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THE IMPACT
OF HUMAN HISTORY
ON EPIDEMIC DISEASE

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PLAGUES & POXES

THE IMPACT OF HUMAN HISTORY ON EPIDEMIC DISEASE

Alfred Jay Bollet, M.D.
This is a sample from Plagues & Poxes

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“We’ve known so much of happiness,
We’ve had our cup of joy,
And memory is one gift of God
That death cannot destroy.”


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ACKNOWLEDGMENTS

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The first edition of *Plagues and Foxes* concentrated on the recurrent appearances and disappearances of new diseases in various parts of the world, and the impact of those diseases on history, especially political and military history. Since its appearance so many new diseases of great importance have appeared that the point of the book is no longer news or surprising. Examples include AIDS, of course, the most important and devastating of the new diseases, but Lyme disease, a new devastating form of asthma, a new form of viral encephalitis, West Nile virus, and a new form of viral hepatitis, hepatitis C, has come to the fore and is now the most serious form of that disease. So many new diseases have appeared that we have books and papers on “Emerging Diseases” and, more specifically, emerging viruses. At the same time, established but relatively new diseases have waned in frequency, most notably peptic ulcers, cancer of the stomach, and rheumatic fever, and deaths from heart disease have decreased considerably. But a new phenomenon has come to the forefront of public consciousness—intentionally caused disease, or bioterrorism. Thinking about the history of disease, these new concerns have brought to mind the fact that historical phenomena—military, political, and technological—have impacted the occurrence and severity of disease for as far back as history goes. This new edition shifted the emphasis to the impact of history on disease, rather than the reverse.

Historical developments have always been causal factors in the production of disease, at least since the first agriculturalists domesticated previously wild animals and caught their diseases. Measles, smallpox, and a variety of bacterial dis-
eases are examples. Knowledge of the deadly nature and contagiousness of disease has lead to military efforts to induce disease in enemies, especially during sieges; bubonic plague and syphilis are major examples dating back to the fourteenth and sixteenth centuries.

On the other hand, knowledge of how diseases are spread has led to useful and sometimes successful efforts to control outbreaks of disease, beginning with quarantine for bubonic plague and, most notably, the successful containment of an outbreak of a serious severe respiratory disease in 2003 (SARS).

Knowledge of the factors that have been of importance in the international spread of major epidemic diseases in the past, both infectious and non-infectious, is worth reviewing in detail, and that is the subject of this new, revised edition of *Plagues and Poxes*. 

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INTRODUCTION

UNINTENTIONAL CAUSES OF EPIDEMIC DISEASES

THE IMPACT OF HUMAN HISTORY ON DISEASE

Many of the worst diseases of the past—infections such as typhoid fever, smallpox, and plague—have now become rare, at least in developed countries. In contrast, noninfectious diseases, such as cancer and coronary heart disease, have replaced them as major epidemic causes of death. It is usually human actions, including warfare, commercial travel, social adaptations, and dietary modifications, that precipitate the rise and fall of diseases.

Some infectious diseases that have caused the most devastating mass mortality in human history can trace their origin and mode of spread to human activity and behavior. Many other diseases, both infectious and noninfectious, have been caused and spread by technological changes that benefited society as a whole, but had serious side effects that resulted in epidemic disease. For example, changes in food technology, mainly the availability of new foods or new means of processing old foods, have inadvertently brought on massive outbreaks of disease. Beriberi and pellagra are prime examples of this phenomenon. In both instances, new technology made more food available and thus supported a much larger population; at the same time, because micronutrients and the conse-
quences of lack of them were not yet known, they induced nutritional deficiency diseases.

Such phenomena are avoidable, and those diseases caused by human actions are preventable. We have seen a most important example of this in recent times in the decreased incidence of coronary heart disease that resulted from changes in smoking and dietary habits in the United States and Western Europe. A clear knowledge of how and why epidemic diseases appear and spread is important in curbing the damage they do. (Although chemical pollution of the environment threatens to cause severe epidemic diseases, thus far only localized outbreaks of illnesses have been caused by air or water pollution. A discussion of the threat posed by these phenomena requires a separate volume and will not be covered here.)

*Plagues and Poxes* concentrates on the history of major outbreaks of both infectious and noninfectious disease caused by human action through the ages. Prime historical examples of how human action resulted in epidemics of infectious diseases include the search for gold in the New World, which spread smallpox and measles among previously unexposed Native American populations; the corresponding introduction of syphilis into the Old World by European adventurers; and the importation of African slaves into the Western hemisphere, which introduced devastating new diseases such as malaria and yellow fever. Such interchange of disease still occurs, with the AIDS epidemic probably the most important example in recent decades. An analysis of the historic spread of these diseases may be useful in preventing new epidemics.

Most of the diseases discussed in the following chapters are side effects—the consequences of human actions that unintentionally caused them. Today, however, we are faced with concern for the intentional spread of disease through acts of bioterrorism. Several chapters are thus devoted to the history and knowledge of those diseases that are thought to be potential candidates for bioterrorism.

**Origins of Some Infectious Diseases.** Before agriculture, humans lived in small hunter-gatherer tribes. A high infant mortality rate probably kept the population small, although evidence suggests that intentional measures, such as infanticide, lengthening the birth interval through prolonged lactation-amenorrhea, sexual abstinence, or abortion, were also used to keep tribal size down to levels that the food supply could support. Most clans or tribes were nomadic, following the seasonal patterns of availability of game and vegetation. Based on bone and skeletal analyses, paleontologic evidence shows that hunter-gatherers (at least the ones who survived to adulthood) were healthy people, maybe even healthier than populations that developed after the introduction of agriculture.
The development of agriculture resulted in a considerable increase in the human population in those areas that adopted the new techniques. With agriculture came a more settled existence that led to larger population units and more complex social structures, including administrative or political systems involving kings, bureaucrats, and taxes. Large clusters of humans thus gave rise to true civilizations in which some people were able to devote their efforts to administrative or artistic skills instead of to simply obtaining food. Unfortunately, these larger and more condensed population groups also gave rise to “crowd diseases.” Large groups of people allowed the spread and perpetuation of infectious diseases agents because susceptible, nonimmune people kept appearing in sufficient numbers to keep a disease from dying out.

The domestication of animals occurred along with organized agriculture. This resulted in larger numbers and greater varieties of animals living in close proximity to humans. Some of the diseases of these animals now could affect humans, or perhaps become genetically modified to become epidemic human diseases. The genetic structure of the relevant organisms provides clues that the animal diseases listed in Table 1-1 are closely related to human diseases. Other diseases may belong on this list, the most important being AIDS, which may be a simian disease that has spread to humans.

