2 Plagues and History

From the Black Death to Alzheimer's Disease

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A broad chronological overview of the plagues of the past and the present provides a basis for understanding how they have arisen, how they have affected societies over time, and how humanity has responded to the challenge of each new wave of deadly disease. Many puzzles still surround the plagues of antiquity, although recent techniques such as DNA analysis of skeletal remains are beginning to provide clues as to their causes; it has, for example, now been confirmed that the plague bacillus, *Yersinia pestis*, was responsible for the 'Black Death' of the mid-14th century. Many other infectious diseases or 'plagues', such as smallpox, typhus, cholera and influenza, have afflicted human populations over the centuries. As the causes of these diseases have become increasingly well understood, humanity has devised ever more effective means for their control. With the extension of human lifespan that has resulted from such progress, other medical conditions have become increasingly common, notably the neurological disorder, Alzheimer's disease. Although not infectious, this disease has become so prevalent in recent years that it is has been called a '21st century plague'. The intrinsic origins of this highly debilitating condition are now being explored intensively by scientists from many different disciplines leading, as with the plagues of the past, to new ideas as to potential strategies for its prevention and treatment.

Most people associate the word 'plague' with the 'Black Death' of the mid-fourteenth century, which in the space of a few years killed between a third and a half of the population of Europe, Asia and the Middle East – with frightening consequences. However, throughout history there have been many other widespread and devastating outbreaks of disease that have been labelled as plagues. The word 'plague' comes from the Latin *plaga*, meaning a stroke or a wound; the Oxford English Dictionary also defines it as an affliction, calamity or a general name for any malignant diseases 'with which men or beasts are stricken'. The word is, moreover, now becoming associated with some disorders that are not infectious, but

https://doi.org/10.1017/9781108147910.004 Published online by Cambridge University Press

which have increased in prevalence so rapidly that they have been likened to the historic plagues.

One such condition in humans is dementia, which has been called the 'twenty-first century plague', and indeed it is perhaps as greatly feared today as the classic plagues were in the past. At the first ever G8 Dementia Summit held in London in December 2013, the British Prime Minister, David Cameron, spoke about the global challenge of this condition, and described it in the following words:

> *It doesn't matter whether you're in London or Los Angeles, in rural India or urban Japan – this disease steals lives; it wrecks families; it breaks hearts and that is why all of us here are so utterly determined to beat it.*[1]

The most common form of adult dementia is Alzheimer's disease, named after Alois Alzheimer (1864–1915), who first described its symptoms and pathological character in a lecture in 1906. Alzheimer's disease is now one of the most distressing and debilitating conditions of the modern age. It is estimated that nearly one million Britons, and some 40 million people worldwide, suffer from this progressive neurodegenerative disease. Its symptoms, which include memory loss and disorientation, are familiar to everyone in a country such as ours, and it is rare for a day to pass without an article on the topic of dementia appearing prominently in the news. Moreover, there are few of us who do not know of a family member or friend with experience of this disease – either as a patient or as a carer – and who has not been deeply affected by its relentless nature and the despair that it engenders. And while its human costs are almost overwhelming, its financial burden – largely the costs of care and lost working days – is huge, estimated to be approaching £30 billion per annum in the United Kingdom alone.

In this chapter we give a broad chronological overview of the plagues of the past to try to understand how they have arisen, how they have affected societies over time, and how humanity has responded to the challenges of each new wave of deadly disease. We conclude that while each of these plagues is the result of diverse factors and pathogens, what is most striking is that they all reflect rapid changes in human activities and lifestyles that have occurred over the ages. In modern times, such

FIGURE 2.1 **Boils and Pustules**
This miniature, from the Swiss manuscript of the Toggenburg Bible, *c.* 1411, has traditionally been thought to depict a couple suffering from the 'buboes' of the deadly Black Death that swept through Europe in the mid-fourteenth century. Recently, scholars have questioned this, noting that this image of the Book of Exodus' sixth plague is not an accurate clinical depiction of bubonic plague and is more likely to represent a smallpox-like disease. [Source: Corbis/Betemann: 42-24063922]

changes are more rapid than ever. Indeed, new outbreaks of infectious diseases are ever threatening, but advances in scientific and medical knowledge have so far managed to avert catastrophes on the scale of those of the past. But it is the very success of modern science and medicine – in enabling large proportions of the population of the world to live to unprecedented ages – that has generated a huge increase in the incidence of afflictions such as dementia. We touch on some of the historical examples of major outbreaks of disease before turning to discuss how our increasing understanding of the origins of Alzheimer's disease has the potential to enable us to defeat this latest challenge to the health and welfare of the human race.

Plagues of the Ancient World

Many people will be familiar with the Biblical plagues of Egypt, about which there has been much speculation and many emotive artistic representations (See Figure 2.1). [2]

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FIGURE 2.2 **The Plague of the Philistines at Ashdod**
This oil painting by the Flemish artist, Pieter van Halen (1612–87) of the 'Plague of the Philistines at Ashdod' is one of several graphic artistic representations of the plagues of antiquity painted during the Renaissance.
[Source: Wellcome Images: L0011603]

While there is little direct evidence for the ten afflictions that are described in the Book of Exodus, the explanation offered in the written account is that they were sent by God, although there have been more recent attempts to rationalise such afflictions as 'rivers turning to blood' in scientific terms. Another Biblical plague was the Plague of the Philistines (See Figure 2.2), where again the explanation given was the wrath of God:

> *. . . after they had carried [the ark] about, the hand of the Lord was against the city with a very great destruction: and he smote the men of the city, both small and great, and they had emerods in their secret parts.*[3]

As 'emerods' are better known as 'haemorrhoids' one can understand the distress that this particular outbreak of sickness must have caused. Other catastrophes of the distant past include the Plague of Athens

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(*c.* 430–426 BC), the Antonine Plague (*c.* AD 165–180) and the Plague of Justinian (AD 541–543) that struck civilisations of the Greek and Roman world, carrying with them a huge toll of death and destruction and even changing the course of history. Procopius of Caesarea (*c.* AD 500–565) vividly described the horrors of the Plague of Justinian 'by which the whole human race came near to being annihilated' and highlighted its puzzling nature as it devastated Constantinople (now Istanbul) and other parts of the Byzantine Empire:

> *For much as men differ with regard to places in which they live, or in the law of their daily life, or in natural bent, or in active pursuits, or in whatever else man differs from man, in the case of this disease alone the difference availed naught.*[4]

Why, how and where these plagues emerged and which specific diseases were involved still remain a mystery but, assuming that they were infectious diseases, their spread can be attributed primarily to the effects of overcrowding in cities, particularly in times of war, as human populations began to increase and people migrated and took refuge from the enemy.

