July 1898.[48] Unfortunately for Ross, the
8 British Army required him to work on kala-azar until February of 1899
9 giving the Italians Amico Bignami, Giovanni Battista Grassi, and Giuseppe Bastianelli the opportunity to finish verifying that anopheline mosquitoes were the vector for malaria and to confirm that the avian life cycle was the same in humans.[49] But the heated rush to decipher the remaining questions in the malaria life cycle pitted the Italians against the near-celebrity Koch who arrived on invitation from the Italian government to "solve the malaria problem."[47] The Italians, bitterly jealous of the German scientific superstar, rushed to publication and failed to give due credit to Ross. The ensuing battle between Ross, Grassi, and Koch was legendary. In fact, when the Nobel committee considered splitting the 1902 Nobel Prize in medicine between Ross and Grassi,[49] Koch's vehement opposition prevented it, allowing Ross the honor alone.[47]

Following the elegant demonstration of yellow fever and malaria transmission, the epidemiology of several other arthropod diseases was described (Table 1-2). Also, many other human diseases caused by viruses were defined in the ensuing decades. The second mosquito-borne human viral infection to be identified was dengue, a reemerging viral infection of increased

TABLE 1-2 The Scientist Credited with the Discovery of Important Vector-Borne Pathogens and the Year of That Discovery

Disease	Disease Vector	Investigator	Year
Babesiosis (Texas cattle fever)	Deer tick	Smith and Kilbourne	1893
Yellow fever	Mosquito	Reed, Carroll, and Lazaer	1900
Dengue	Mosquito	Bancroft, Craig, and Asburn	1906
Rocky Mountain spotted fever	Wood tick	Ricketts, King	1906
Typhus, epidemic	Body louse	Nicolle	1909
Sandfly fever	Sand fly	Doerr, Franz, and Taussig	1909
Murine typhus	Rat louse	Mooser	1931
	Rat flea	Dyer	1931
Colorado tick fever	Wood tick	Topping, Cullyford, and Davis	1940
Rickettsial pox	Mite	Huebner, Jellison, and Pomerantz	1946
Lyme disease	Deer tick	Burgdorfer	1982
Cat scratch fever and bacillary angiomatosis	Cat flea	Koehler	1994
Human monocytic ehrlichiosis	Dog tick and lone star tick	Maedo et al	1986
Human granocytic ehrlichiosis	Deer tick	Chen et al	1994

importance today. Dengue is spread by the same mosquitoes that transmit yellow fever, *A. aegypti*. The means of transmission and the fact that dengue was a filterable virus were discovered by the Australian Thomas Bancroft et al.[12] in the Philippines in 1906.

The 20th Century

The identification of the causative microorganisms of specific infections allowed for a much better understanding of their epidemiology, which in turn informed prevention strategies. The disciplines of microbiology, virology, and immunology paralleled and complemented the disciplines of epidemiology, statistics, and public health in the prevention of infectious diseases. Despite advances, epidemic diseases continued to occur in the United States, particularly in the nation's port cities. Cholera, first seen in the Western Hemisphere in 1832,[27] yellow fever, malaria, and plague were constant concerns. Although public health authorities had a better understanding of the diseases, treatments lagged behind, and quarantine remained the staple tool of prevention. Several US congressional acts in 1887, 1901, and 1902 were responsible for creating what would ultimately become the National Institute of Health (NIH). Congress charged the future NIH with the study of "infectious and contagious diseases and matters pertaining to the public health." The first employee was Joseph J. Kinyoun who promoted the science of health and introduced laboratory diagnostics for the confirmation of cholera cases. The Public Health Service was instrumental in addressing sanitation issues during the First World War and also during the influenza epidemic of 1918. In 1930, a financially strapped US government still found funds under the Ransdell Act to further expand the NIH and charged it with investigating basic medical and clinical science. During the Second World War the NIH concentrated on disease of particular importance to the military, including yellow fever and typhus vaccines. After the war, the 1946 Public Health Service Act established the NIH's grant mechanism to fund nonfederal scientists. Finally in 1948, the National Institute of Health was given its last name change and became the National Institutes of Health reflecting the diversity of diseases under study at the NIH.[52]