Another disease that might be discussed is typhus. However, although a great deal has been written about typhus in history, in many outbreaks it is hard to establish that the diseases being described before the mid-nineteenth century were in fact typhus. For example, typhoid fever was not distinguished as a separate entity distinct from typhus until the 1830s, and was named for its clinical resemblance to typhus. After that time typhus was less and less commonly diagnosed and typhoid became more and more a dominant disease and cause of death. There is a lot of evidence that typhus became common after the beginning of the sixteenth century, especially among armies, and that it was spread

<table>
<thead>
<tr>
<th>Human disease</th>
<th>Genetically related animal disease</th>
</tr>
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<tbody>
<tr>
<td>Measles</td>
<td>Rinderpest of cattle</td>
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<tr>
<td>Tuberculosis</td>
<td>Tuberculosis of cattle</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Pox viruses of domestic animals, including cowpox</td>
</tr>
<tr>
<td>Influenza</td>
<td>Influenza in pigs, ducks, and chickens</td>
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<tr>
<td>Whooping cough</td>
<td>Similar disease in pigs and dogs</td>
</tr>
<tr>
<td>Falciparum* malaria</td>
<td>Malaria in birds (perhaps chickens and ducks)</td>
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* The most severe form of malaria, which causes high rates of mortality in humans.
primarily by the troops during wars. It became a constant threat to prisoners in jails (where it was often called “jail fever”), to people crowded on ships (“ship fever”), and when troops were gathered together for training (“camp fever”). During the American Civil War there were virtually no cases of typhus diagnosed despite optimal conditions for its spread. Soldiers existed in crowded living conditions and virtually all the soldiers and officer on both sides were heavily infested with lice; in addition, many of the soldiers were recent immigrants from European areas where typhus was common. But typhoid was the major killer disease while typhus—well known to Civil War doctors—was very rare. In view of the voluminous literature on typhus and doubts as to the accuracy of the diagnoses before the mid-nineteenth century, I have omitted coverage of that disease.

Epidemics of Noninfectious Diseases. Histories of epidemic disease concentrate on those infectious diseases that caused famous outbreaks and affected the course of historic events, but great epidemics of noninfectious diseases occurred as well. These epidemics were possibly less dramatic because of their gradual onsets. However, many were as devastating as many infectious diseases in terms of numbers of deaths they caused. The most notable examples are the nutritional deficiency diseases, scurvy being the most famous from the standpoint of its effect on history. However, the concept of a deficiency of a specific, individual nutrient as a cause of disease was not understood before the early twentieth century. From the late eighteenth century onward, it was believed that disease was caused by the presence of something abnormal; how then, could it be due to the absence of something? Once the concept of micronutrient deficiency was understood, measures to limit the occurrence of these diseases began. Modern scientific methods soon identified deficient nutritional components, isolated them, and synthesized them so that supplements could be made available in adequate quantities to combat these dietary diseases.

The first deficiency diseases appeared when early human populations settled into farming communities, and the wide variety of foods enjoyed by nomadic hunter-gatherer groups was no longer available. Through paleopathology—the study of ancient remains—we can safely guess that the first epidemic nutritional deficiency disease was probably iron-deficiency anemia. In long-standing iron-deficiency anemia, bones, especially those of the skull, show changes caused by an increase in the size and number of blood forming spaces filled by the bone marrow, along with a corresponding enlargement of the marrow as it tries to compensate for the lack of iron by making more red blood cells. Such bony changes, called porotic hyperostosis, are seen in modern humans with long-standing anemia,
especially those caused by genetic deficiency syndromes that begin in childhood. Although data is limited, a higher frequency of such changes has been found in the skulls and bones of early agricultural societies compared to the bones of hunter-gatherer groups. These findings most likely point to a lack of dietary iron, a vital nutrient present mainly in red meat but mostly absent in vegetables. As agriculture led to a more settled, less nomadic existence, the human diet changed from one of primarily meat, in the form of game, to vegetables and grains. This inevitably led to iron deficiency.

Although the domestication of animals provided new sources of meat, paleopathologic evidence of iron deficiency shows that these supplies were often inadequate for the burgeoning population. To compound the problem, settled agricultural societies are more prone to parasitic infections spread by the fecal contamination of water supplies; many of these parasites cause intestinal blood loss, thus aggravating the problem of anemia. Iron deficiency is most severe in individuals who need iron most—growing children and menstruating women.

Iron deficiency causes functional impairment, including weakness, lassitude, and a general lack of energy. Other enzymes in the body require iron in addition to hemoglobin, and the effects of iron deficiency are widespread in the body, as shown by the clinical observation that treatment of such patients with iron results usually in marked symptomatic improvement before the hemoglobin level begins to rise.

Changes in the availability and nature of specific foods continued to affect both the size of population groups and the health of these groups throughout history. For example, when New World maize (corn) was introduced to Europe, the greater caloric yield per acre resulted in a considerable population increase in areas that grew it, especially Spain and Italy. Potatoes introduced into Ireland from the New World resulted in a great increase in population there.

In Ireland during the 1840s and 1850s, severe famine resulted from the loss of the potato crops to a fungal infestation, coupled with British laws that required the export of food that was raised. The population of Ireland had risen from about 2 million to about 4 million after the potato was introduced. Deaths from famine (with scurvy diagnosed in a high proportion of the people), coupled with emigration, resulted in the population decreasing back to 2 million within a decade.

The effect of maize on population growth was similar to that of the potato, but the reason for the epidemic disease that followed was quite different. In both cases, the problem was the fragile nutritional state that results when any single vegetable crop is the main source of food. However, in the case of maize, an epidemic of pellagra resulted from the almost exclusive use of maize as a staple food. The epidemic was severe in southern Europe late in the eighteenth century and
A BRIEF HISTORY OF BIOLOGICAL WARFARE. Biological warfare is not a new phenomenon. Although war has always helped to spread disease, attempts have been made to intentionally cause epidemic disease almost since the dawn of recorded history. For example, since antiquity, wells and other water sources for armies and civilian populations under attack have been purposely contaminated with animal or human cadavers as well as with excrement. Among the earliest recorded examples of the use of agents thought to cause disease in battle are the actions of Scythian archers, who used arrows dipped in blood, manure, or fluids from decomposing bodies when trying to stop the invading Assyrians in the seventh century BCE.

Spontaneous diarrhea and dysentery have always been the scourge of armies in the field, vastly impairing the effectiveness of soldiers. In the fighting among the Greeks in the sixth century BCE, Solon of Athens had water supplies poisoned with hellebore, a purgative. During the American Civil War when diarrhea was ubiquitous—Walt Whitman said the war was “about nine hundred and ninety-nine parts diarrhea to one part glory”—a tradition arose not to shoot a man “while he is attending to the urgent call of nature” and was honored by both sides throughout the war.

As described in the chapter on bubonic plague, human cadavers were used in the fourteenth century in an attempt to spread disease during the outbreak of plague called the “Black Death.” The epidemic began in an area of Russia, near
the Crimea, during the siege of Kaffa (now Feodossia in the Ukraine). The besieging Tartars were dying in large numbers of a disease that caused the appearance of buboes in the groin, the classic lesion of bubonic plague. The Tartars attempted to spread the disease that was killing their soldiers by catapulting cadavers into the city with their hurling machines. Although the fleas that transmit plague may leave cadavers to seek living hosts on which to feed, the corpses catapulted over the walls of Kaffa probably were not carrying competent plague vectors. It is more likely that the disease appeared in the city because rats could move into and out despite the siege, bringing their fleas and plague bacilli with them. Soon, there was so much plague in the city that it was uninhabitable. It was abandoned, and the inhabitants boarded ships and retreated to their home port in Genoa, stopping at several other Mediterranean ports along the way. Plague was widely spread in this fashion.