While scholars continue to debate the impact and cause of these plagues, recent DNA evidence makes it likely that the Plague of Justinian was the first recorded outbreak of 'bubonic plague' – whose name reflects the characteristic 'buboes' (from the Greek, *boubón*, 'groin' or 'swelling in the groin') that appeared on the bodies of its victims. The plague bacillus, *Yersinia pestis*, enters at the site of the bite of an infected flea and travels through the lymphatic system to the nearest lymph node where it replicates itself. The lymph node then becomes inflamed, tense and painful, and is called a 'bubo'. Besides bubonic plague, there are two other forms of the disease – pneumonic plague – a highly virulent form (when *Y. pestis* travels to the lungs) and septicaemic plague – the most deadly of all (when the infection spreads directly through the bloodstream without forming a 'bubo').

Plagues of the Medieval World

The 'Black Death' that struck Europe in the mid-fourteenth century (*c.* 1346–53), has etched itself into the memory of the Western world as the classic plague. Possibly triggered by environmental or climatic

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disturbances which enabled the disease to jump from its natural reservoir in wild rodents, such as gerbils or marmots, to black rats (the species known as *Rattus rattus*) which live in close proximity with humans, the Black Death spread from Asia westwards along increasingly widely used maritime and land trade routes, and again especially affected overcrowded and insanitary ports and inland settlements. The Black Death resulted in the deaths of between 25 and 50 million people in Europe, alone. It was the greatest demographic crisis of the medieval period and, in terms of the proportion of the population that was killed, the single most calamitous epidemiological event in all of human history.

The term 'Black Death' was coined only much later, the word 'black' referring possibly to the sheer horror of the pestilence (from the Latin, *atra mors*, which can mean 'terrible' or 'dreadful' death, the connotation of which was the 'black death') or, as some have suggested, to the blackened bodies of its victims. Contemporaries called the epidemic the 'Great Pestilence', the 'Great Mortality' or the 'Big Sickness'. They described a range of symptoms, including buboes – the size of eggs or even apples – on the groin and under the armpits, as well as blotches, boils, bruises, black pustules and the coughing up of blood, vomit and sputum.

The poignant accounts writers left behind ring with the terrible sorrows it brought in its wake. The Italian poet Petrarch (1304–74) expressed the perplexity and loneliness that must have haunted those who survived:

> *Where are our dear friends now? Where are the beloved faces? Where are the affectionate words, the relaxed and enjoyable conversations? What lightning bolt devoured them? What earthquake toppled them? What tempest drowned them? What abyss swallowed them? There was a crowd of us, now we are almost alone.*[5]

Giovanni Boccaccio (*c.* 1313–75), author of *The Decameron* (*c.* 1348–53) – set during the pestilence in Florence – also described its tragic consequences:

> *How many valiant men, how many fair ladies . . . breakfasted in the morning with their kinsfolk . . . and that same night supped with their ancestors in the other world!*[6]

Perhaps no other single 'plague' has so changed the world. The sheer scale of the Black Death in terms of the numbers killed over the course of just seven or so years resulted in huge demographic, social and economic upheavals. The impact on individuals, families and communities at the time hardly bears thinking about but survivors did adapt to new circumstances and in some countries the position in society of, for example, formerly landless labourers and rural tenants gradually improved for the better after the Black Death (addressed in Chapter 3 and Chapter 6). Indeed, historian John Hatcher reminds us of the complexities for England of the outcome of this calamitous event:

> *But it should always be remembered that the rising living standards and improved status that the ordinary folk came to enjoy were brought at the huge cost of a terribly high and unpredictable mortality . . . Such momentous mortality naturally had the potential to create confusion and disorder, but equally striking is the speed and power with which forces within society and economy moved to restore stability . . . Whereas the historian is struck by the continuities, contemporaries would have been overwhelmed by the scale of changes.*[7]

Plagues of the Early Modern World

Bubonic plague continued to strike over the following centuries, and wreaked havoc despite the imposition of measures that attempted to restrict the spread of disease, including cleaning up the filth of cities, as well as shutting up the infected in their homes or in pesthouses, and the introduction of quarantine – a word that comes from the Italian for 'forty days' (*quaranta giorni*) – the time that ships had to wait in port before delivering their potentially infectious passengers and cargoes.

The most famous (or infamous) outbreak of early modern plagues in Britain, some three centuries after the Black Death, was the Great Plague of London in 1665–6. This tragic and memorable event is thought to have killed 70,000–100,000 people, or one-fifth to one-quarter of the overcrowded population of insanitary London, causing panic and terror. 'Searchers' – frequently illiterate 'elderly matrons' – were sent to seek out the dead and ascertain the cause of death. Bills of Mortality recorded the numbers who had died of the plague and other diseases. Dead-carts travelled the streets at night with their drivers calling 'bring out your

dead'; they carried away the corpses, filling up mass graves to the brim. Perfumes, along with prayers, wafted through the churches, which were described by Daniel Defoe (*c.*1660–1731) as 'like a smelling-bottle; in one corner it was all perfumes; in another aromatics, balsamics, and variety of drugs and herbs.'[8] Following traditional advice during times of epidemics of 'flee early, flee far, return late', many who could afford to do so left the City, including not only King Charles II and his Court, but also priests and physicians. As Samuel Pepys (1633–1703) wrote on 16 October 1665 in his famous *Diary*:

> *But Lord, how empty the streets are, and melancholy, so many poor sick people in the streets, full of sores, and so many sad stories overheard as I walk, everyone talking of this dead, and that man sick, and so many in this place, and so many in that.*[9]

Contemporary ideas to explain the cause of plague included supernatural phenomena, divine vengeance, contagious particles, miasmas and foul smells. In some towns 'plague doctors' were recruited to treat the sick – their protective costumes reflecting the idea that the disease was thought to be highly contagious (See Figure 2.3).

Remedies ranged from prayer and penance to quack medicines sold to gullible and desperate people, as well as persecution of those groups in society suspected to have brought about these events. Although by the eighteenth century widespread epidemics of plague no longer struck Western Europe (for reasons which are still debated, though isolation and quarantine measures may have helped), the disease continued to be a substantial problem in other parts of the world, especially Asia, and between the 1890s and 1940s resulted in 15 million deaths worldwide. For the first time the plague spread to North America, sub-Saharan Africa and Australia via increasingly rapid forms of ocean transportation.