Greater understanding of the biology of disease pathology also led to better treatments. Treatments for diphtheria with antitoxin and the development of vaccines for rabies, anthrax, diphtheria, and tetanus were developed. However, many of the antisera that were developed and antiseptics that were tried for the therapy of infectious diseases were of only limited effectiveness. Complicating their use was the risk of contamination in the production of these medications. Kinyoun worked hard to establish standards in production of drugs and vaccines. After the death of 13 children in Saint Louis from contaminated diphtheria antitoxin, the US Congress passed the Biologics Control Act.[51] Under this act, standards in biologics were developed and licenses granted to pharmaceutical companies for specific medications or vaccines. In 1924, investigators at the Bayer pharmaceutical company in Germany synthesized a new antimalarial drug, pamaquine (Plasmoquine). Shortly thereafter, they synthesized other antimalarial compounds, including quinacrine (Atabrine).[52] The development of these new drugs gave some

hope that specific, effective antimicrobial treatments could be developed for infectious diseases. In 1932, Gerhardt Domagk, experimenting with synthetic dyes, discovered that Prontosil could cure mice challenged with lethal doses of hemolytic streptococci.[52] This led to the development of several sulfa drugs. The sulfonamides were shown during World War II to be quite effective against a number of highly fatal infections, such as meningococcal meningitis. In the 1930s and 1940s, Alexander Fleming, Howard Florey, and Ernst Chain at Oxford University conducted experiments that led to the demonstration that penicillin, a mold product, was effective against many pathogenic organisms.[52] Penicillin was shown to be effective against syphilis, gonorrhea, and pneumococcal infections. For the first time, it was possible to effectively treat a wide range of infections, and this gave birth to the search for new antibiotics produced by organisms in nature or synthesized in the laboratory.

After the conclusion of the Second World War in 1946 the Center for Disease Control (CDC) was established in Atlanta, Georgia.[53] The CDC grew out of an organization known as "Malaria Control in War Areas," which had the mandate to control malaria and other tropical infections, especially scrub typhus and hook worm, in the southern United States. Its founder, Dr. Joseph Mountain, was a visionary public health leader who had high hopes that the CDC would eventually play an important role in public health in the United States. Subsequently, the role of CDC, under the leadership of Dr. Alexander Langmuir, grew dramatically to include surveillance of infectious and noninfectious diseases, the provision of expert scientific advice on health issues to policy makers in the United States, serve as a reference laboratory to the states and inform the public about health issues through the *Morbidity and Mortality Weekly Report*. Today, epidemiologists from CDC routinely assist state health departments in investigating and controlling outbreaks of infectious and noninfectious diseases. In its role in the field investigation of outbreaks, the CDC is unique among national public health organizations. Since its establishment the CDC has grown to provide leadership, often in partnership with the World Health Organization (WHO), in controlling emerging infectious diseases worldwide.

Although some vaccines were developed earlier, the number and impact of vaccines developed in the 1900s century was monumental. The renamed Centers for Disease Control and Prevention in 1999 published a review of the 10 great public health achievements in the United States during the 1900s.[54] At the top of its list is vaccination. The vaccines developed and licensed to prevent vaccine-preventable diseases are shown in Table 1-3, and an estimate of their effect on reported infectious disease morbidity is shown in Table 1-4.

During the previous century, the average life span of persons in the United States lengthened by about 30 years, and 25 years of this gain has been attributed to advances in public health. The public health actions to control infectious diseases in the 1900s, which included marked improvements in sanitation, chlorination of nearly all public water supplies, and development and use of vaccines to prevent infectious diseases and antibiotics for their treatment, along with improved methods for diagnosis, were reviewed recently by the CDC (Figure 1-3). During the 1900s, infectious disease mortality declined from about 800/100,000 population to under

TABLE 1-3 The Year Effective Vaccines Were Developed Against Different Human Diseases

Smallpox*	1798†	Mumps*	1967‡
Rabies	1885†	Rubella*	1969‡
Typhoid	1896†	Anthrax	1970‡
Cholera	1896†	Meningitis	1975‡
Plague	1897†	Pneumonia	1977‡
Diphtheria*	1923†	Adenovirus	1980‡
Pertussis*	1926†	Hepatitis B*	1981‡
Tetanus*	1927†	*Hemophilus influenzae* type b*	1985‡
Tuberculosis	1927†	Japanese encephalitis	1992‡
Influenza	1945‡	Hepatitis A	1995‡
Yellow fever	1953‡	Varicella*	1995‡
Poliomyelitis*	1955‡	Lyme disease	1998‡
Measles*	1963‡	Rotavirus*	1998‡

* Vaccine recommended for universal use in US children. For smallpox, routine vaccination was ended in 1971.
† Vaccine developed (i.e., first published results of vaccine usage).
‡ Vaccine licensed for use in the United States.