Smallpox devastated the Native American populations when it was accidentally introduced by the Conquistadors. The Spaniards were immune to it because they had been exposed earlier in life. Smallpox also has been spread deliberately as a weapon of biowarfare. During the French and Indian War (1754–1763), Sir Jeffrey Amherst, commander of British forces in North America, suggested that smallpox be intentionally spread to “reduce” Native American tribes hostile to the British. During the fighting around Fort Pitt (now Pittsburgh), Captain Ecuyer, one of Amherst’s subordinates, gave blankets and a handkerchief from patients in the smallpox hospital to the Native Americans and recorded in his journal, “I hope it will have the desired effect.” Fomites, objects used by sick people that can harbor and potentially transmit disease agents, are not an efficient method of spreading smallpox, since the disease is spread primarily by airborne respiratory droplets. However, an epidemic of smallpox did occur among Native American tribes in the Ohio River Valley. Other contacts between Native Americans and Europeans might have been responsible, since smallpox had been affecting the Native Americans for more than 200 years, but the records reveal this act as a deliberate attempt to spread disease during war.

An important example of biowarfare in the Western Hemisphere was the use of curare by South American natives. Curare was made in a variety of ways, using extracts of the active principle from the bark of a variety of trees, with various plant additives and sometimes snake venom or venomous ants included. The mixture was boiled in water for about two days, then strained and evaporated to become a viscid paste. The potency of the paste was tested, for example, by pricking a frog with a stick dipped in the curare preparation and counting the number of leaps it would take before it collapsed and died. Darts dipped in
the curare were then fired accurately through blowguns made of hollow grass stems such as bamboo. Since curare was scarce and difficult to prepare it was rarely used in tribal warfare—it was too valuable as a weapon for hunting. After being stuck by an arrow tip with curare on it, birds would die in one to two minutes, small mammals in up to ten minutes, larger mammals in up to 20 minutes, and the prey could be tracked until it died. The active agent in curare blocks the transmission of nerve impulses to the receptors in muscle fibers, paralyzing the muscles. Studies of its nature and actions led to improved understanding of the nature of the neuromuscular junction and the development of potent pharmaceutical agents with properties similar to those of curare. These drugs are used during major surgery to obtain good muscle relaxation, although the patient must breathe mechanically. In a sense, biological warfare can have its positive side!

Biological warfare made its greatest strides during the twentieth century. During World War I, the use of poison gases by the Germans on the Western Front is well known. Several agents were used, including chlorine and mustard gas, causing large numbers of deaths and horrific painful distress in survivors. The Allies countered with similar agents, but on a lesser scale.

Also during World War I, the Germans undertook covert biological warfare operations in neutral countries that traded with the Allies. Animal feed contaminated with anthrax and glanders \((\text{Pseudomonas } [\text{Burkholderia} \ mallei])\) was used to infect Romanian sheep being raised for export to Russia. In 1916, cultures of these two organisms were confiscated from the German legation in Romania. Allegedly, the organism for glanders was also used by German saboteurs operating in Mesopotamia to inoculate 4,500 mules used in British operations against the Turks, and in France, saboteurs infected French cavalry horses. Argentinean livestock intended for export to Allied countries also were infected with anthrax and glanders, resulting in the death of more than 200 mules in 1917 and 1918. In the United States, during the early years of World War I, Germans attempted to contaminate animal feed and to infect horses intended for export.

Such biowarfare was banned by the 1925 Geneva Protocol for the “Prohibition of the Use in War of Asphyxiating, Poisonous, or other Gases, and of Bacteriological Methods of Warfare.” The treaty prohibited the use of biological weapons, but did not proscribe basic research, production, or possession of biological weapons, and many of the countries that ratified the protocol stipulated that they retained the right of retaliation. A number of these countries, including Belgium, Canada, France, Great Britain, Italy, the Netherlands, Poland, and the Soviet Union—all parties to the Geneva protocol, began basic research programs to develop biological weapons after World War I. The United States did not ratify the Geneva protocol until 1975.
Between 1932 and 1945, the Japanese conducted an extensive program to study biological weapons, which they tested on Chinese prisoners. At a site near the town of Pingfan in Northeastern China, close to the city of Harbin, a program was set up that included about 150 buildings, five satellite camps, and a staff of more than 3,000 scientists and technicians. Additional units were located at Mukden, Changchen, and Nanking. Observations were made on prisoners infected with pathogens, including *Bacillus anthracis* which causes anthrax; *Neisseria meningitides*, the cause of cerebrospinal meningitis; various species of *Shigella* and *Salmonella*, which cause dysentery; *Vibrio cholera*, the agent of cholera; and *Yersinia pestis*, the cause of bubonic plague. At least 10,000 Chinese prisoners died as a direct result of these experimental infections or were executed after experimentation.

In addition, the Japanese also mounted biological attacks on at least eleven Chinese cities. The attacks include contamination of water supplies and food items with cultures of the organisms that cause anthrax, cholera, and dysentery. Cultures were sprayed directly into homes from sources on the ground or sprayed on urban areas from aircraft. The Japanese purposely tried to start an epidemic of bubonic plague by breeding fleas in a laboratory and allowing them to feed on plague-infected rats. The infected fleas were then released from aircraft over Chinese cities. As many as 15 million plague-fed fleas were released per attack when flea bombs with small amounts of explosive were released over Ningpo, in October 1940. The Chinese noticed that the Japanese planes came in very low and that the ground was white with jumping, snowlike particles, after the bombs fell. Cases of plague appeared in the town, and panic spread. About 500 deaths resulted, and a local shortage of coffins made it necessary for survivors to bury victims two to a coffin.

Some attempts by the Japanese to spread diseases among the Chinese backfired. In 1941, a biological attack on Changteh reportedly sickened the assaulting Japanese troops, causing approximately 10,000 casualties and 1,700 deaths among them, mostly due to cholera. Field trials were terminated in 1942, although basic research continued in the laboratories at Pingfan until the end of the war.

In Germany during World War II, Hitler reportedly issued orders prohibiting biological weapons development. Nevertheless, high-ranking Nazi party officials supported German scientists who performed such research. While no German battlefield attacks with biological weapons ever materialized, prisoners in Nazi concentration camps were forcibly infected with two species of *Rickettsia*, the organisms that cause typhus; hepatitis A virus; and several species of malaria. They were then treated with investigational vaccines and drugs. The only known use of biological warfare by Germany was the pollution with sewage of a
large reservoir in northwestern Bohemia in May 1945, near the end of the war in Europe. (Unconfirmed reports state that the Germans considered releasing live, plague-infected rats from submarines so that they would swim to shore and spread the disease in Britain. They decided it wouldn’t work.)

