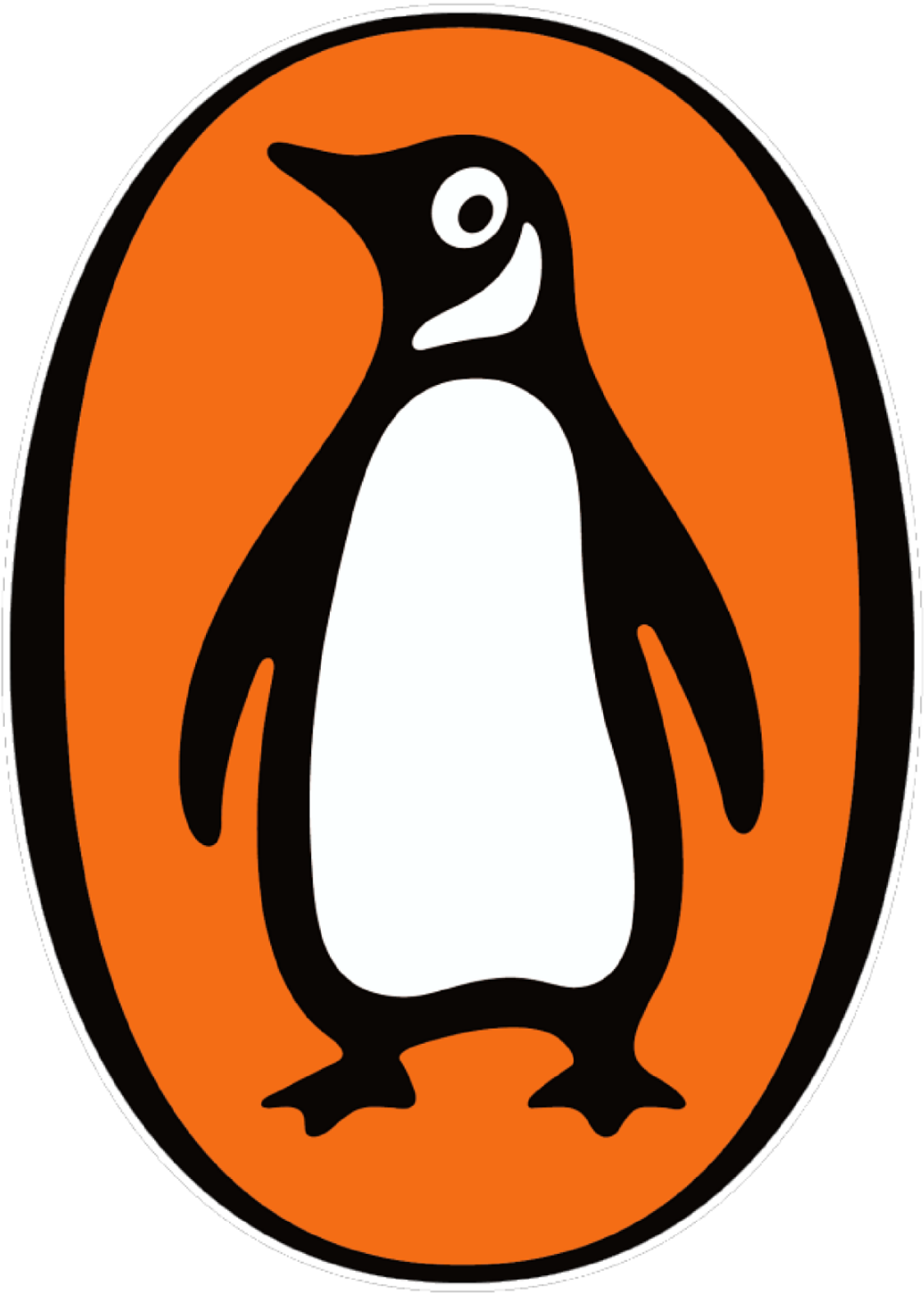

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About the Author

Mark Honigsbaum is a medical historian, journalist, and author of five books including *The Pandemic Century: One Hundred Years of Panic, Hysteria, and Hubris* and *The Fever Trail: In Search of the Cure for Malaria*. He hosts the podcast series, 'Going Viral: The Mother of all Pandemics', marking the centenary of the 1918 influenza pandemic. His TED-ED animation, 'How Pandemics Spread', has been viewed more than 2.75 million times. He is a former chief reporter of the Observer and holds a PhD in medical history. He is currently a lecturer at City University, London.