50/100,000 and accounted for most of the improvement in US life expectancy. In 1900, 30.4 percent of all deaths occurred in children under five years of age. In 1997, the proportion of total mortality in this age group was only 1.4 percent.[55,56]

What Lies Ahead

The science of health moved forward at breakneck speed in the previous century. The effectiveness of treatments and vaccines coupled with increased financial support fueled spectacular advances as the underlying science of diseases was unraveled. Although many advances are noteworthy, perhaps the discovery of the structure of DNA and ultimately the determination of the entire human genome will have the greatest impact on the future of health research. It was February 28, 1953, when James Watson and Francis Crick first determined the double helix structure of DNA and the mechanism by which it could copy itself and thus serve as the bases for hereditary information. Rosalind Franklin and Maurice Wilkins from King's College in London created images of DNA with X-ray diffraction, and these images, combined with cardboard models, allowed Watson to finally determine the binding of adenine and thymine and guanine and cytosine to form the ladder rungs of the double helix.[57] Franklin died of cancer in 1958, and was unable to share in the Nobel Prize with Watson, Crick, and Wilkins in 1962. Since that time gradual progress in deciphering and manipulating the genetic code of animals and plants had occurred. Dolly the sheep, born July 5, 1996, was the first higher animal to be cloned, and several other animals have followed.[57] In 1990, the US Human Genome Project was undertaken to identify all of the approximately 25,000 genes in human DNA. The project was completed ahead of schedule and in April 2003 the human genome was published in several articles in *Nature* and *Science*.[58,59] The sequencing project has identified over 10 million locations where single-base DNA differences (SNPs) occur.[60] Today

TABLE 1-4 A Comparison of Morbidity from Infectious Diseases Before and After the Availability of Vaccines

Disease	Baseline 20th Century Annual Morbidity	1998 Provisional Disease Morbidity	Percent Decrease
Smallpox	48,164*	0	100
Diphtheria	175,885†	1	100‡
Pertussis	147,271§	6,279	95.7
Tetanus	1,314‖	34	97.4
Poliomyelitis (paralytic)	16,316¶	0#	100
Measles	503,282**	89	100‡
Mumps	152,209††	606	99.6
Rubella	47,745‡‡	345	99.3
Congenital rubella syndrome	823§§	5	99.4
Hemophilus influenzae type b	20,000‖‖	54¶¶	99.7

*Average annual number of cases 1900–1904.
†Average annual number of reported cases 1920–1922, three years before vaccine development.
‡Rounded to nearest tenth.
§Average annual number of reported cases 1922–1925, four years before vaccine development.
‖Estimated number of cases based on reported number of deaths 1922–1926, assuming a case-fatality rate of 90%.
¶Average annual number of reported cases 1951–1954, four years before vaccine licensure.
#Excludes one case of vaccine-associated polio reported in 1998.
**Average annual number of reported cases 1958–1962, five years before vaccine licensure.
††Number of reported cases in 1968, the first year reporting began and the first year after vaccine licensure.
‡‡Average annual number of reported cases 1966–1968, three years before vaccine licensure.
§§Estimated number of cases based on seroprevalence data in the population and on the risk that women infected during a childbearing year would have a fetus with congenital rubella syndrome.12
‖‖Estimated number of cases from population-based surveillance studies before vaccine licensure in 1985.39
¶¶Excludes 71 cases of *Hemophilus influenzae* disease of unknown serotype.

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it is recognized that differences in SNPs between individuals directly affects a person's susceptibility to infection and disease. The fields of genomics and proteomics, the study of protein expression, are rapidly evolving fields that hold great promise for understanding the interaction of humans with infectious pathogens.