The 'plague bacillus' (*Y. pestis*) was, however, eventually found to be the cause of the disease by Alexander Yersin (1863–1943), working in Hong Kong at the end of the nineteenth century during this so-called third pandemic of bubonic plague. Once the rat-flea-human cycle of plague was elucidated and confirmed in the early twentieth century, measures were taken to trap and kill the rats that harboured the fleas that carried and transmitted the infection to humans. By the second half of the twentieth

FIGURE 2.3 **A plague doctor**

A plague doctor dressed in a seventeenth century preventive plague costume. While many professionally trained physicians did their best to avoid the infection, some brave souls (including those lured by the lucrative pay offered to volunteers, given the risk of death involved) were specifically hired as 'plague doctors'. This iconic image of the plague doctor shows him fully garbed in a head-to-toe protective costume, with the long, beak-like nosepiece stuffed with aromatic substances to combat the stench associated with plague. A popular seventeenth-century poem describes the plague doctor's costume:

In Rome the doctors do appear,
When to their patients they are called,
In places by the plague appalled,
Their hats and cloaks, of fashion new,
Are made of oilcloth, dark of hue,
Their caps with glasses are designed,
Their bills with antidotes all lined,
That foulsome air may do no harm,
Nor cause the doctor man alarm,
The staff in hand must serve to show
Their noble trade where'er they go.

[Source: Wellcome Images: V0010642]

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century, antibiotics became available to treat the plague, and there are now only around 1000 to 2000 reported human cases a year. *Y. pestis* has recently been identified in skeletal remains of medieval plague victims, confirming that this bacterium was the cause of the Black Death (as well as the Plague of Justinian).

In fact, bubonic plague is a classic example of a 'zoonosis' when a disease jumps from animals (in this case rodents) to humans, a concept also known as 'spillover'. As we shall see later, this mode of the emergence of diseases in the human population is now thought to be extremely common, with 'bird flu', 'swine flu', Ebola, HIV/AIDS, SARS and MERS-CoV as well recognised examples. Once seeded in the human population, however, there is also the possibility that such diseases can be spread directly by human-to-human transmission. In the case of plague, patients may develop the 'pneumonic' form of the disease when the bacilli enter the lungs. Pneumonic plague is highly transmissible via infective airborne droplets. Untreated pneumonic plague has a very high case-fatality ratio and, while thought to be the least common form of plague, some scholars have suggested that an airborne mode of transmission may have accounted for the devastating death toll of the Black Death. There are, however, still many puzzles and lively ongoing debates about the origins and epidemiological histories of the plague pandemics of the past – not least, as some media headlines have recently put it: Was the much-maligned black rat (*Rattus rattus*) really 'to blame' for the Black Death and repeated outbreaks of plague across Europe? [10]

Although bubonic plague was ravishing parts of Europe until the beginning of the eighteenth century, it did not reach the Americas until the early twentieth century when it struck a number of cities, including San Francisco, in short outbreaks. Other types of 'plagues', however, spread across the world in the early modern period as a consequence of a new era in human history during which travels between distant lands became increasingly common. The disease with the most widespread global effects at this time was smallpox, an airborne viral infection that probably dated back to the rise of the first agricultural settlements some ten thousand years ago. Like other so-called crowd diseases, smallpox depended on a sufficient density of population to spread from human to human and appears to have become increasingly virulent during the early

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modern period. In Europe it became known as the dreaded 'speckled monster', attacking princes and paupers alike. By the sixteenth century it accounted for up to 15 per cent of all deaths and it left those who survived pockmarked and scarred. As the historian Lord Macaulay (1800–59) commented:

> *. . . the small pox was always present, filling the churchyards with corpses, tormenting with constant fears all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden the objects of horror to the lover.*[11]

Smallpox first crossed the Atlantic with the Spanish conquistadors when they arrived in Central and South America in the 1490s. There it spread rapidly as the indigenous American populations had never experienced this infection in previous times and had acquired no immunity against it. Other infectious diseases too, such as measles, were transported across the ocean. Historians have suggested that the effects of these so-called virgin soil epidemics contributed to the collapse of the Aztec empire in Mexico and the Inca civilisation in Peru, though unravelling the many complex reasons for the demographic decline of the indigenous populations still remains an area of historical debate.[12]

The transport and transfer of disease was, probably, not just a one-way transmission from Europeans to Native Americans. The so-called Columbian disease exchange is thought to have introduced syphilis (the 'Great Pox') to the Old World from the New World – though, again, this is a topic that is still much debated by medical historians. Nonetheless, we know that serious epidemics of this sexually transmitted bacterial disease began to occur in Europe from the late fifteenth century onwards.[13] As with other apparently 'new' diseases, its dramatic effects were alarming, in this case often leading to gross disfigurement and debilitating neurological symptoms before a painful death. One chronicler, Joseph Grünpeck (*c.*1473–*c.*1532) thus described syphilis:

> *In recent times I have seen scourges, horrible sicknesses and many infirmities affect mankind from all corners of the earth. Amongst them has crept in . . . a disease which is so cruel, so distressing, so appalling that until now nothing so horrifying, nothing more terrible or disgusting, has ever been known on this earth.*[14]

With the opening up of the African continent and the horrendous transportation of slaves across the Atlantic, further exchanges in the disease pools of the Old and New Worlds took place. As explorers reached the Pacific, smallpox arrived in Australia in 1789, only a year after the first English settlement was established. It resulted in a similar demographic and psychological shock to the indigenous population as that in the Americas. It has been estimated that half of the aboriginal people who had contact with the newly arrived settlers died of this disease.

Ways of controlling diseases such as smallpox were, however, increasingly being explored. In the early eighteenth century, Lady Mary Wortley Montagu (1689–1762), the wife of the British ambassador to the Ottoman court, learned about the practice of inoculation during her time in Constantinople from the local population and introduced smallpox inoculation into Britain. This traditional method (which had been used in a number of countries from the tenth century AD) involved the introduction of pus from smallpox eruptions into healthy people, for example under the skin or into the nose, to induce a mild case of the disease and thence immunity. An even more exceptional method of preventing smallpox came with the discovery by Edward Jenner (1749–1823) of vaccination (using pus from cowpox – *vacca* is the Latin word for cow) at the end of the eighteenth century (See Figure 2.4).

Vaccination proved to be much safer and more effective than inoculation, and this practice was adopted around the world with extraordinary speed, showing that medical interventions could travel almost as rapidly as the diseases themselves.