For Mary-Lee

“Everyone knows that pestilences have a way of recurring in the world; yet somehow we find it hard to believe in ones that crash down on our heads from a blue sky. There have been as many plagues as wars in history; yet always plagues and wars take people equally by surprise.”

Albert Camus, *The Plague*, 1947.

PROLOGUE

Sharks and Other Predators

Sharks never attack bathers in the temperate waters of the North Atlantic. Nor can a shark sever a swimmer's leg with a single bite. That's what most shark experts thought in the blisteringly hot summer of 1916 as New Yorkers and Philadelphians flocked to the beaches of northern New Jersey in search of relief from the sweltering inland temperatures. That same summer the East Coast had been gripped by a polio epidemic, leading to the posting of warnings about the risk of catching "infantile paralysis" at municipal pools. The Jersey shore was considered a predator-free zone, however.

"The danger of being attacked by a shark," declared Frederic Lucas, director of the American Museum of Natural History, in July 1916, "is infinitely less than that of being struck by lightning and … there is practically *no* danger of an attack from a shark about our coasts." As proof, Lucas pointed to the reward of $500 that had been offered by the millionaire banker Hermann Oerlichs "for an authenticated case of a man having being attacked by a shark in temperate waters [in the United States, north of Cape Hatteras, North Carolina]"—a sum that had gone unclaimed since Oerlichs had posted the challenge in the *New York Sun* in 1891.[1]

But Oerlichs and Lucas were wrong, and so were Dr Henry Fowler and Dr Henry Skinner, the curators of Philadelphia's Academy of Natural Science who had categorically stated, also in 1916, that a shark lacked the power to sever a man's leg. The first exception to these *known* facts had come on the evening of 1 July 1916, when Charles Epting Vansant, a wealthy young broker holidaying in New Jersey with his wife and family, decided to go for a pre-dinner swim near his hotel at Beach Haven. A graduate of the University of Pennsylvania's class of 1914, Vansant, or "Van" to his chums, was a scion of one of the oldest families in the country—Dutch immigrants who had settled in the United States in 1647—and famed for his athleticism. If he had any concerns about entering the cool Atlantic waters that evening, they would have been offset by the familiar sight of the beach lifeguard, Alexander Ott, a member of the American Olympic swimming team, and a friendly Chesapeake Bay retriever that ran up to him as he slid into the surf. In the fashion of young Edwardian men of the time, Vansant swam straight out beyond the lifelines, before turning to tread water and call to the dog. By now his father, Dr Vansant, and his sister, Louise, had arrived on the beach and were admiring his form from the lifeguard station. Much to their amusement, the hound refused to follow. Moments later, the reason became apparent—a black fin appeared in the water, bearing down on Vansant from the east. Frantically, his father waved for his son to swim to shore, but Vansant spotted the danger too late and when he was fifty yards from the beach he felt a sudden tug and an agonizing pain. As the sea around him turned the colour of wine, Vansant reached down to discover that his left leg was gone, severed neatly at the thigh bone.

By now Ott was at his side and dragging him through the water to the safety of the Engelside Hotel where his father desperately tried to stem the bleeding. But it was no use—the wound was too deep—and to his father and young wife's horror Vansant died then and there, the first known victim of a shark attack in the North Atlantic. From that moment on, neither would be able to look at Jersey's Atlantic seaboard without imagining the jaws lurking beneath the surface.

They were not alone. Within fourteen days, four more bathers would also be attacked on the Jersey shore and three would be killed, sparking an obsessive fear of "man-eating" sharks[fn1] that persists to this day.[2] It makes little difference that sightings of great whites and other large sharks in the North Atlantic are rare and attacks on swimmers rarer still. Beachgoers now *know* better than to swim too far from shore, and should they become blasé about the risks and dismissive of the menace, there is always a rerun of *Jaws* or an episode of the Discovery channel's *Shark Week* to set them straight. The result is that many children and a fair number of adults are now terrified of playing in the surf, and even those brave enough to venture beyond the breakers *know* to keep a wary eye on the horizon for the tell-tale sight of a dorsal fin.