In an ironic twist, the combination of a vaccine and a serologic test was used as a biological defense against the Nazi program of exportation and extermination of civilians. The German army carefully avoided civilian areas known to be infected with epidemic typhus by testing the inhabitants for serum antibodies that indicated the presence or prior exposure to the disease (the Weil-Felix reaction). Consequently, physicians in one area of occupied Poland injected people with killed organisms (Proteus OX-19) that can produce a positive Weil-Felix test. Thus, they induced false positive tests for typhus, and those residents of the area who had positive tests were not deported to concentration camps.

The Allies developed biological weapons during World War II. Weaponized spores of anthrax were used in studies conducted on Gruinard Island near the coast of Scotland. As a result, the island remained heavily contaminated with viable anthrax spores, and no humans or livestock could use it safely until it was decontaminated in 1986.

The United States established a research and development facility at Camp (later Fort) Detrick in Maryland, as well as at several other sites. Experiments were conducted to study the organisms of anthrax and brucellosis (Brucella suis). During World War II, 5,000 bombs filled with anthrax spores were produced at a pilot plant; these bombs were destroyed after the war. The program was expanded during the Korean War (1950-1953), when a large-scale production facility with strong biosafety measures was constructed at Pine Bluff, Arkansas. A program to develop countermeasures to protect troops from biological attack was begun in 1953. Vaccines and antisera were studied, as were other therapeutic agents.

Voluntary human experiments at Fort Detrick were performed in a large aerosolization chamber known as the “eight ball.” Volunteers were exposed to tularemia and to Coxiella burnetti, the organism of Q fever, the only rickettsial disease that does not require an insect vector. Q fever is transmitted by inhalation and causes a flu–like syndrome and pneumonia.

Other studies were done with essentially harmless agents that could simulate dangerous microbes, including various fungi and several species of bacteria. Such simulants were released by aerosolization over New York City, San Francisco, and other cities between 1949 and 1968, so that the spread and survival of the biological agents could be studied. Despite the low pathogenicity of these agents, concerns about public health hazards led to these studies being discontinued.
During the Korean War, the Soviet Union, China, and North Korea accused the United States of using biological warfare against North Korean and Chinese soldiers. The United States denied the accusation and requested an impartial investigation, but neither China nor North Korea would cooperate with requests by the International Committee of the Red Cross and the World Health Organization to investigate. The episode demonstrated the propaganda value of biological warfare allegations even though no basis for the charges existed. Other accusations were made—including some by the Soviets, that U.S. tests of biological weapons resulted in a plague epidemic among Canadian Eskimos and an epidemic of cholera in southeastern China. The United States also was accused of covert release of dengue fever virus in Cuba.

Similar accusations against Soviet forces, made by the United States, were also widely regarded as erroneous. These accusations stated that yellow rain (aerosolized trichothecene mycotoxins derived from fungi of the genus *Fusarium*) was used in Laos, Kampuchea, and Afghanistan. Supporting evidence was not uncovered, and this particular species of Fusarium is so widely present in the environment that the tiny amounts found in these surveys were probably naturally occurring.

In 1972, a convention was adopted on “The Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and Their Destruction.” The United States implemented a policy never to use biological weapons, including toxins, under any circumstances whatsoever, except for research efforts directed exclusively to the development of defensive measures, diagnostic tests, vaccines, and the treatment of potential biological weapons attacks. Stockpiles of pathogens and the entire biological arsenal were destroyed between May 1971 and February 1973. One factor in the willingness of the United States to terminate an offensive biological weapons program was thought to be the availability of nuclear weapons for similar purposes. However, biological weapons are of much lower cost, a great deal easier to produce and disseminate secretly, and can give comparable—or even greater—mortality than nuclear agents. For this reason, they have become the weapon of choice for terrorists.

A biological agent was used for covert assassinations during the 1970s. Ricin, the lethal toxin derived from the ubiquitous castor bean, was weaponized by the Secret Service of the Soviet Union and deployed by the Bulgarian Secret Service. Metallic pellets 1.7 mm in diameter were cross-drilled, filled with ricin, and then sealed with wax that would melt at body temperature. The pellets were discharged from spring-powered weapons disguised as umbrellas. In 1978, such weapons were used to assassinate Georgie Markov, a Bulgarian defector living in
London, and in an unsuccessful attack on another Bulgarian defector, Vladimir Kostov. Similar weapons may have been used in at least six other assassinations.

In April 1979, an epidemic of anthrax occurred among people who lived or worked in a narrow zone downwind and within four kilometers of the Soviet military microbiology facility in Sverdlovsk (now Katerinberg) Russia. In addition, livestock as far as 50 km along an extension of the downwind epidemic zone died of anthrax. Although at the time the Soviets denied that this epidemic was caused by the release of agents from their biological weapons program, in 1992, President Boris Yeltsin admitted that the epidemic had been caused by the accidental release of anthrax spores. At least seventy-seven human cases and sixty-six deaths occurred from inhalation of anthrax, the largest documented epidemic of inhalational anthrax known to history.

During the 1970s and 1980s, the Soviet Biopreparat organization worked on biological weapons. It operated at least six research laboratories and five production facilities and employed 55,000 scientists and technicians.

At the time of the Gulf War, in 1991, at least 150,000 U.S. troops received toxoid vaccine against anthrax and 8,000 received a botulinum toxoid vaccine, both FDA approved for investigational use. In addition, 30 million 500 mg oral doses of ciprofloxacin were stockpiled in the Gulf area, enough to provide a one-month course of antibiotic prophylaxis for the 500,000 U.S. troops in the area in the event that anthrax spores were used as a biological weapon.

After the war, Iraqi officials admitted to having had an offensive biological weapons program that included basic research on anthrax, rotavirus, camelpox virus, aflatoxin, botulinum toxin, mycotoxins, and an anticrop agent called wheat cover rust. However, no such weapons were employed during the war, and claims that the Iraqi government has since destroyed these biological agents and nerve gases are being investigated as this is being written.

**A BRIEF HISTORY OF BIOTERRORISM.** The biological threat posed by non-state-sponsored terrorists was demonstrated in late September 1984, when the Rajneeshee cult intentionally contaminated salad bars in Oregon restaurants with a bacterial agent that causes dysentery, *Salmonella typhimurium*. The incident resulted in 751 cases of gastroenteritis and 45 hospitalizations. Despite extensive investigation of this outbreak, the origin of the epidemic as a deliberate biological attack was not confirmed until a cult member admitted to it the following year.