Although there were objectors to vaccination – on ethical and religious grounds – and 'anti-vaccinationists' fought hard to suppress the practice (discussed in detail in Chapter 3), it offered the pox-ridden world a huge opportunity to defeat this ancient and appalling viral disease. Indeed, in 1806 President Thomas Jefferson (1743–1826) wrote to Jenner from America:

> *Medicine has never before produced any single improvement of such utility . . . You have erased from the calendar of human afflictions one of its greatest ... Future nations will know by history only that the loathsome small-pox has existed and by you has been extirpated.* [15]

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FIGURE 2.4 **Smallpox vaccination**
In this oil painting of 1884 by Eugène-Ernest Hillemacher, Edward Jenner (1749–1823) is seen vaccinating a small boy. Jenner's introduction of vaccination to prevent smallpox in the late eighteenth century was a remarkable example of empirical ingenuity that was highly effective before the causative agent of the disease was known. Vaccination, based on the principles established by Jenner, led to the official announcement of the global eradication of this ancient scourge in 1980. Today, vaccination plays a major role in preventing many infectious diseases.
[Source: Wellcome Images: L0029094]

It did, however, take many years for smallpox to be 'extirpated'. But over a century and a half after Jenner's pioneering discovery, the increasing efficacy of smallpox vaccines, and their widespread availability, enabled the World Health Organization to mount a campaign to eradicate the disease (even without a cure). By 1979 the world was declared free of smallpox and in 1980 it was removed from the list of world diseases. Smallpox was the first disease ever eliminated by human ingenuity – an outstanding triumph in the history of medicine.

Plagues of the Victorian World

During the Industrial Revolution of the nineteenth century another major change in human behaviour took place as a result of mass migration to the rapidly expanding cities, where employment and production were

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concentrated in factories – the 'dark satanic mills' of Victorian Britain and, increasingly, of other industrialising nations. A series of 'pandemics' (from the Greek, *pan-*, 'all', and *demos*, 'people') swept through densely populated and polluted cities. The most dramatic of these diseases was Asiatic cholera that spread across the world from its heartland in the Ganges Delta in the Indian subcontinent. With expanding empires and towns and cities interlinked through long-distance trade networks the threat of a 'new' disease reaching the shores of Europe was terrifying, as one doctor emphasised when cholera first struck Britain in 1831/2:

> *Our other plagues were home-bred, and part of ourselves, as it were . . . But the cholera was something outlandish, unknown, monstrous . . . a terror which . . . seemed to recall the memory of the great epidemics of the middle ages.*[16]

Cholera, with its dramatic symptoms of vomiting and rice-water diarrhoea and rapid death through dehydration, hit the insanitary cities of Europe. It added to the mortality toll of diseases such as typhus (a louse-borne bacterial disease which had devastated Napoleon's Army during his Russian campaign in 1812), and typhoid (a waterborne bacterial disease which is said to have killed Prince Albert, Queen Victoria's beloved husband, in 1861). Tuberculosis (an airborne bacterial disease, often known as the 'white plague' from the pallor of its victims) was also responsible for countless deaths at this time.

People realised that the appalling conditions and lack of sanitation were serious problems within cities such as London, as this heartfelt appeal printed in *The Times* in 1849 shows all too clearly:

> *Sur . . . We live in muck and filth. We aint got no priviz, no dust bins, no drains, no water-splies, and no drain or suer in the hole place. The Suer Company . . . take no notice watsomdever of our complaints. The Stenche of a Gulley-hole is disgustin . . . if the Cholera comes Lord help us.* [17]

There was, however, no clue as to the real cause of cholera and all sorts of possible explanations were aired (See Figure 2.5).

Contemporaries debated whether the disease was caused by 'miasmas' from the foul air (in which case sanitary reforms were needed), or by 'contagious' particles, spread from person to person (which should be controlled by maritime quarantine measures). An editorial in *The Lancet* in 1853 questioned:

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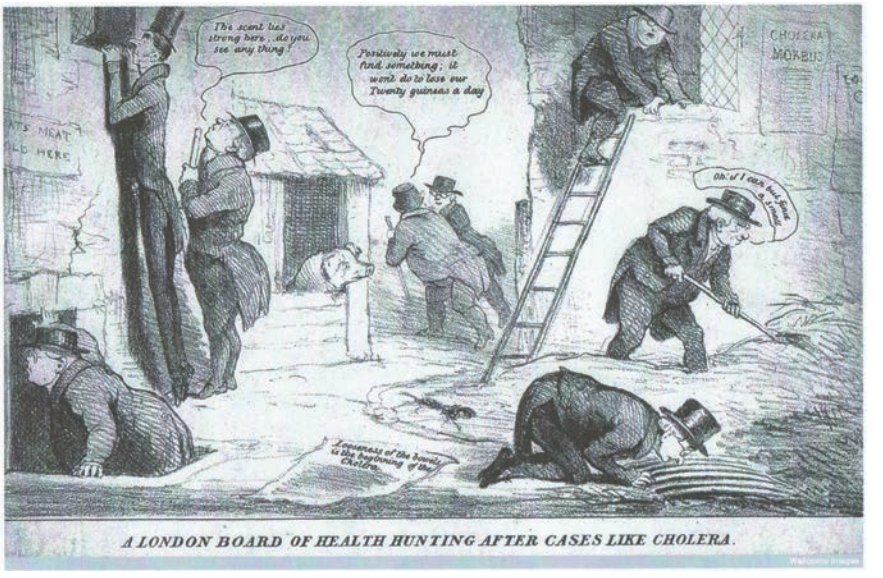

FIGURE 2.5 **Hunting for cases of cholera**
A London Board of Health searching for the cause of cholera when it first hit Britain in 1832. Edwin Chadwick (1800–90), the English social reformer, believed that '*all smell is disease*'. In 1854, John Snow (1813–58) recognised that cholera was spread by contaminated water, which led, ultimately, to practical measures of separating sewage from drinking water. In a recent UK poll of doctors and the public, 'sanitation' topped the list of the greatest fifteen medical milestones since the mid-nineteenth century.
[Source: Wellcome Images: V0010896]

> *What is cholera? Is it a fungus, an insect, a miasm, an electrical disturbance, a deficiency of ozone, a morbid offscouring from the intestinal canal? We know nothing; we are at sea, in a whirlpool of conjecture.* [18]

But, as ever, there were some people able to rise to such challenges and investigate the causes of the various diseases and the means of their prevention. A classic example involved the brilliant detective work by John Snow (1813–58) in London in the mid-nineteenth century; Snow recognised from the pattern of infection that cholera was carried by contaminated water, and famously requested the removal of the handle of a pump in Broad Street in London's Soho district to stop the spread of an outbreak of cholera. Such epidemiological studies demonstrated the need for effective public health and hygiene

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measures, which were subsequently of major significance in the control of a host of infectious diseases.

The recognition of the ways that diseases such as cholera could be transmitted, together with advances in laboratory research, led to a transformation in the understanding of infectious illnesses. Of seminal importance was the discovery of the existence of 'germs' in the late nineteenth century, beginning with the pioneering work of the French scientist Louis Pasteur (1822–95) and including the identification by the German scientist Robert Koch (1843–1910) of the bacteria that cause tuberculosis in 1882 and cholera in 1883–4. Ultimately, these medical milestones were followed by the development of drugs (antibiotics) able to kill specific bacteria, especially the introduction of penicillin and its derivatives into clinical medicine from the mid-twentieth century. Sadly, the uncontrolled use of antibiotics has resulted in the emergence of resistant strains of bacteria in the modern world with potentially disastrous consequences for the future, as we discuss below.