* * *

At first glance, the New Jersey shark attacks would seem to have little to do with the Ebola epidemic that engulfed West Africa in 2014 or the Zika epidemic that broke out in Brazil the following year, but they do, for just as in the summer of 1916 most naturalists could not conceive of a shark attack in the cool waters of the North Atlantic, so in the summer of 2014 most infectious disease experts could not imagine that Ebola, a virus previously confined to remote forested regions of Central Africa, might spark an epidemic in a major city in Sierra Leone or Liberia, much less cross the Atlantic to threaten citizens of Europe or the United States. But that is precisely what happened when, shortly before January 2014, Ebola emerged from an unknown animal reservoir and infected a two-year-old boy in the village of Meliandou, in south-eastern Guinea, from whence the virus travelled by road to Conakry, Freetown, and Monrovia, and onward by air to Brussels, London, Madrid, New York and Dallas.

And something very similar happened in 1997 when a hitherto obscure strain of avian influenza, known as H5N1, which had previously circulated in ducks and other wild waterfowl, suddenly began killing large numbers of poultry in Hong Kong, triggering a worldwide panic about bird flu. The great bird flu scare, of course, was followed by the panic about Severe Acute Respiratory Syndrome (SARS) in 2003, which was followed, in turn, by the 2009 swine flu—an outbreak that began in Mexico and set off an alarm about the threat of a global influenza pandemic that saw the drawdown of stockpiles of antiviral drugs and the production of billions of dollars' worth of vaccines.

Swine flu did not turn into a man-eater—the pandemic killed fewer people globally than common or garden strains of flu have in the United States and the United Kingdom most years—but in the spring of 2009 no one knew that would be the case. Indeed, with disease experts focused on the re-emergence of bird flu in Southeast Asia, no one had anticipated the emergence of a novel swine flu virus in Mexico, let alone one with a genetic profile similar to that of the virus of the 1918 "Spanish flu"—a pandemic that is estimated to have killed at least 50 million people worldwide and is considered a byword for viral Armageddon.[fn2]

* * *

In the nineteenth century, medical experts thought that better knowledge of the social and environmental conditions that bred infectious disease would enable them to predict epidemics and, as the Victorian epidemiologist and sanitarian William Farr put it in 1847, “banish panic.” But as advances in bacteriology led to the development of vaccines against typhoid, cholera, and plague, and fear of the great epidemic scourges of the past gradually receded, so other diseases became more visible and new fears developed. A good example is polio. The month before sharks began attacking bathers on the Jersey shore, a polio epidemic had broken out near the waterfront in South Brooklyn. Investigators from New York’s Board of Health immediately blamed the outbreak on recent Italian immigrants from Naples living in crowded, unsanitary tenements in a district known as “Pigtown.” As cases of polio multiplied and the papers filled with heart-breaking accounts of dead or paralyzed infants, the publicity prompted hysteria and the flight of wealthy residents (many New Yorkers headed for the Jersey shore). Within weeks, the panic had spread to neighbouring states along the eastern seaboard, leading to quarantines, travel bans, and enforced hospitalizations.[3] These hysterical responses partly reflected the then-prevalent medical conviction that polio was a respiratory disease spread by coughs and sneezes and by flies breeding in rubbish.[fn3]

In his history of poliomyelitis, the epidemiologist John R. Paul describes the epidemic of 1916 as “the high-water mark in attempts at enforcement of isolation and quarantine measures.” By the time the epidemic petered out with the cooler weather in December 1916, 27,000 cases and 6,000 deaths had been recorded in twenty-six states, making it the world’s then-largest polio outbreak. In New York alone there had been 8,900 cases and 2,400 deaths, a mortality rate of around one child in four.[4]

The scale of the outbreak made polio appear a peculiarly American problem. But what most Americans did not realize is that a similarly devastating outbreak had visited Sweden five years earlier. During that outbreak, Swedish scientists had repeatedly recovered polio virus from the small intestine of victims—an important step in explicating the true aetiology and pathology of the disease. The Swedes also succeeded in culturing the virus in monkeys who had been exposed to secretions from asymptomatic human cases, fuelling suspicion about the role of “healthy carriers” in the preservation of the virus between epidemics. However, these insights were ignored by leading polio experts. The result is that it was not until 1938 that researchers at Yale University would take up the Swedish studies and confirm that asymptomatic carriers frequently excreted the polio virus in their stools and that the virus could survive for up to ten weeks in untreated sewage.