In March 1995, a Japanese cult called Aum Shinrikyo attacked civilians on a Tokyo subway using sarin, a poisonous nerve gas; twelve people were killed and about 5,000 sickened. The cult conducted research on anthrax, botulinum, and...
Q fever; when seized by police, their arsenal allegedly contained an aerosolized form of botulinum toxin and drone aircraft equipped with spray tanks. The cult reportedly launched three other biological attacks in Japan, using anthrax and botulinum toxin that, fortunately, failed due to inadequate microbiological technique, deficient aerosol-generating equipment, or internal sabotage. Botulism spores are ubiquitous, and cult members obtained them from soil collected in northern Japan. In 1992, the cult also sent members to Zaire to obtain Ebola virus for weapons development.³

Bioterrorist attacks, funded or aided by rogue governments, are even more likely than biological warfare conducted by governments. Given the enormous potency of the agents known and the likelihood that such attacks will occur in the future, the history and status of these epidemic diseases is covered in this new edition of Plagues and Poxes.

ADDITIONAL READING


3 GW Christopher et al. Biological warfare: a historical perspective, JAMA 1997; 278: 412 – 417
PART ONE

Infectious Diseases

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CHAPTER 1

BUBONIC PLAGUE
THE PROTOTYPE
OF PANDEMIC DISASTERS

All epidemics of deadly diseases in human history have been called plagues to stress how devastating these outbreaks are. However, whenever actual bubonic plague appears, panic develops, quarantine measures are instituted, and people flee the area. Although primarily a disease of rats and other small mammals, and their fleas, bubonic plague is spread from place to place by human commerce and travel, an excellent route for the migration of the animal vectors of the disease.

Formally known as bubonic plague because of the enlarged, painful, abscessed lymph nodes, or buboes, it produces, bubonic plague was also called the Black Death during a devastating pandemic in the mid-fourteenth century. The name most likely arose because patients with severe disease develop septicemia, a widespread contamination of the blood system. This, in turn, leads to a syndrome formally known as disseminated intravascular coagulation (DIC), in which multiple hemorrhages and patches of gangrene develop in the skin, turning large areas of the body black.

Like most other epidemic infectious diseases, war has played an important role in the spread of plague and, as early as 1347, plague was successfully employed as a form of biological warfare. As recently as World War II, the Japanese used airplanes to spread infected fleas over several Chinese cities, as discussed earlier.

Plague does not readily spread directly from person to person; its transmission depends on small animal hosts, especially rats and their fleas. Hungry fleas feed on infected rats and, when these rats die, the fleas may move on to a human
host. Plague can be spread directly from person to person when it causes pneumonia and, although the same organisms that cause the bubonic form of the disease can cause pneumonia, severe lung disease does not occur frequently enough to rely on airborne pathogens to purposely spread the disease.

The septicemia that occurs in extremely sick plague patients can spread the disease without the help of rats. A flea directly feeding on the contaminated blood of a septicemic patient could pick up sufficient numbers of organisms to infect another person with its bite.

Sporadic cases of plague still occur in the United States, primarily in the Southwest, where small wild mammals and their fleas serve as a reservoir for the disease. When a couple from a rural area near Santa Fe, New Mexico arrived in New York early in 2003 they were unknowingly incubating bubonic plague. Their hospitalization led to alarming news reports. The husband barely survived after developing septicemic disease with DIC and gangrenous changes in his legs that required bilateral below-the-knee amputations. No further cases occurred, however, and public concern (and news media interest) quickly waned. The two cases that startled New Yorkers were no surprise to people of the Southwest, where a few cases occur almost every year.

**Bubonic Plague in History.** Bubonic plague has caused major epidemics since ancient times, with huge mortality rates. Some historians suspect that the Plague of Athens, described by Thucidides during the Peloponnesian War (in the fifth century BCE, with outbreaks occurring in 430, 429, and 427), was actually bubonic plague. Epidemiologists disagree; Thucidides does not describe buboes, and mortality among doctors was the highest of all groups, suggesting human-to-human spread (contagion). Such spread does not occur unless the plague victim has developed pneumonia (pneumonic plague), and this form of infection usually primarily affects family members.

Thucidides reported that when human remains were left lying unburied because of the number of deaths, scavengers avoided them or, if they did taste the flesh died soon afterward. Such spread of bubonic plague could occur if the deceased person had infected fleas still on his body, but it has not been described in other epidemics that were more likely plague. Thucidides also mentioned that second attacks occurred, a very unlikely occurrence in plague, which gives its victims immunity; however, he points out that the second attacks were never fatal, suggesting some degree of increased resistance to the infection.

The disease reportedly spread to Athens from Egypt; Athens was a busy commercial city with a nearby port, whereas its enemy, Sparta, was inland, which might explain why it was spared the epidemic. The extremely high mor-
tality in Athens, which claimed Pericles and his two sons among its victims, crippled its defenses. Sparta eventually won the Peloponnesian War, thus ending the Golden Age of Athens. (One author wrote that more ink has been spilled trying to explain this fateful plague than blood spilt during the war itself.)

In its early years, Rome was attacked by many severe epidemics of uncertain nature. Plague has been suggested as an explanation for many of them, but no descriptions of cases suggest that disease. The Antonine Plague of 164–180 CE, described by Galen, was spread rapidly by the return to Rome of infected soldiers in 166. Marcus Aurelius died of it. Galen’s description is not recognizable to us, and some authors think this epidemic was more likely smallpox than plague; others favor typhus. In 251–266, the Plague of Cyprian, or the Aurelian Plague, in which half the population of Alexandria perished, also seems more likely to have been smallpox than plague. This epidemic also affected the invading Goths, who often gathered into crowds.

Many severe epidemics that occurred in the interval between the Justinian Plague of 542 and the Black Death of the fourteenth century have been labeled bubonic plague, but this identification is questionable. The high mortality rate of some of these epidemics suggests plague, but more persuasive evidence is lacking. The evidence for the Plague of Justinian having been bubonic plague is more convincing. Procopius clearly describes buboes during that epidemic. He also wrote, “There was a pestilence, by which the whole human race came near to be annihilated ... And this disease always took its start from the coast and from there went up into the interior.” He added that, “at Pelusium [on the Mediterranean coast near the present-day entrance to the Suez canal, the plague] then moved to Alexandria and reached Constantinople in 542.” Notably, the historical record of many devastating epidemics affecting the ancient world includes observations of the disease beginning in Egypt, or in Ethiopia and spreading to Egypt, then traveling down the Nile to cities in the delta and to other ports in the Mediterranean. Spread by human movements, and specifically by commerce, is a prominent feature of these and later epidemics.

THE BLACK DEATH. The most famous pandemic of bubonic plague was the Black Death of the mid-fourteenth century. The history of its appearance and spread illustrates how human activities, especially commerce, can cause the dissemination of a devastating disease, even one that primarily affects an animal species. The history of the Black Death and how it was spread is a model for the spread of many major epidemic diseases, since bubonic plague goes where travelers go. And, it is a history that starts with an attempt at biological warfare.
The story of the Black Death begins in 1338–1339, in the vicinity of Lake Issyk-Kul, in southern Russia near the Crimea, where a cemetery contains an unusual number of burials. Inscriptions state that the deaths were due to the plague. The disease spread from there along the main caravan routes from the Far East toward Western Europe and the Middle East. Even before the great pandemic traveled from the Crimea to the Mediterranean and other parts of the world, there is evidence of plague in southern Russia. For example, in 1346, outbreaks of plague accompanied traders along the Silk Road in Astrakhan (at the mouth of the Volga River) and Sarai (farther up the Volga). Records reveal the presence of the disease at caravan stations on the lower Volga River and, in 1347–1348, Ibn Battata, an Arab traveler and scholar returning along the Spice Route from India, reported hearing about the plague when he reached Aleppo in northern Syria. He noted that it had not been seen there before that year.