Plagues of the Modern World

It was a virus, not a bacterium, however, that led to the most lethal pandemic that the human race had ever experienced in a short space of time: the 'Spanish flu' of 1918–19, which is estimated to have killed over 50 million people across the globe, more than the number of people who died during the First World War (See Figure 2.6).

With the trauma of the war this appalling pandemic initially attracted much less attention than it would otherwise have done, although its relevance to modern outbreaks of disease has now generated tremendous interest in its nature. As an editorial in *The Times* of London remarked in December 1918:

> *Never since the Black Death has such a plague swept over the face of the world; never, perhaps, has a plague been more stoically accepted.* [19]

Like the great plagues of the past, the origins of this disease, which has been described by historians as *'the greatest single demographic shock that the human species has ever received'*, were unknown. In fact, influenza is probably an ancient disease and, like smallpox, only became a highly

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FIGURE 2.6 **The 1918-19 influenza pandemic**
The Spanish flu of 1918–19 was one of the most lethal pandemics in history, killing within a short time some 50–100 million people. This contemporary image shows soldiers from Fort Riley, Kansas, ill with Spanish influenza at a hospital ward at Camp Funston. [SOURCE: Wikimedia Commons (http://en.wikipedia.org/wiki/1918_flu_pandemic/media/File:CampFunstonKS-InfluenzaHospital.jpg]

transmissible disease once the density of human and domestic animal populations increased with the development of agricultural communities. The word 'influenza' was coined by the Italians – from the Latin, *influentia coeli*, or 'heavenly influence' – and introduced into the English language in the eighteenth century. The 1918–19 'Spanish flu' was so-called not because it started in Spain but because Spain was not a belligerent country and its press was not prevented by government censors from freely reporting its alarming impact when it struck there in May 1918. But why influenza afflicted so many parts of the globe, almost simultaneously, remains puzzling, as does the fact that it was so virulent and devastating and why, unlike seasonal flu (which mostly affects the elderly and very young), it primarily targeted young adults in the prime of life.

Efforts to prevent the spread of the disease – especially once its severity was evident and widely acknowledged – included prohibiting public gatherings, disinfecting streets and homes, sterilising water fountains, banning spitting and shaking hands (which, in some places, became

a punishable offence), quarantining ships and enforcing the wearing of gauze masks. Some invoked folk remedies, such as carrying garlic, sulphur, cucumbers or potatoes to ward off infection, and, as in earlier times, any number of quack remedies and lung tonics were sold as 'sure cures'.

The discovery that influenza was caused by a virus was eventually made following the development of the electron microscope in the 1930s, and recently the advent of gene sequencing techniques has enabled the specific strain of the 1918–19 pandemic to be identified from preserved lung tissue, as well as from bodies of victims that had been buried in permafrost in Norway and Alaska. Vaccines and drugs have been developed to combat influenza, but we now know that the influenza virus can mutate and recombine genes, often in animal hosts, with frightening rapidity, resulting in outbreaks of forms of this disease for which existing vaccines are ineffective. Recent examples include certain types of avian and swine flu, the former ('bird flu') related to the strain giving rise to Spanish flu, adding to fears of the emergence of novel and highly contagious forms of this disease that are beyond our ability to control.

And again changes in human lifestyles make these fears all too real. Not only has the global population increased hugely in recent years along with the rise of 'mega-cities', but so, too, has the speed of travel and hence the transmission of contagious diseases. The world can now be circumnavigated in a couple of days or less, whilst a century or two ago it took many months. Indeed, it took several years for bubonic plague to spread across Asia to Europe in the fourteenth century, but the SARS (severe acute respiratory syndrome) virus travelled from Hong Kong to Canada in just a few days in 2003. SARS is a flu-like respiratory disease arising from a 'new' coronavirus and is yet another example of a zoonotic disease that crossed the species-barrier from animal hosts (bats and civets) to humans in crowded markets in China (See Figure 2.7).

As Ron Barrett and George Armelagos remind us:

> *The major themes governing our susceptibility to infectious diseases today are essentially the same as those of our ancient past: they are merely intensified by our massive populations, our cities, and technologies now at our disposal . . . modern humans are essentially "stone agers living in the fast lane."*[20]

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FIGURE 2.7 **International health alerts during the SARS pandemic**
As a deadly outbreak of a 'new' disease, known as SARS (severe acute respiratory syndrome), threatened the globe in 2003, a number of measures were rapidly put into effect, such as quarantining the infected and monitoring the health of travellers at international borders to prevent its spread. SARS affected twenty-nine countries, reminding us that any infection is only a plane flight away.
[Source: Corbis DWF15-692817]

Another terrible and tragic affliction of modern times is AIDS (acquired immune deficiency syndrome), which is caused by the virus known as HIV (human immunodeficiency virus). HIV is also of zoonotic origin, having evolved from simian immunodeficiency viruses (SIV) of several non-human primate species. HIV was probably acquired by humans through the hunting and consumption of 'bush meat' in Africa. Estimates of the timing of its emergence in humans vary from fifty to one hundred years before its appearance in the United States in the early 1980s, when HIV/AIDS shocked the world as a new type of human disease. In 1983 the HIV retrovirus (an RNA virus whose DNA copy becomes incorporated into the host genome and so persists indefinitely as long as infected cells live) was identified and characterised.

Multiple epidemics of HIV/AIDS, with very different epidemiological and demographic patterns, have spread across the world. The impact of

this new 'silent' plague, that typically takes several years to manifest itself as the human immune system is slowly destroyed, has been most devastating in the poorer countries of the world, especially sub-Saharan Africa. Here, this disease has often been spread by people who do not know they carry HIV, typically killing young adults and leaving behind millions of orphans. As one epidemiologist in Kampala, Uganda, wrote:

> *It all started as a rumour. Then we found we were dealing with a disease. Then we realized that it was an epidemic. And, now we have accepted it as a tragedy.* [21]

HIV is transmitted through sexual interactions, contaminated needles or infected blood products, and can also be passed from HIV-infected mothers to infants. The recognition of its public health dangers in the early 1980s led to a clamour for action, and campaigns for prevention and behavioural changes became the key targets of national and global health organisations. Around the world people were advised about the risks of contracting HIV/AIDS and the ways of avoiding or spreading it. The 'Stop AIDS' campaign became one of the biggest health-education drives the world had ever seen. Within just a few years a therapeutic breakthrough was made and AZT, the first drug licensed for this disease, was in use by 1987, having been fast-tracked through the US Food and Drug Administration (FDA). Soon the concept of a cocktail of antiretroviral drugs (combination therapy) was developed to combat the growing problem of anti-viral resistance, and now is so effective at containing the escape and replication of HIV that its use has become known as the 'Lazarus effect'.