Today, it is recognized that in an era before polio vaccines, the best hope of avoiding the crippling effects of the virus was to contract an immunizing infection in early childhood when polio is less likely to cause severe complications. In this respect, dirt was a mother’s friend and exposing babies to water and food contaminated with polio could be considered a rational strategy. By the turn of the nineteenth century, most children from poor immigrant neighbourhoods had become immunized in exactly this way. It was children from pristine, middle-class homes that were at the greatest risk of developing the paralytic form of the disease —people like Franklin Delano Roosevelt, the thirty-second president of the United States, who escaped polio as a teen only to contract the disease in 1921 at the age of thirty-nine while holidaying at Campobello Island, New Brunswick.

* * *

This is a book about the way that advances in the scientific knowledge of viruses and other infectious pathogens can blind medical researchers to these ecological

and immunological insights and the epidemic lurking just around the corner. Ever since the German bacteriologist Robert Koch and his French counterpart, Louis Pasteur, inaugurated the “germ theory” of disease in the 1880s by showing that tuberculosis was a bacterial infection and manufacturing vaccines against anthrax, cholera and rabies, scientists—and the public health officials who depend on their technologies—have dreamed of defeating the microbes of infectious disease. However, while medical microbiology and the allied sciences of epidemiology, parasitology, zoology, and, more recently, molecular biology, provide new ways of understanding the transmission and spread of novel pathogens and making them visible to clinicians, all too often these sciences and technologies have been found wanting. This is not simply because, as is sometimes argued, microbes are constantly mutating and evolving, outstripping our ability to keep pace with their shifting genetics and transmission patterns. It is also because of the tendency of medical researchers to become prisoners of particular paradigms and theories of disease causation, blinding them to the threats posed by pathogens both known and unknown.

Take influenza, the subject of the first chapter. When the so-called “Spanish flu” emerged in the summer of 1918, during the closing stages of World War I, most physicians assumed it would behave in a similar way to previous flu epidemics and dismissed it as a nuisance. Few thought the pathogen might pose a mortal threat to young adults, much less to soldiers en route to the Allied lines in northern France. This was partly because they had been informed by no less an authority than Koch’s protégé, Richard Pfeiffer, that flu was transmitted by a tiny Gram-negative bacterium, and that it would only be a matter of time before bacteriologists trained in German laboratory methods had manufactured a vaccine against the influenza bacillus, just as they had against cholera, diphtheria, and typhoid. But Pfeiffer and those who put their faith in his experimental methods were wrong: influenza is not a bacterium but a virus that is too small to be seen through the lens of an ordinary optical microscope. Moreover, the virus passed straight through the porcelain filters then used to isolate bacteria commonly found in the nose and throat of influenza sufferers. Although some British and American researchers had begun to suspect that flu might be a “filter-passer,” it would be many years before Pfeiffer’s misconception would be corrected and influenza’s viral aetiology divined. In the meantime, many research hours were wasted and millions of young people perished.

However, it would be a mistake to think that simply knowing the identity of a pathogen and the aetiology of a disease is sufficient to bring an epidemic under control, for though the presence of an infectious microbe may be a necessary condition for ill health, it is rarely sufficient. Microbes interact with our immune systems in various ways, and a pathogen that causes disease in one person may leave another unaffected or only mildly inconvenienced. Indeed, many bacterial and viral infections can lie dormant in tissue and cells for decades before being reactivated by some extrinsic event or process, whether it be coinfection with another microbe, a sudden shock to the system due to an external stress, or the waning of immunity with old age. More importantly, by taking specific microbial predators as our focus we risk missing the bigger picture. For instance, the Ebola virus may be one of the deadliest pathogens known to humankind, but it is only when tropical rain forests are degraded by clear-cutting, dislodging from their roosts the bats in which the virus is presumed to reside between epidemics, or when people hunt chimpanzees infected with the virus and butcher them for the table, that Ebola risks spilling over into humans. And it is only when the blood-borne infection is amplified by poor hospital hygiene practices that it is likely to spread to the wider community and have a chance of reaching urban areas. In such circumstances, it is worth keeping in mind the view expressed by George