Genetics will have also play a role in unlikely places. On August 11, 2005, the genome of rice was reported. This was the first of the cereal grains to be deciphered. This genome will be informative for all grains, as rice, corn and wheat diverged from a common grass ancestor only 50,000 years ago.[61] Cereals make up the majority of calories in most of the world. Earlier researchers manipulated the rice genome to insert a daffodil gene which added vitamin A to rice.[62,63] Vitamin A is crucial to immunologic health,[64] and the use of enhanced food products holds promise for improving health.

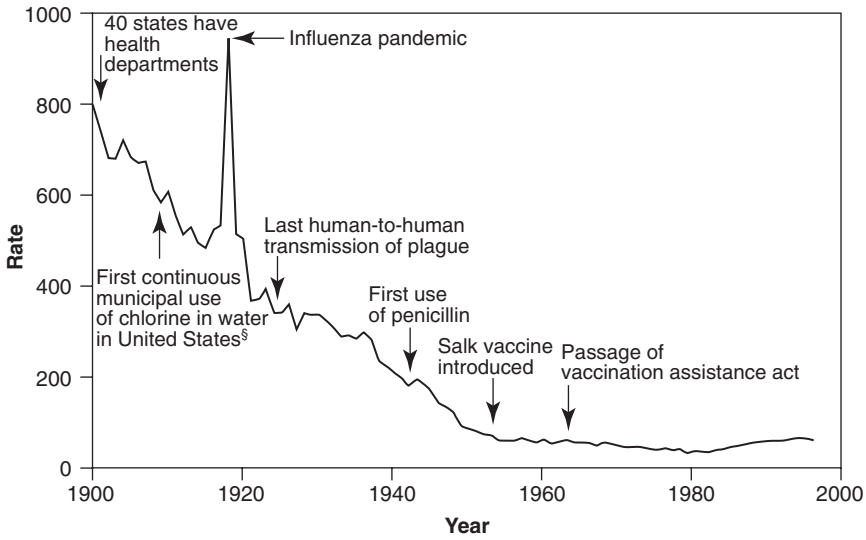

FIGURE 1-3 Crude death rate for infectious disease, United States, 1990–1996.

Unfortunately, although genetically modified foods hold great promise, they are also highly controversial. Hardier plants, enhanced with insect repellant genes or drought resistance, threaten to drive out native plants, which could ultimately reduce global genetic diversity. Highly successful seeds are patented, and this elevates the cost of seed beyond the reach of subsistence farmers. The concentration of ownership of seeds is severe, and only a handful of companies own the rights to most of the food seed sold in the world.[65] These controversies, and those surrounding manipulation of the human, and other genomes, will determine the ethical boundaries and ultimate potential of genomic and proteomic science.

The Infectious Diseases Challenge

In the previous century, such spectacular progress was made in infectious disease control that many health professionals felt that antibiotics and vaccines would soon eliminate infectious disease threats from most developed nations. The confidence of the 1970s was shattered by the 1980s when the AIDS pandemic exploded. The first scientific report of AIDS was June 5, 1981, in the *Morbidity and Mortality Weekly Report*.[67] In this report, cases of *Pneumocystis* pneumonia in previously healthy gay men were described by Dr. Michael Gottlieb. Since that time the magnitude and severity of the HIV/AIDS epidemic has not abated; it is now estimated that more than 5 million people become infected with HIV every year. Because most people infected with HIV acquired it through sexual contact, it is predominately a disease of young adults. The introduction of highly active antiretroviral therapies (HAART) has modified the disease course for those able to afford them, but to date there is neither an effective cure nor a vaccine. HIV and the immune sup-

pression it causes has also allowed for a resurgence of tuberculosis in much of the world. Unfortunately, drug resistant strains of tuberculosis have also emerged making control even more difficult. Several other diseases emerged, or reemerged, in the last of the previous century. The unfounded optimism of the mid-1900s has been replaced by greater resolve to solve some of the most intractable problems in infectious diseases.

The remainder of this book will lay out the techniques and tools of infectious disease epidemiology and then describe some of the important infectious diseases. The book is not intended to be a comprehensive study of all infectious diseases, but we hope it will give the fundamental tools and knowledge necessary to advance the readers understanding of infectious disease epidemiology.

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