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Susan Scott and Christopher J. Duncan

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# 1

## Introduction

We first became interested in plagues when studying the demography of northwest England (Duncan *et al.*, 1992; Scott & Duncan, 1998), where an epidemic in the town of Penrith in 1597–98 killed some 40% of the population and initiated endogenous oscillations in the annual numbers of births and deaths. In this way, its effects persisted for 150 years. The outbreak spread rapidly, travelling 20 to 30 miles in 2 or 3 days and it was obvious that it was a biological impossibility that this was an outbreak of bubonic plague. We initially thought that this must have been an isolated outbreak of an unknown and unique infectious disease (Scott *et al.*, 1996) but further study convinced us that this regional epidemic had many points in common with other outbreaks in England that were believed to be bubonic plague.

In this book, we have attempted an objective (though not exhaustive) study of the plagues that have ravaged humankind for hundreds of years, giving the biological, demographic and epidemiological viewpoints of the available historical evidence. Obviously, the difficulties faced are vastly greater than those of a modern epidemiologist investigating a new outbreak of an unknown disease today. He or she has an array of techniques available from microbiology and molecular biology, can take biopsy and autopsy samples with the back-up of a pathology laboratory, can make on-site investigations of the ecology and epidemiology of the disease, and can discover the clinical features and mode of transmission of the infection. Even so, some features of present-day outbreaks of Ebola, such as the elucidation of the reservoir host, are not yet established with certainty. Where the disease has a complex biology, as in bubonic plague, it took years of painstaking study before all the details were elucidated.

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### 1.1 What is a plague?

The Bible uses the word ‘plague’ to describe an affliction that was regarded as a sign of divine displeasure or as an affliction of humankind such as the plague of locusts. Nowadays, it is a term used to describe a deadly epidemic or pestilence and *The Wordsworth Encyclopedia of Plague and Pestilence* (Kohn, 1995) lists a seemingly endless catalogue of historical epidemics from all over the world, including smallpox, cholera, typhus and malaria. They were all infectious and potentially lethal, caused high mortality and were serious historic events. The influenza pandemic of 1917–19, with a final death toll worldwide estimated at more than 20 million, is a good example. The incubation period was often less than 2 days so that its worldwide spread was dependent on 20th century means of rapid travel that could move people in bulk, namely steamtrains and steamships of which the troop ships of the First World War are a good example.

However, the basic etiology of these diseases is now usually well understood and, in spite of the terrible death toll, the percentage mortality of the affected populations was not relatively high (Langmuir *et al.*, 1985). In this book, we are mainly, but not exclusively, concerned with the Black Death, arguably the most awful epidemic ever to have struck, which raged in Europe from 1347 to 1350, and the unremitting succession of plagues that followed it for 300 years. These reached their peak in continental Europe during 1625–31 and in England in 1665–66, but they then disappeared completely after about 1670. When these plagues struck a naive population, where we have reasonably accurate data available in Italy and England, mortality could reach about 50%; we do not know what was the causative agent in these terrible epidemics.

### 1.2 Four ages of plague

From whence did the Black Death come? The probable answer to this question is that it originated in the Levant, but Europe had suffered from a series of mysterious plagues for many years before 1347 and it is possible to identify tentatively and arbitrarily four historic ages of plague.

#### 1.2.1 Plague at Athens, 430–427 BC

The epidemic that struck Athens in 430 BC remains one of the great medical mysteries of antiquity and has been discussed by a number of scholars (Morens & Littman, 1972, 1994; Poole & Holladay, 1979;

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Longrigg, 1980; Langmuir *et al.*, 1985; Kohn, 1995; Olson *et al.*, 1996; Retief & Cilliers, 1998), but the first vivid description was given by Thucydides, himself a victim who survived the outbreak (see Page, 1953). It is sometimes termed the Thucydides syndrome because of his evocative narrative.

People were stricken suddenly with severe headaches, inflamed eyes, and bleeding in their mouths and throats. The next symptoms were coughing, sneezing, and chest pains followed by stomach cramps, intensive vomiting and diarrhoea, and unquenchable thirst. The skin was flushed, livid and broken with small blisters and open sores. The patients burned with fever so extreme that they could not tolerate being covered, choosing rather to go naked. Their desire was to cast themselves into cold water, and many of those who were unsupervised did throw themselves into public cisterns, consumed as they were by unceasing thirst. Many became delirious and death usually came on the seventh or eighth day of the illness, although those who survived the first phase often died from the weakness brought on by constant diarrhoea. Many who recovered had lost their eyesight, their memory, or the use of their extremities.