Bernard Shaw in *The Doctor's Dilemma*, namely that "The characteristic microbe of a disease might be a symptom instead of a cause." Indeed, updating Shaw's axiom for the present day, we might say that infectious diseases nearly always have wider environmental and social causes. Unless and until we take account of the ecological, immunological, and behavioural factors that govern the emergence and spread of novel pathogens, our knowledge of such microbes and their connection to disease is bound to be partial and incomplete.

In fairness, there have always been medical researchers prepared to take a more nuanced view of our complex interactions with microbes. For instance, in 1959 at the height of the antibiotics revolution, the Rockefeller researcher René Dubos railed against short-term technological fixes for medical problems. At a time when most of his colleagues took the conquest of infectious disease for granted and assumed that the eradication of the common bacterial causes of infections was just around the corner, Dubos, who had isolated the first commercial antibiotic in 1939 and knew what he was talking about, sounded a note of caution against the prevailing medical hubris. Comparing man to the "sorcerer's apprentice," he argued that medical science had set in motion "potentially destructive forces" that might one day usurp the dreams of a medical utopia. "Modern man believes that he has achieved almost completely mastery over the natural forces which molded his evolution in the past and that he can now control his own biological and cultural destiny," wrote Dubos. "But this may be an illusion. Like all other living things, he is part of an immensely complex ecological system and is bound to all its components by innumerable links." Instead, Dubos argued that complete freedom from disease was a "mirage" and that "at some unpredictable time and in some unforeseeable manner nature will strike back."[5]

Yet for all that Dubos's writings were hugely popular with the American public in the 1960s, his warnings of a coming disease Armageddon were largely ignored by his scientific colleagues. The result was that when, shortly after Dubos's death in 1982, the Centers for Disease Control and Prevention (CDC) coined the acronym AIDS, to describe an unusual autoimmune condition that had suddenly appeared in the homosexual community in Los Angeles and was now spreading to other segments of the population, it took the medical world by surprise. But really the CDC shouldn't have been surprised because something very similar had happened just eight years earlier when an outbreak of atypical pneumonia among a group of war veterans who had attended an American Legion convention at a luxury hotel in Philadelphia sparked widespread hysteria as epidemiologists scrambled to identify the "Philly Killer" (the outbreak initially flummoxed the CDC's disease detectives and it took a microbiologist to identify the pathogen, *Legionella pneumophila*, a tiny bacterium that thrives in aquatic environments, including the cooling towers of hotels). That year, 1976, saw not only a panic over Legionnaires' disease, but a panic over the sudden emergence of a new strain of swine flu at a US Army base in New Jersey—an emergence event for which the CDC and public health officials were likewise unprepared and that would eventually result in the needless vaccination of millions of Americans. And something very similar happened again in 2003 when an elderly Chinese professor of nephrology checked into the Metropole Hotel in Hong Kong, igniting cross-border outbreaks of a severe respiratory illness that was initially blamed on the H5N1 avian influenza virus but which we now know to have been due to a novel coronavirus[fn4] associated with SARS. In that case, a pandemic was averted by some nifty microbiological detective work and unprecedented cooperation between networks of scientists sharing information, but it was a close call, and since then we have seen several more unanticipated—and initially misdiagnosed—emergence events.

This is a book about these events and processes, and the reasons why, despite our best efforts to predict and prepare for them, they continue to take us by

surprise. Some of these epidemic histories, such as the panic over the 2014–16 Ebola epidemic or the hysteria over AIDS in the 1980s, will be familiar to readers; others, such as the pneumonic plague outbreak that erupted in the Mexican quarter of Los Angeles in 1924, or the great "parrot fever" panic that swept the United States a few months after the Wall Street Crash, less so. Whether familiar or not, however, each of these epidemics illustrates how quickly the received medical wisdom can be overturned by the emergence of new pathogens and how, in the absence of laboratory knowledge and effective vaccines and treatment drugs, such epidemics have an unusual power to provoke panic, hysteria, and dread.