Antiretroviral drugs were some of the first effective therapeutic compounds for any viral disease and their development represents a triumph of a massive and concerted programme of research involving academic laboratories and pharmaceutical companies – supported by both public and private funding as a result of intense lobbying in the United States in particular. Although not a cure, for those with access to these sophisticated drugs, HIV/AIDS is now seen as a chronic and manageable condition rather than a death sentence. Nevertheless, the disease has already claimed some 40 million lives and large numbers of people (probably some 35 million) are currently living with HIV infection. If left untreated, the slow destruction of the immune system leaves the body open to all

sorts of life-threatening opportunistic infections and can, also, substantially worsen the manifestations of other co-infecting pathogens – especially tuberculosis. With increased availability of, and access to, antiretroviral drugs, particularly amongst those who urgently need them in the developing countries, there are hopes for an 'AIDS-free world'. Challenges still remain and scientists are continuing to search for the ultimate cure or a vaccine to combat this complex retrovirus that has become a fearful scourge of modern times (see also Chapter 5 by Stephen O'Brien).

Plagues of the Future World

Despite the tremendous progress that has been made in the fight against infectious diseases, there are still many 'ancient' diseases, particularly in the tropical parts of the world, which continue to plague humanity. These include malaria, tuberculosis, pneumonia and diarrhoeal diseases which are primarily associated with poverty, malnutrition, poor sanitation or a lack of access to a good standard of health care. Indeed, a number of viral, parasitic and bacterial infections, such as dengue fever ('breakbone fever'), onchocerciasis ('river blindness'), schistosomiasis ('snail fever'), African trypanosomiasis ('sleeping sickness') and Hansen's disease ('leprosy'), are now classed as 'Neglected Tropical Diseases' (NTDs) for which further attention is urgently needed. Moreover, the threat of emerging strains of infectious pathogens that are resistant to antimicrobial drugs is a problem that must be counteracted if the plagues of the past are not to re-emerge in even the most affluent societies.

The recent and severe outbreak in West Africa of Ebola (also known as Ebola haemorrhagic fever [EHF] or Ebola virus disease [EVD]) has made headline news. Like a number of other diseases we have discussed, Ebola is a zoonotic disease, thought to have originated in Africa from human contact with infected wildlife carriers (including bats). In August 2014, Ebola was labelled by the World Health Organization as an 'international health emergency'. This viral disease, once an initial 'spill-over' has occurred, can be spread directly from person-to-person by bodily fluids, and is an example of a relatively 'new' disease as it was first identified in humans only in 1976. It is so extraordinarily deadly that,

during the height of the crisis in 2014, experimental treatments were administered that had not been subject to the usual degree of clinical scrutiny. In 2016, the emergence and spread of Zika virus, transmitted by mosquitoes, has also led to alarm bells ringing across the world. The threat of pandemics of infectious diseases with infected individuals rapidly criss-crossing around the globe has become the subject of vivid and shocking Hollywood productions with apocalyptic scenarios, such as *Outbreak* (1995) and *Contagion* (2011).

Notwithstanding such global attention and the local fear and panic they generate, these recurring themes remind us of the relationships of recent outbreaks of disease to earlier historical pandemics. Nevertheless, there have been incredible developments in humanity's response to outbreaks of 'plagues'. Over the past century or so, alongside public health, medical and surgical interventions and a phenomenal increase in our understanding of the biological, genetic and social determinants of diseases, there have also been major improvements in standards of nutrition, hygiene and health care in many (though, sadly, not all) parts of the world. A combination of such diverse efforts has enabled us to control many of the plagues of the past and, while we may still fear the threat of both 'old' or 'new' infectious diseases in our interconnected world, there are improvements being made in global surveillance systems that can track and monitor the spread of infections and, hopefully, prepare and protect us in the future from such global horrors of the past as the Black Death and the Spanish flu.

One of the most dramatic results of such medical and scientific advances is increasing life expectancy. For example, in the mid-nineteenth century the average life expectancy in the Western world was only about forty years, although, because of the shockingly high rates of child mortality, for those who survived until the age of twenty the average age of death was almost sixty years. Today, however, average life expectancy from birth in many parts of the world is eighty years or more. This extension of lifespan – in a large part as a result of combating infectious diseases – has, nevertheless, come at a price. Chronic diseases such as cancer and heart disease have become familiar and distressing afflictions of the modern age, but such conditions have fortunately received a very great deal of

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attention and funding. In 1969, US cancer specialist Sidney Farber (1903–73) is quoted as saying:

> *We are so close to a cure for cancer. We lack only the will and the kind of money and comprehensive planning that went into putting a man on the moon.* [22]

In 1971, the US Congress passed the National Cancer Act, which committed more funds and resources to cancer research and raised the profile of cancer enormously. A huge global industry, funded by governments, charities and pharmaceutical companies, grew up around what had become known as the 'War against Cancer'. Cardiovascular diseases (heart disease and stroke) have also attracted worldwide attention as serious and life-threatening conditions. And advances in heart surgery including transplantation, along with improvements in lifestyle risk factors, have had a major role in reducing early mortality from cardiovascular diseases.

There is a long way to go before the global toll of cardiovascular diseases and cancers (the two leading causes of death worldwide) is likely to be very significantly reduced, but we are clearly making substantial progress. By contrast, dementias, notably Alzheimer's disease, have silently crept up on us, and because of their very marked age dependence, we are only now beginning to acknowledge the serious burden that this 'twenty-first century plague' could have on us in the future (See Figure 2.8).