This plague is believed to have originated in Ethiopia and travelled through Egypt and the eastern Mediterranean before reaching Athens. The first cases appeared in Piraeus, the Athenian port and base for many travellers and merchants who probably contracted the disease in their journeys abroad. It spread rapidly to the upper city and whole households were left empty. Mortality among doctors, as among other attendants of the sick, was especially high. Fearful of an attack by the Spartans, the Athenian leader Pericles ordered the inhabitants of the surrounding countryside to move inside the city, where they could be protected by the army and the fortified walls. Many country dwellers, coming to an already overpopulated city, had no place to live except in poorly ventilated shacks and tents. This mass of people, crowded together in the hot summer, created a situation that was ideal for the rapid transmission of the disease. Though there were many dead bodies lying unburied, there was said to be a complete disappearance of birds of prey and dogs. Apparently it was rare to catch the disease twice, or if someone did, the second attack was never fatal. A peak case rate was reached during the Spartan siege, which lasted 40 days, after which the crowded refugees dispersed. The disease remained at a low level through 429 BC (when Pericles died of it) and returned in force in the summer of 428 BC at the time of another Spartan siege. The disease was quiescent, or even absent, from the winter of 428 BC until the summer of 427 BC, but broke out again in the autumn or early winter of

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427 BC. This epidemic lasted no less than a year, but there is no further mention of the disease. The total number of Athenians who died is not recorded but, over the 3-year period, of 13 000 enrolled hoplites (soldiers), 4400 died – a mortality rate of 33%. Hagnon took the fleet and sailed to Potidaea carrying the plague there also and this made dreadful havoc among the Athenian troops. Even those who had been there previously and had been in good health caught the infection and so 1050 men out of 4000 were lost in about 40 days.

There have been several identifications of the causative agent of the plague at Athens, including smallpox (Littman & Littman, 1969), scarlet fever, measles and typhus (Shrewsbury, 1950; Page, 1953) but these are all now discredited. Langmuir *et al.* (1985) concluded that the clinical descriptions clearly indicated the involvement of specific organ systems and that there was an obvious inflammatory condition of the eyes and respiratory tract; this acute respiratory infection was severe and probably necrotising; the initiation with vomiting followed by empty retching and later by ‘watery diarrhoea’ strongly suggested a gastroenteropathy mediated by the central nervous system rather than a local inflammatory process. Langmuir *et al.* (1985) believed that the skin lesions were suggestive of bullous impetigo. They did not suggest that the Thucydides syndrome was identical with the modern toxic shock syndrome but believed that the same basic pathogenic mechanisms were involved, in that there was infection in predisposed hosts by a possibly non-invasive *Staphylococcus* sp. that was capable of producing an exotoxin similar to toxin-1 of the toxic shock syndrome (Rasheed *et al.*, 1985). This toxin may have differed from toxin-1 in that it produced predominantly enterotoxic effects and less profound circulatory collapse, and had only moderate or no erythrogenic potential.

Morens & Littman (1992, 1994) have approached the plague at Athens from a different viewpoint and have arrived at a conclusion that is strongly opposed to that of Langmuir *et al.* (1985). We describe their hypothesis briefly because they use mathematical modelling techniques that we shall also employ to elucidate the epidemiological parameters of later plagues. They have reduced the reliance on clinical symptoms in favour of the epidemiology of the disease because pre-modern descriptions, which lack detailed information on serology and accurate accounts of rashes and other clinical features, always retain a high degree of uncertainty. Use of the Reed and Frost mathematical model (section 2.5) led them to conclude that, under any conditions of crowding that probably prevailed in Athens in 430 BC, an epidemic of influenza would have died out rapidly in a few

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weeks. They excluded all common diseases and most respiratory diseases and concluded that the cause of the Athenian epidemic could be limited to either a reservoir disease (zoonotic or vector-borne) or one of the few respiratory diseases that are associated with an unusual means of persistence: either environmental/fomite persistence, or adaptation to indolent transmission among dispersed rural populations. They suggested that the diseases in the first category include typhus, arboviral diseases and bubonic plague and, in the second category, smallpox. Retief & Cilliers (1998) also reviewed the epidemiological evidence and agreed that the only possibilities are epidemic typhus, bubonic plague, arboviral disease and smallpox.