Far from banishing panic, better medical knowledge and surveillance of infectious disease can also sow new fears, making people hyperaware of epidemic threats of which they had previously been ignorant. The result is that just as lifeguards now scan the sea for dorsal fins in the hope of forewarning bathers, so the World Health Organization (WHO) routinely scans the internet for reports of unusual disease outbreaks and tests for mutations that might signal the emergence of the next pandemic virus. To some extent this hypervigilance makes sense. But the price we pay is a permanent state of anxiety about the next Big One. It's not a question of *if* the Apocalypse will occur, we're repeatedly told, but *when*. In this febrile atmosphere it is not surprising that public health experts sometimes get it wrong and press the panic button when, in reality, no panic is warranted. Or, as in the case of the West African Ebola epidemic, misread the threat entirely.

To be sure, the media plays its part in these processes—after all, nothing sells like fear—but while 24/7 cable news channels and social media help to fuel the panic, hysteria, and stigma associated with infectious disease outbreaks, journalists and bloggers are, for the most part, merely messengers. I argue that by alerting us to new sources of infection and framing particular behaviours as "risky," it is medical science—and the science of epidemiology in particular—that is the ultimate source of these irrational and often prejudicial judgments. No one would wish to deny that better knowledge of the epidemiology and causes of infectious diseases has led to huge advances in preparedness for epidemics, or that technological advances in medicine have brought about immense improvements in health and well-being; nevertheless, we should recognize that this knowledge is constantly giving birth to new fears and anxieties.

Each epidemic canvassed in this book illustrates a different aspect of this process, showing how in each case the outbreak undermined confidence in the dominant medical and scientific paradigm, highlighting the dangers of overreliance on particular technologies at the expense of wider ecological insights into disease causation. Drawing on sociological and philosophical insights into the construction of scientific knowledge, I argue that what was "known" before the emergence event—that water towers and air conditioning systems *don't* present a risk to hotel guests and the occupants of hospitals, that Ebola *doesn't* circulate in West Africa and *can't* reach a major city, that Zika is a relatively harmless mosquito-borne illness—was shown to be false; and I explain how, in each case, the epidemics would spark much retrospective soul-searching about "known knowns" and "unknown unknowns"[fn5] and what scientists and public health experts should do to avoid such epistemological blind spots in the future.[6]

The epidemics canvassed in this book also underline the key role played by environmental, social, and cultural factors in changing patterns of disease prevalence and emergence. Recalling Dubos's insights into the ecology of pathogens, I argue that most cases of disease emergence can be traced to the disturbance of ecological equilibriums or alterations to the environments in which pathogens habitually reside. This is especially true of animal origin or zoonotic

viruses such as Ebola, but it is also true of commensal bacteria such as streptococci, the main cause of community-acquired pneumonias. The natural host of Ebola is thought to be a fruit bat. However, though antibodies to Ebola have been found in various species of bats indigenous to Africa, live virus has never been recovered from any of them. The reason, most likely, is that as with other viruses that are adapted to their hosts as a result of long evolutionary association, the Ebola virus is quickly cleared from the bloodstream by the bat's immune system, but not before, presumably, it has been transmitted to another bat. The result is that the virus circulates continually in bat populations, without leading to the destruction of either. A similar process occurs with pathogens that have evolved so as to infect only humans, such as measles and polio, with a first infection in childhood usually resulting in a mild illness, after which the subject recovers and enjoys lifelong immunity. However, every now and again these states of immunological balance are disrupted. This may occur naturally if, for instance, sufficient numbers of children escape infection in childhood to cause herd immunity to wane, or if the virus suddenly mutates, as occurs frequently with influenza, leading to the circulation of a new strain against which people have little or no immunity. But it can also occur when we accidentally interpose ourselves between the virus and its natural host. This is presumably what happened with Ebola in 2014 when children in Meliandou began taunting long-tailed bats roosting in a tree stump in the middle of their village. And it is thought that something very similar may have prompted the spillover[fn6] of the HIV progenitor virus from chimpanzees to humans in the Congo in the 1950s. Tracing the precise genesis of these epidemics is the subject of ongoing research. In the case of AIDS, there is little doubt that the inauguration of steamship travel on the Congo River at the turn of the twentieth century and the construction of new roads and railways in the colonial period were important contributing factors, as was the greed of loggers and timber companies. However, social and cultural factors also played a part: were it not for the practice of consuming bushmeat and widespread prostitution near the camps supplying labour to the rail and timber companies, the virus would probably not have spread so widely or been amplified so rapidly. Similarly, were it not for entrenched cultural beliefs and customs in West Africa—in particular, people's adherence to traditional burial rituals and their distrust of scientific medicine—it is unlikely that Ebola would have morphed into a major regional epidemic, let alone a global health crisis.