In this area of Central Asia, marmots were trapped for their fur, which was then sold to various traders who transshipped them along these caravan routes. Hunters and trappers always were happy to find sick or dying animals that they could catch easily, and around this time many untrapped marmots were found dead; trappers skinned these animals and sent the furs to be shipped to buyers in the West. Bales of marmot fur probably contained living fleas that became very hungry without a live animal on which to feed. Reports of illness in trappers were ignored. The furs reached Astrakhan and Sarai first and, when the bales were opened, the hungry fleas jumped out.

The area north of the Crimea, in what is now Russia, the Ukraine, and Rumania, was controlled by Mongols, descendants of the Golden Horde of Genghis Khan. The Russians called these people Tartars. The ports of the Crimea were used by rival Genoese and Venetian traders, who each allied themselves with rival Khans. The Tartar prince Janiberg Khan, who ruled the area known as Western Kipchak, became allied with Venice in 1340. His forces attacked the Genoese and their allies near the ports of the Crimea, forced them behind the walls of the fortified city of Kaffa (now Feodossia in the Ukraine), and besieged them there.

Gabriel De Mussis (1280–1356) left an account of the progress of the plague from the Crimea to his home in Piacenza in 1348. He described how, among the besieging forces of the Khan, “infinite numbers of Tartars and Saracens suddenly fell dead of an inexplicable disease....” They developed buboes in the groin and “putrid fever,” and many died. “Tartars, fatigued by such a plague and pestiferous disease, ... observing themselves dying without hope ... ordered cadavers placed on their hurling machines and thrown into the city of Kaffa, so that by means of these intolerable passengers the defenders died widely. Thus there were projected mountains of dead.... And soon all the air was infected and the water
poisoned, corrupt and putrefied, and such a great odor increased....” Thus we have a record of an early form of intentional biological warfare.

Because fleas leave cadavers to parasitize living hosts, it has been suggested that the corpses catapulted over the walls of Kaffa may not have been carrying competent plague vectors. Rats were not catapulted, but the city must have had its own supply. The cadavers may still have had infected fleas on them (either human or rat fleas, or both) and could thus have spread the disease inside the besieged city, or the infection could have been spread by rats migrating into and out of the city despite the siege. Either way, sickness made Kaffa uninhabitable during the winter of 1347–1348. The survivors fled to their boats and returned to the Mediterranean, spreading plague as they went, probably assisted by the ships’ rats. Plague first appeared at Constantinople, the exit from the Black Sea and the capital of the Byzantine Empire; then it appeared in the Mediterranean ports of Egypt and the Near East.

When the Genoese ships from Kaffa arrived at Constantinople, crewmen were lying dead at the oars. Similar reports emanated from other port cities. Byzantine Emperor John VI [Ioannes VI Contacuzenus (1292?–1383)] wrote a history of his empire from 1320–1356 (he abdicated in 1352), stressing the Black Death “which ... attacked almost all the sea coasts of the world ... and all the islands, ... and spread throughout almost the entire world.” He reported outbreaks on the Greek Islands of the Aegean and along the coast of Anatolia. In all, about sixteen galleys brought plague into Italian ports in 1348. Three made it to Genoa. One carried Venetians to their home port.

Twelve ships from the Crimea reached Messina in Sicily. When the citizens of Messina realized that ships were bringing plague, they drove them out of the ports. One ship went to Marseilles and carried the disease westward from there to Barcelona; the plague then spread throughout Spain and Portugal.

The Genoese realized that the ships from Kaffa brought plague with them and drove them away, but it was too late. The routes of the ships and of the refugees fleeing the affected cities illustrate how people spread the disease. It spread throughout Italy, northward into Switzerland and Bavaria, and east to the Balkans. From Marseilles it spread by ship along the Mediterranean coast and up the Rhone River to Avignon, then the seat of the papacy. Because there were too many bodies to bury, Pope Clement VI (1300–1368) consecrated the river, so that dead bodies might be dumped in it. Plague also spread along the Mediterranean coast from Marseilles to Toulon and either down the Garonne River or by ship to Bordeaux. In August 1348, boats from Bordeaux carrying claret to Great Britain brought the disease there.

There is a record of a wool-carrying ship with full crew that left London bound for Bergen, Norway, in May 1349. Some days after leaving, the ship was...
found drifting off the coast of Norway with the entire crew dead. The disease then appeared in Norway and spread by ship to the rest of Scandinavia and to Germany; it reached Poland in 1351.

Plague reached into the depths of Russia in 1351 or 1352, not by spreading north from the region around the Crimea where the outbreak began, but via Sweden and Poland, because that was the direction in which trade flowed. The disease followed the trade routes and thus came back to Russia by ship via the Mediterranean, the Atlantic, and the Baltic Sea.

Boccaccio (1313–1375), whose father died of plague in 1348, described the disease in some detail. He mentioned buboes appearing in the groin and armpits, and added that, “the mere touching of the clothes or of whatever other thing had been touched or used of the sick appeared of itself to communicate the malady to the toucher.” Air was “tainted by the scent of dead bodies” and people went about “carrying in their hands, some flowers, some odoriferous herbs, and other some divers kind of species, which they set to their noses.” This practice, intended to ward off poisonous miasmas and disgusting, sickening odors, continued as a preventive measure until near the end of the nineteenth century. According to some sources, it is the origin of the practice of sending flowers to funerals.

Plague may have reached the Mesopotamian area independently of the Crimean ships, via caravans from Samarkand, in Turkestan, that traveled the southern route, south of the Caspian Sea, along the silk and spice routes, reaching Baghdad, Damascus, and then the Mediterranean coast. Ships carrying silks, slaves, and furs to Alexandria brought plague as early as 1347. From there it spread to Cairo, Gaza, and Beirut.

Inhabitants of seaports realized the danger of the plague and drove ships away, trying to institute a form of quarantine, but it was too little and too late. By the spring of 1348, Black Death was well established in Italy. Quarantine, derived from the Italian word for forty, lasted forty days, a period long enough for any incipient disease to become manifest and run its course. Quarantine became a standard practice whenever plague or any other feared disease appeared until well into the twentieth century. Facilities were established outside city walls for travelers to spend their period of quarantine before being allowed to enter the city. On land, quarantine was primarily designed to keep people outside the city, but infected rats and their fleas could still escape and infect a city. Keeping ships away from a port was more effective, but usually incomplete. There were few pockets of freedom from the Black Death.