Other workers have suggested that the plague at Athens was an early manifestation of Ebola (sections 1.3 and 13.15). Olson *et al.* (1996) stated that a modern case definition of Ebola virus infection records sudden onset, fever, headache, pharyngitis followed by cough, vomiting, diarrhoea, maculopapular rash, and haemorrhagic diathesis, with a case fatality rate of 50% to 90%, death typically occurring in the second week of the disease. In a review of the 1995 Ebola outbreak in Zaire, the Centre for Disease Control and Prevention reported that the most frequent initial symptoms were fever (94%), diarrhoea (80%), and severe weakness (74%), with dysphagia and clinical signs of bleeding also frequently present. Symptomatic hiccups were also reported in 15% of patients. Olson *et al.* (1996) concluded that the profile of the plague at Athens was remarkably similar to that of the recent outbreaks of Ebola in Sudan and Zaire. Certainly, as we shall see, this devastating epidemic had features in common with later plagues in Europe (section 1.3).

### 1.2.2 The plague of Justinian

Procopius, the Greek historian, believed that this epidemic (like the plague of Athens) originated near Ethiopia. The pandemic began in Egypt in AD 541 and it then moved through Asia Minor, Africa and Europe, arriving in Constantinople, the capital of the Byzantine Empire, in the late spring and summer of AD 542. Merchant ships and troops then carried it through the known western world and it flared up repeatedly over the next 50 years, causing an enormous mortality, perhaps aided by wars, famines, floods and earthquakes. The plague raged in Constantinople for 4 months in AD 542, with the death toll rising from 5000 to 10000 per day and even higher during the three most virulent months. The Byzantine emperor Justinian fell ill and recovered, but 300000 people were said to have died in Constantinople alone in the first year, although Russell (1968) and Twigg

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(1984) believed these figures to be greatly exaggerated. The officials were completely overwhelmed by the task of disposing of the dead bodies (Kohn, 1995).

Procopius recorded that people (understandably) were terrified, knowing that they could be struck without warning. The first symptoms were a mild fever which did not seem to be alarming, but bubonic swellings followed within the next few days. Once the swellings appeared, most sufferers either went into a deep coma or became violently delirious, sometimes paranoid and suicidal. It was difficult to feed and care for them properly, although mere contact with the sick did not seem to increase the chances of contracting the disease. Most victims died within a few days, but recovery seemed certain for those whose buboes filled with pus. Black blisters were a sure sign of immediate death; otherwise, doctors often could not predict the course of the disease or the success of various treatments. Autopsies revealed unusual carbuncles inside the swellings and these clinical features led to the conclusion that the Justinian plague was a pandemic of bubonic plague (Kohn, 1995). Shrewsbury (1970) agreed, but suggested that other serious diseases, such as smallpox, diphtheria, cholera and epidemic influenza were also present. It is not possible to be certain from the evidence available, but the rapid spread over great distances, the heavy mortality and other biological features of the pandemic suggest that bubonic plague was not the major component, but that some other infectious disease, spread person-to-person, was responsible.

### ***1.2.3 The Great Age of plagues: the Black Death and thereafter***

The Black Death erupted in Sicily in 1347 and the pandemic spread through Europe during the next 3 years, reaching Norway (where two-thirds of the population died; Carmichael, 1997) and Sweden and crossing to England (and thence to mainland Scotland, the Hebrides, Orkney and the Shetland Islands) and to Ireland (Biraben, 1975) and, possibly, to Iceland and Greenland (Kohn, 1995). Its arrival presaged a continuous succession of epidemics in Europe for the next 300 years before it disappeared completely around 1670. The enormous mortality of the Black Death had a major impact on the demography of Europe, and the population of England did not fully recover for 150 years. Events during 1347–50 are described in Chapter 4 and the demographic consequences of a major mortality crisis on a population are discussed further in section 13.17. Were the multiplicity of plagues throughout Europe from 1350 to 1670 all the result of the same causative agent as that responsible for the Black Death,

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albeit with some minor mutations during that time? It is not possible to answer this question with certainty, but we believe that the most probable explanation of the etiological and epidemiological details is that it was so.