Although a small proportion of cases of Alzheimer's disease are 'early-onset' forms associated with specific genetic mutations, the large majority of cases are termed 'sporadic'. The risk of onset in these circumstances increases dramatically above the age of sixty-five, and it appears that over one third of people who have reached the age of eighty-five have at least some symptoms of this disorder. With the changing demographic patterns of modern societies – it has, for example, been estimated that more than half of all the people in human history who have reached the age of sixty-five are alive at the present time – the number of people suffering from this disease is likely to triple in the next forty years unless effective treatments are discovered. Without such treatments, however, the disruption to family and social life caused by Alzheimer's disease will become increasingly serious, as will the financial consequences; the cost

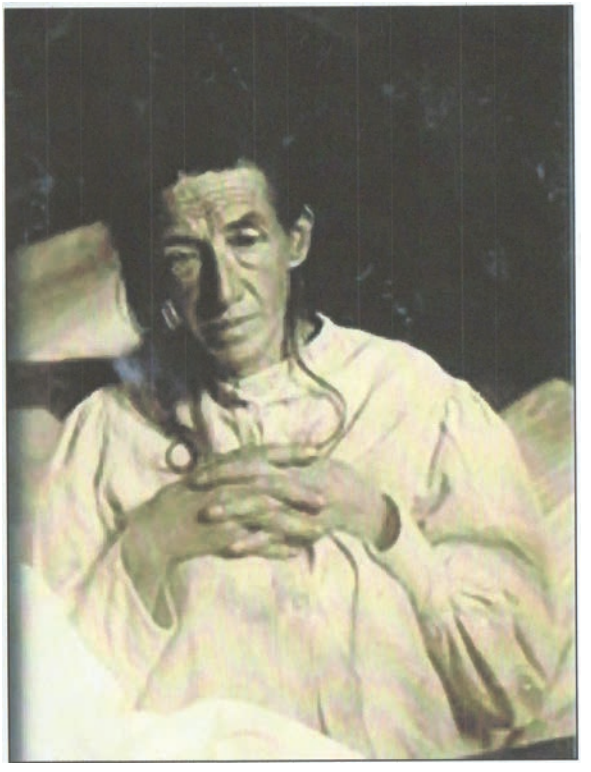

FIGURE 2.8 **The first recorded case of Alzheimer's disease**
In 1901 Auguste Deter was admitted to the Institution for the Mentally Ill and for Epileptics in Frankfurt, Germany, suffering from memory loss, delusions and other psychological problems. Alois Alzheimer examined her and noted that she was suffering from a 'peculiar disease'; after her death in 1906 he conducted an autopsy where he saw dramatic shrinkage of the brain and abnormal deposits around nerve cells. Such deposits had previously been observed in brain tissue by Rudolf Virchow (1821–1902) and had been named 'amyloid' because they stained with dyes used to detect starch (*amylum* in Latin); subsequently, it was shown that these deposits are in fact composed of aggregated protein molecules. As Deter was only fifty-one years old when Alzheimer first examined her, it is likely that she was suffering from an early onset form of disease caused by a genetic mutation, a conclusion that has recently been confirmed by analysis of preserved brain tissue using modern technologies.
[Source – Google Images]

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of the disease in the United States alone is predicted to pass $1 trillion per annum by 2050. And dementia is not just an affliction of the richer nations. The World Health Organization estimates that some 70 per cent of the nearly 140 million sufferers of Alzheimer's disease anticipated by 2050 will be in low- and middle-income countries, putting an incalculable burden on already stretched health care budgets. [23]

Like most emerging diseases, the cause of Alzheimer's disease was at first unknown. In words reminiscent of those given above in the context of cholera in the mid-nineteenth century, the organiser of a research workshop in 1984 made the following comment:

> *We are still uncertain whether Alzheimer's disease is a specific, discrete,* qualitative *disorder such as an infectious process, endogenous or exogenous toxic disorder, or biochemical deficiency, or whether it is a* quantitative *disorder, in which an exaggeration and acceleration of the normal aging processes occur and dementia appears when neural reserves are exhausted and compensatory mechanisms fail.* [24]

Since then, however, much has been learned and it is now clear that Alzheimer's is a specific disease and not an inevitable consequence of ageing. Moreover, it has emerged that Alzheimer's disease is one of a family of some fifty types of medical conditions that are collectively known as 'protein misfolding diseases', which have only come to prominence in recent years. These disorders include other well-known forms of neurodegenerative conditions such as Parkinson's and Huntington's diseases, which like Alzheimer's disease are age-related, and also quite different disorders, notably type II diabetes, a condition that is itself proliferating rapidly, with more than 300 million affected individuals worldwide at present. This chronic affliction has resulted because of a different type of lifestyle change – in this case, lack of exercise and alterations in diet leading to the prevalence of obesity. It is predicted that the huge rise in the number of cases of type II diabetes could soon bring to an end the present steady increase in life expectancy in many parts of the world.

It turns out that this family of diseases is the result of the effects of 'pathogens', but unlike the historic plagues these pathogens are not external agents such as bacteria or viruses, but are generated within

our bodies because of the aberrant behaviour of some of the very molecules on which our lives depend. Living systems are highly complex molecular machines made up of trillions of cells of many different types, from erythrocytes (red blood cells) and lymphocytes (white blood cells) to hepatocytes (liver cells) and neurons (nerve cells). These cells carry out all the processes necessary for life (for example, enabling us to breathe, fight disease, digest food and process information). The agents that enable all these functions to occur are proteins, long chains of chemical building blocks called amino acids; by varying the number and order of these building blocks (defined by the inherited information contained within our DNA) our bodies are able to make tens of thousands of different types of protein molecules, which together possess all the functional properties that are needed for life.

In order for proteins to gain their functions after the building blocks are joined together, however, they need to fold up into highly specific, compact, and often intricate, shapes. The process of protein folding is a complex and fascinating one, and although carefully regulated in our cells it sometimes goes wrong and results in 'misfolded' proteins. These misfolded proteins not only fail to function properly, but can also stick to each other to form clumps of molecules (known as amyloid) that can be highly toxic to cells, thereby disrupting the well-managed processes that ensure good health. Each disease is associated with the conversion of a specific type of protein molecule into the amyloid state, and there are therefore inherent similarities between the molecular origins and means of progression of this whole class of diseases. Indeed, to ensure that misfolding is not normally a problem, we have a wide range of protective mechanisms within our bodies to detect and degrade misfolded proteins and prevent pathogenic amyloid structures from being formed. These protective systems work very well under the types of conditions that have existed throughout human evolution. But in the last century or so all this has changed; in affluent parts of the world we live on average very much longer than ever before and have more than enough to eat without needing to exert the degree of effort that was previously required to acquire and produce food.