It is estimated that the Black Death killed 25 million people during the years 1348–1350, a loss of one-third of the population of Europe and the Middle East. It has also been estimated that no less than 70 percent of those who contracted
the disease died. In France, towns lost an estimated 50 percent and rural areas 30 percent of their inhabitants. The Black Death was followed by widespread famine because of insufficient labor to raise food. Malnutrition resulted in deaths from a variety of other diseases, probably including smallpox and typhus. “Sweating sickness” hit Britain at this time, with considerable mortality, but its nature is uncertain.

Severe epidemics of plague continued to occur in parts of Europe after the mid-fourteenth century. An outbreak began in Germany in 1356. As late as 1630–1631, 1.5 million people are thought to have died of plague in Italy, largely in Lombardy. In 1709, epidemic plague killed 300,000 people in Prussia. In 1720–1722, a severe epidemic in France affected Marseilles and Toulon, where 50 percent of the entire population died; in other cities, including Avignon, the death rate ranged between 30 and 50 percent. Napoleon’s troops encountered plague when they invaded Egypt and the Middle East in 1801.

Beginning early in the eighteenth century, Europe was protected from the spread of plague from Ottoman areas by a barrier erected by Austria (the Habsburg-Ottoman frontier), primarily running through Hungary. Over 100,000 men manned it, with quarantine and checkpoint stations. This “Sanitary Cordon” limited human traffic and trade, and thus the spread of infectious diseases such as plague. The term cordon sanitaire has been used since for any attempt to wall off and prevent disease (or unwanted political influences).

Plague was endemic in England from fourteenth through the seventeenth centuries, with numerous outbreaks in the seventeenth century, some of them shutting down Shakespeare’s theater. Severe epidemics occurred in London from 1604 to 1610, and 1640 to 1649, with at least four milder epidemics between those two larger ones. Outbreaks of plague in London ended with great fire of 1666.

The gradual ascendance of brown rats over black rats has been suggested as a factor in the subsidence of plague epidemics. Black rats tend to live in inhabited areas of houses, whereas brown rats prefer dark cellars and sewers, in less close contact with people. Because the rat flea can jump only 90 mm (3.5 inches), proximity to people may be important. However, the theory weakens, when we consider that brown rats had replaced black rats in Moscow before a particularly severe epidemic of plague struck during the 1770s, and brown rats did not reach England until 1727, over 60 years after the last “bout of the plague.” Plague is not very particular about which species it affects. Rabbits, ferrets, dogs, and cats were also involved in other outbreaks, with the pattern of disease similar regardless of the original source.

Plague reappeared in England in 1902–1903, and again in 1906–1918, when twenty-four cases were described in a rural area of Suffolk. Six cases recovered.
(four bubonic and two pneumonic). Only four cases were confirmed bacteriologically; the rest were considered likely to be bubonic plague. Investigators found infected rats and rat fleas—*Ceratophyllus fasciatus*, not the usual tropical rat flea—and a couple of infected rabbits, but no black rats were found in Suffolk during the period of that outbreak. To control the outbreak, rat catchers were used, and all 15,332 of the rats caught were dissected. Infected rats were found in twenty-seven areas. A key town in this outbreak was a port on River Orwell, where ocean-going traffic tied up. Investigators concluded that the most likely source of the disease was infected rats coming ashore. In subsequent years, investigators found infected ferrets, rabbits, and rats in rural areas.

Another theory about the history of plague is that a new, less pathogenic form of the causative organism, *Yersinia pestis*, may have evolved, or that resistance appeared in rats and man, decreasing the amount of plague in rats. The appearance and spread of a closely related organism, *Y. pseudotuberculosis*, may have been a factor—human infections with that organism are mild and give rise to cross resistance to *Y. pestis*. This observation is compatible with the theory of a famous parasitologist, Theobald Smith, who postulated that parasites evolve to less virulent forms that become able to co-exist with their hosts. Genetic studies have shown that two genes play an important role in the pathogenic differences between *Y. pseudotuberculosis* and *Y. pestis*. A mutation in one or both of these genes may account for the emergence of less virulent organisms, and these organisms may have replaced *Y. pestis* in rat populations, thus accounting for the subsidence of the disease.

*The Plague of the 1890s.* During the 1890s, a major epidemic of plague developed in Hong Kong and mainland China. It was spread by maritime commerce, as plague usually is, and appeared in major port cities around the world. Ports in Thailand, Indo-China, and Java were affected, as were Manila, Sydney, Capetown, Buenos Aires, Oporto, Honolulu, Glasgow, Mauritius, and Auckland. It returned to China, where a severe epidemic occurred in Yunan. Plague also appeared in Manchuria and Japan. Some cases of plague occurred in Australia and on the Essex-Suffolk border near the coast of England. The progress of this epidemic illustrates the role of human maritime commerce in spreading plague.

**Finding the Cause of Plague.** In 1894, the causal agent of plague was identified simultaneously by two physicians who had participated in the epochal early studies of the germ theory of disease in Europe: Dr. Alexandre Yersin, who
had worked with Louis Pasteur in Paris, and Dr. Shibasaburo Kitasato, who had worked in the other main site of discovery of disease-producing agents, the laboratory of Dr. Robert Koch in Berlin. (By that time, after millennia of speculation about disease-producing miasmas, causative agents of the major infectious diseases of the era were being identified at the rate of one a year.) When the plague broke out, Dr. Yersin had left France to go to Hanoi, capital of French Indo-China, and Dr. Kitasato had returned to his native Japan. During the 1890s, public health authorities in various countries became concerned, even alarmed, by reports of outbreaks of plague in the Far East, knowing how it spread by sea to commercial ports worldwide. The French government set up a commission to study the disease and asked Yersin to head it. Concerned for their own safety, the Japanese took a similar step, sending Kitasato to China. The plague bacilli turned out to be relatively easy to observe, stain, and culture. Almost simultaneously, both investigators identified the organism that became known as Pasteurella pestis. Kitasato apparently was the first to make the observation but published his findings in Japanese and English. Yersin found the same organism and recognized its role, but he published in French in a leading scientific journal of the time that quickly published short reports. Thus, his results appeared first. Yersin’s priority of publication prevailed, and in 1970, the bacillus was renamed Yersinia pestis.

Although the role of the rat flea was not yet known, insect vectors were suspected. In 1894, Yersin found that the flies in his Hong Kong plague laboratory died in great numbers, their bodies “crowded with the specific bacillus.” He injected tissues from the dead flies into guinea pigs, which developed plague and died of it. Later in 1894, Simond identified the tropical rat flea, Xenopsylla cheopis, as the vector in an article in the journal of the Pasteur Institute. This theory had been put forward previously by Ogata, a Japanese investigator, but disregarded. Since then, a wide variety of small mammals, including marmots and rabbits and their fleas, have been shown to be capable of carrying plague bacillus.