During the second half of the 14th century, the epidemics in England and continental Europe were less virulent but the infection gradually regained its ferocity, reaching its peak around 1630 in France and 1665–66 in England.

### 1.2.4 *Bubonic plague in the 20th century*

The details of the complex biology of bubonic plague were finally unravelled around 1900: it is a bacterial disease of rodents depending on the rat flea for its spread and on a reservoir of resistant rodent species for the maintenance of the disease. Only occasionally does the infection spread to humans when one is bitten by a rat flea but, in the days before antibiotics and modern medicine, this was usually fatal and serious epidemics could be established.

Unfortunately, historians of Europe in the 20th century, almost universally, have concluded that all plagues in the Middle Ages were bubonic, in spite of the fact that the people at that time saw clearly that it spread person-to-person and, even in the 14th century, had already instituted specific quarantine periods. A major objective of this book is to examine the historical facts dispassionately, eschewing any preconceived notions about the behaviour of rats and fleas and to determine the nature of the epidemics of the Middle Ages in Europe. Normally, we refer to these as plagues, but where there is possible confusion with bubonic plague, we designate the former as haemorrhagic plague. To distinguish between haemorrhagic and bubonic plagues we begin in Chapter 3 with a detailed account of the complex biology, etiology and epidemiology of bubonic plague and explain how, in consequence, the spread and maintenance of the disease in rodents and humans is strictly constrained.

Although we have described bubonic plague from 1900 to the present day as the fourth age of plague, the disease has been identified (presumably correctly) and recorded in detail from China since AD 37 (Wu, 1926; Wu *et al.*, 1936) and it is likely that it has been present in India and in a gigantic swathe across central Asia for hundreds of years. It probably extended westwards to the Levant and the north African coast and may have erupted sporadically in the warm Mediterranean coastal regions in the 6th century AD (Twigg, 1984) and it was certainly present there in the Middle Ages and continued with occasional epidemics in the 18th century (see Chapter 12).

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Where climatic conditions were suitable and reservoir rodent species were present locally, endemic bubonic plague could be established. Where only the climate was suitable, as in the coasts of France, Spain and Italy, epidemics of bubonic plague could potentially break out, having been brought into the ports by sea, but these terminated once the local rats had died. During the third age of plagues, 1347–1670, therefore, Europe probably experienced minor outbreaks of bubonic plague along the Mediterranean coasts of Italy, Spain and France in addition to the major epidemics of haemorrhagic plague.

Finally, endemic bubonic plague erupted in a series of epidemics in India at the very end of the 19th century and spread across southeast Asia, and so began the fourth age of plagues. As we show in Chapter 3, the arrival of steamships then allowed rats and their fleas carrying bubonic plague to be rapidly transported from the grain stores on the docks of China to sub-tropical regions wherever suitable indigenous rodents occurred.

### 1.3 The dangers of emerging plagues

From whence did the plague of Athens, the Justinian plague and the Black Death come? How did they emerge with such sudden ferocity? We have seen in the 20th century the emergence of a number of new deadly diseases that are largely resistant to medical science: scientists have identified more than 28 new disease-causing microbes in 1973 (Olshansky *et al.*, 1997). Indeed, it has been suggested that the history of our time will be marked by recurrent eruptions of newly discovered diseases (e.g. Hantavirus in the American West), epidemics of diseases migrating to new areas (e.g. cholera in Latin America), diseases that become important through human technologies (water cooling towers provided an opportunity for legionnaires' disease) and diseases that spring from insects and animals because of human-engendered disruptions in local habitats. Two of the terrors that haunt are the fears that new, unstoppable infectious diseases will emerge and that antibiotics will be rendered powerless. To some extent, these processes have been occurring throughout history. What is new, however, is the increased potential that at least some of these diseases will generate large-scale pandemics, such as a resurgence of the 1918 influenza pandemic; the global epidemic of human immunodeficiency virus (HIV) is the most powerful and recent example. Yet the acquired immune deficiency syndrome (AIDS) does not stand alone; it may well be just the first of the modern, large-scale epidemics of infectious diseases. The world has rapidly become much more vulnerable to the eruption and, most critically, to the



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widespread and even global spread of both new and old infectious diseases. This new and heightened vulnerability is not mysterious; the dramatic increases in the worldwide movement of people, goods, and ideas is the driving force behind the globalisation of disease because not only do people travel increasingly, they also travel much more rapidly, and go to many more places than ever before. The lesson is clear: a health problem in any part of the world can rapidly become a widespread health threat (Mann, 1995).