Under these circumstances, our protective mechanisms have an increasing tendency to fail, enabling misfolded proteins to accumulate,

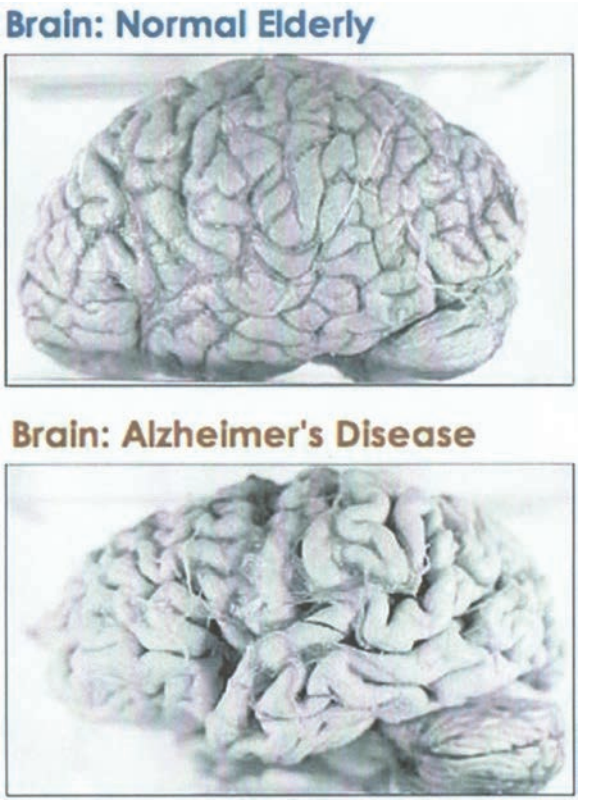

FIGURE 2.9 **Changes in the brain associated with Alzheimer's disease** Alzheimer's disease is characterised by loss of memory and cognitive impairment that results from the death of vital cells (neurons) in crucial areas of the brain. Such changes can be attributed to the misfolding and aggregation of proteins, ultimately forming amyloid plaques and also neurofibrillary tangles. The consequences of advanced neuronal loss and tissue atrophy are evident in the marked shrinkage of the brain shown in the lower image. [Source: The Sanders-Brown Center on Aging, University of Kentucky]

losing their normal functions and also generating pathogenic amyloid structures that can progressively damage or destroy the cells in their vicinity. If these pathogenic agents are in the brain, this phenomenon can give rise to dementia; indeed the clumps of misfolded proteins can accumulate to form the well-known 'amyloid plaques' in the brains of sufferers of Alzheimer's disease that are characteristic of this condition (See Figure 2.9).

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A consequence of our extended life-spans, resulting in large part from the successful control and treatment of diseases that had ravaged human populations in the past, is therefore the proliferation of the number of cases of dementia, in many ways as terrible an affliction as many of the plagues of the past. In the words of Margaret Chan, Director General of the World Health Organization, in 2013:

> *I can think of no other condition that places such a heavy burden on society, families, communities, and economies. I can think of no other condition where innovation, especially breakthrough discoveries, is so badly needed.*[25]

Fortunately, our current understanding of the key elements of Alzheimer's disease, along with the continuing advancement of scientific and medical knowledge, is such that we have every opportunity to take control of our own future and ensure that we do not experience a catastrophe on the scale that afflicted so many of our ancestors.

Conclusions

We have discussed in this chapter how 'plagues' are very generally associated with rapid changes in human lifestyle and behaviour. Throughout history, humanity has responded by striving to discover the underlying causes of disease, and, armed with such understanding, find effective methods of prevention and even cures. In the case of infectious diseases, success has been demonstrated time and time again. The global eradication of smallpox has been the outstanding triumph and, indeed, following further vaccination campaigns, we now optimistically await the eradication of another serious viral disease – polio – from the globe. Yet as Albert Camus (1913–60) reminded us in his 1947 allegorical story, *La Peste* ('The Plague'), set in the Algerian port city of Oran (and discussed by Rowan Williams in Chapter 9), we must not be too complacent:

> *. . . the plague bacillus never dies or vanishes entirely . . . and that perhaps the day will come when . . . the plague will rouse its rats and send them to die in some well-contented city.* [26]

In addition to the emergence of old or new threats, as we respond with new medical advances, strains of bacteria, parasites and viruses emerge

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that are resistant to even our best antimicrobials or vaccines, and are a cause of huge international concern. It is essential that urgent action is taken to reduce disease risks by simple preventative measures, such as improving standards of hygiene, and to use existing antimicrobials and vaccines more prudently. Major efforts are underway to develop new classes of therapeutics to combat the threat of diseases that possess the potential to cause global pandemics. As Sally Davies, the UK Government's Chief Medical Officer, said recently:

> *If we don't take action, then we may all be back in an almost 19th Century environment where infections kill us as a result of routine operations. We won't be able to do a lot of our cancer treatments or organ transplants.* [27]

Nevertheless, we are now in a position where we can take advantage of the great advances that have taken place, and continue to take place, in scientific and medical knowledge. Attempts to develop drugs to combat Alzheimer's disease and related disorders have so far been unsuccessful because of the lack of knowledge of their molecular nature and inherent origins. Over the last twenty years or so our understanding of the underlying causes of these diseases, however, has been transformed through innovative research programmes that bring together scientists from a wide range of physical, biological and medical disciplines. The international scientific community is now in the process of devising rational diagnostic and therapeutic strategies for protein-misfolding disorders including Alzheimer's disease. We are optimistic that very significant breakthroughs will emerge from these efforts, just as the efforts of medical pioneers in earlier times resulted in ways of confronting the plagues of the past. Nevertheless, a great deal of highly innovative research will be needed to translate fundamental understanding of disease into effective drugs.[23]

Of crucial importance in securing such breakthroughs is a greater general understanding of the threat that these diseases, with their common underlying origins, albeit influenced by a complex mix of genetic, lifestyle and age-related risk factors, poses for our present populations. It is vital that there is a wider recognition that this threat will increase yet more dramatically in the future unless the global community provides substantial human and material resources specifically to prevent

and combat these disorders. When a 'war' was declared on cancer in 1971, it resulted in huge increases in research funding by public and private organisations alike. This investment and dedication has had a very significant effect in developing new and powerful therapies. But funding for research into future plagues such as dementia is even now only a fraction – less than 10 per cent – of that spent on cancer. We have the knowledge and skills to combat dementia, but not yet the resources to do so quickly enough to avert the 'time-bomb' that is ticking ever more rapidly. As the late Terry Pratchett, author and former Patron of Alzheimer's Research United Kingdom, said in 2008:

> *We are facing . . . a worldwide tsunami of Alzheimer's and other dementia diseases. There's only two ways it can go: researchers, with as much help you can give them, may come up with something that reduces the effects of this dreadful, inhuman disease, or we will have to face the consequences of our failure to prevent the final years of many of us being a long bad dream. The strain on carers and their support is bad enough now; before very long the effects on the health service and society itself, will be unbearable.* [28]

History tells us that great civilisations have in the past suffered terribly from the effects of plagues, but that they also adapted and responded with remarkable tenacity. The increasing recognition of dementia as a rapidly developing 'plague' of the modern era is at last drawing attention to one of the greatest future global challenges. It is vital that we act at once, with real determination, to address this challenge, building on the progress that has been made in understanding the origins of the disease, and so grasp the opportunity of the moment for the sake of our children, and indeed for all future generations of the human race.

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