Twentieth Century Epidemics of Bubonic Plague in the U.S. A series of plague epidemics occurred in California between 1900 and 1924. In 1899, two cases of plague were known to have occurred on a ship from Hong Kong bound for San Francisco. Although the victims had recovered by the time it arrived, the ship was quarantined on Angel Island and searched. Eleven stowaways were discovered. The next day two of them were missing; later, their bodies were found in the Bay. The plague bacillus, identified during the outbreak in the Far East a few years earlier, was relatively easy to culture, and it was recovered from the two
bodies. Although officials were worried that the disease would spread in California, no further cases appeared at that time. However, nine months later, on March 6, 1900, plague bacilli were found in an autopsy of a Chinese man, and California officials felt that some action was needed to prevent an epidemic of the disease.

At that time, despite earlier observations establishing the relationship of the disease to rats and their fleas, the most likely means of spread was thought to be contaminated food or water, or direct acquisition of the organism through defects in the skin. During the previous decade, such mechanisms of infection were shown to occur in other major diseases, including typhoid fever, dysentery, cholera, diphtheria, and wound infections. Disinfection campaigns were instituted, including pouring carbolic acid into sewers, which actually hastened the spread of the disease by flushing out infected rats and their fleas. Strong anti-Chinese sentiment led to efforts to quarantine Chinatown. The Chinese objected, as did the business community, believing it was bad for business for people to think there was plague in the city. The quarantine of Chinatown was lifted, but health officials conducted house-to-house inspections of the area. Despite resistance to the inspectors, two more plague victims were discovered.

When the Board of Health finally admitted that plague was present in the city, the governor refused to believe it and rejected suggestions that he do something about it. However, the denials of the existence of plague by some officials were not convincing, and more and more states began to avoid trading with California. The Surgeon General of the U.S. Public Health Service finally got permission from President McKinley to enforce standard anti-plague regulations. Commissions and boards were formed, disbanded, and reformed, continually fighting with the governor, who persisted in denying the existence of the disease, still fearing what he felt would be needless alarm. A prominent epidemiologist from the Rockefeller Institute in New York, Simon Flexner (1863–1946) headed one commission responsible for a massive cleanup campaign of the houses and shops in Chinatown. In 1903, a new governor took office and vowed to help the boards of health in every way. Despite little having been done, new cases stopped appearing, and the last victim of this outbreak died on February 29, 1904. The known cases totaled about 120, of whom all but eight died; the high mortality rate probably meant that most nonfatal cases were not discovered.

In 1906, plague reappeared in San Francisco after the devastating earthquake and fire. Rats, as well as people, were made homeless by the destruction and both took up residence in refugee camps. This time, officials launched a new kind of campaign that was based on the scientific knowledge that had been accumulated about the plague: They offered a bounty on rats. A similar rat-
catching campaign had been used successfully a few years earlier to fight an outbreak of plague in New Orleans, and it helped in San Francisco. Although this second epidemic was larger than the first, it was brought to halt in 1909 and was the last urban outbreak of plague in the United States. Scattered cases continued to occur in rural areas, however, with marmots apparently the main reservoir of the disease.

**Rats and Plague.** Despite the success of rat-catching campaigns, it is worth noting that decreasing the rat population could have increased the spread of plague, at least temporarily. Eliminating rats minimizes the reservoir of infection, but leaves hungry fleas looking for a new source for their blood meals. Humans are a satisfactory alternate source of nutrition. Therefore, the infected fleas are more likely to bite and infect humans as a result of the depletion of the rat population, at least until the population of infected fleas dies off. In many medieval epidemics, the records show that the finding of large numbers of dead rats in a community was shortly followed by outbreak of human cases of plague. (The New Mexican couple who recently became ill with plague in New York City had found a dead rat on their property just before leaving for New York, but they were not aware that they had been bitten by its fleas.)

The fact that rats were associated with the disease was noted long before the role of their fleas was elucidated. In Manson’s *Tropical Diseases* (1898), he pointed out, “Many observers have remarked the great mortality among rats and other animals which sometimes precedes and accompanies outbreaks of plague in man.” He quotes a report that, in a Himalayan town where plague was epidemic in 1864, “the rats quitted the various villages in anticipation of the advent of the disease; the people, taught by experience, on seeing this exodus recognized it as a warning.” During an epidemic in Canton in the 1890s, “from districts of the city where the plague had been raging for some time the rats entirely disappeared, whilst they kept on dying in other quarters to which the disease afterward spread.”

Recent studies have elucidated the complexities of the relationship between rats and people and help us to understand the history of this disease. When fleas feed on an infected rat, the fleas become infected. When the infected rat dies, its fleas leave and search for a new host. The fleas usually find other rats, infect them, and spread plague through the rodent community. The spread in rats is slow: When the density of rats is low, as it is when rats die in large numbers, fleas are forced to find alternative hosts such as humans, and a human epidemic begins. Rarely, person-to-person spread of pneumonic plague occurs, usually after a human epidemic has already begun. Studies of the disease in recent years
suggest that if the infection rate in a given rat population is low (e.g., 25–50 percent), human infection is rare or unlikely. If over 80 percent of a given rat population is infected, human infection occurs. Thus a rat epizootic can smolder for long periods without the appearance of human cases.

Once the disease appears in humans, control of the rat population can actually be deleterious. If the rat population is kept at a permanently low level, then the risk of a large rodent outbreak is low, and therefore the risk of human cases is reduced. However, if a cull is brought into effect after the first human cases have been reported, it can create a far larger pool of infection for humans, since a cull releases many infected fleas that seek human hosts. Any area with a rat population density of about 3,000 per sq km exceeds the threshold and is at risk for appearance of the disease. Areas with rodent reservoirs of plague include the United States, southern Africa, southern Asia (including Vietnam, where American servicemen encountered the disease), and South America.

Cases of bubonic plague continue to be reported from many parts of the world, sometimes with long intervals between outbreaks in a given area. In the 1990s, bubonic plague was observed in Madagascar, Mozambique, and Surat. These modern outbreaks suggest that the disease can exist in animals as an epizootic that later starts to infect people, or that it can be reintroduced from other areas, probably by commercial trade.

Vaccination to Prevent Plague. Infection can be prevented in individuals through vaccination, but vaccination cannot eliminate plague. Because of its rodent reservoir, the infection can reappear whenever unvaccinated people appear in a given vaccinated area. One hundred percent of a population must be vaccinated to prevent any cases of the disease. The vaccination of American troops in Vietnam prevented the infection in the troops, but it did occur in the native population.

Summary. With its tragically high mortality and seemingly inexorable spread, bubonic plague remains the prototype of severe outbreaks of disease. Although the plague is a primarily a zoonosis—a disease of rats and other small animals, especially rodents and their fleas, its effects on humans are legendary. It has been spread by humans through the inadvertent transport of rats and their fleas. It has been purposely induced as a form of biowarfare since the first appearance of the Black Death in the Crimea, through World War II, and it may be used again in the future.
Although thought of as an ancient disease, severe human outbreaks still occur in areas where animal reservoirs exist, and people traveling into those areas can be infected. A vaccine exists, but because it is not possible to immunize the entire population in affected areas, the disease will undoubtedly continue to appear in humans because of its persisting animal reservoirs.

**ADDITIONAL READING**


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