Most emergent viruses are zoonotic, with natural animal reservoirs a more usual source of new viruses than is the spontaneous evolution of a new entity. Human behaviour increases the probability of the transfer of viruses from their endogenous animal hosts to humans. The original source of the AIDS pandemic has been traced back to a subspecies of chimpanzee that has been used for food in West Central Africa, the hunters being exposed to infected blood during the killing and dressing. The virus has probably been living harmlessly in chimpanzees for hundreds of years and may have been transferred to humans throughout history, but the socio-economic changes in Africa provided the particular circumstances leading to the spread of HIV and AIDS.

An outbreak of encephalitis in Malaysia in 1999, which killed 76 people may have been caused by a more deadly version of the Hendra virus, which was first identified in Australia 5 years previously. The difference is that, whereas the virus in the earlier outbreak did not spread easily between animals, the Malaysian version apparently did: all the Malaysian victims were connected with pig rearing. Health officials in Asia now fear that a dangerous new human pathogen has emerged that has spread from fruit bats via pigs and consequently more than 300 000 pigs were slaughtered in southern Malaysia as an initial precautionary measure. The spinal fluid taken from five patients contained a paramyovirus (named 'Nipah') and analysis of the amino acid and RNA sequences confirmed that it is related to the deadly Hendra virus. Why has the virus suddenly begun to kill pigs and people when the bats may have harboured it safely for centuries?

The Ebola virus, a member of the Filoviridae, burst from obscurity with outbreaks of severe haemorrhagic fever. It was first associated with an outbreak of 318 cases and a case fatality rate of 90% in Zaire and caused 150 deaths among 250 cases in Sudan. Smaller outbreaks continue to appear periodically, particularly in East, Central and southern Africa. In 1989, a haemorrhagic disease was recognised among cynomolgus macaques imported into the USA from the Philippines; strains of Ebola virus were isolated and serologic studies indicated that the virus is a

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prevalent cause of infection among macaques. Epidemics have resulted from person-to-person transmission, nosocomial spread and laboratory infections but it must be emphasised that the mode of primary infection and the natural ecology of these viruses are unknown. The possible role of the Ebola virus as the causative agent in haemorrhagic plague is discussed in section 13.15.

A mysterious epidemic of Marburg virus (related to Ebola virus) broke out in a remote area of the Democratic Republic of Congo, Central Africa, in December 1998. At least 72 miners suffered from fever, pain, rash and bleeding and 52 had died by May 1999. The victims had spent time in caves and bats are considered to be the leading contender for an animal reservoir of the virus; monkeys die too quickly from the virus for them to be considered for this role.

A virulent influenza pandemic struck from 1917 to 1919, with a final worldwide estimated death toll of more than 20 million lives (Kohn, 1995). It has been termed Spanish influenza (dryly known as ‘the Spanish Lady’) because this was believed to be the first serious point of attack, with 8 million Spaniards falling ill in 1917–18. It then struck at military bases throughout Europe and death rates mounted ominously in 1918. At the same time (beginning in March 1918) acute respiratory infections were reported at military installations in the USA and by October some US army camps were reporting a death every hour; Britain was then counting 2000 deaths per week, with London at about 300 deaths per week. Country after country felt the ravages of the disease. The weak, the young and the old usually suffer worst in epidemics, but the age group 21 to 29 years proved to be the most vulnerable in this outbreak of Spanish influenza. While manifesting the ordinary symptoms of influenza (headache, severe cold, fever, chills, aching bones and muscles), the Spanish form also generated complications such as severe pneumonia (with purplish lips and ears and a pallid face), purulent bronchitis, mastoid abscess and heart problems. The frightening disease subsided after the end of the First World War and later vanished completely but, by then, it had attacked every country in the world, particularly China, India, Persia, South Africa, Britain, France, Spain, Germany, Mexico, Canada, the USA and Australia.

A radical genetic mutation, called antigenic shift, accounts for the appearance of new viral subtypes capable of engendering influenza pandemics. New viral types originate in ducks, chickens, pigs and other animals, in which reservoirs of influenza viruses change genetically and are then passed into the environment, and to human beings. The strain that caused the 1918 epidemic, H1N1, was found inside pigs and there is always