However, perhaps the most important insight medical history can bring is the long association between epidemics and war. Ever since Pericles ordered Athenians to sit out the Spartan siege of their harbour city in 430 BC, wars have been seen as progenitors of deadly outbreaks of infectious disease (this was certainly the case in West Africa in 2014, where decades of civil war and armed conflict had left Liberia and Sierra Leone with weak and under-resourced health systems). Though the pathogen responsible for the plague of Athens has never been identified and perhaps never will be (candidates include anthrax, smallpox, typhus, and malaria), there is little doubt that the decisive factor was the crowding of upwards of 300,000 Athenians and refugees from Attica behind the Long Walls of the Greek city. That confinement created the ideal conditions for the amplification of the virus—if virus it was—turning Athens into a charnel house (as Thucydides informs us, as there were no houses to receive the refugees from the countryside "they had to be lodged at the hot season of the year in stifling cabins, where the mortality raged without restraint"). The result was that by the third wave of the disease in 426 BC, Athens's population had been reduced by between one-quarter and one-third.[7]

In the case of the Athenian plague, for reasons that are unclear, the disease does not appear to have affected the Spartans, or spread far beyond the borders

of Attica. But 2,000 years ago, towns and cities were more isolated and there was far less passage of people and pathogens between countries and continents. Unfortunately, this is not the case today. Thanks to global trade and travel, novel viruses and their vectors are continually crossing borders and international time zones, and in each place they encounter a different mix of ecological and immunological conditions. This was nowhere more true than during World War I, when the congregation of tens of thousands of young American recruits in training camps on the eastern seaboard of the United States and their subsequent passage to and from Europe provided the ideal conditions for the deadliest outbreak of pandemic disease in history.

1
The Blue Death

It was an unassuming village, much like any you would have encountered on a rural tour of New England in 1917. Blink and you might have missed it. Set in drab scrubland thirty-five miles northwest of Boston, Ayer comprised fewer than three hundred cottage-like dwellings, plus a church and a couple of stores. Indeed, were it not for the fact that the village sat at the junction of the Boston and Maine and Worcester and Nashua railroads and boasted two stations, there would have been little to recommend it. But in the spring of 1917, as America prepared to go to war and military planners began looking for suitable sites to train thousands of men responding to the draft, those railroad stations and empty fields marked Ayer out as special, unusual even. Perhaps that is why in May 1917 someone in Washington, DC stuck a pin with a red flag in a map of Lowell County, Massachusetts, and designated Ayer as the site of the cantonment of the new Seventy-Sixth Division of the US Army.

In early June leases were signed with owners of some 9,000 acres of treeless "sprout" land adjacent to the Nashua River, and two weeks later engineers arrived to transform the site into a camp fit for Major General John Pershing's doughboys. In the space of just ten weeks, engineers constructed 1,400 buildings, installed 2,200 shower baths, and laid sixty miles of heating pipes. Measuring seven miles by two, the cantonment contained its own restaurant, bakery, theatre, and fourteen huts for reading and fraternizing, plus a post and telegraph office. Arriving from Ayer—a short half-mile walk that led across the tracks of the Fitchburg railroad—the first sight to greet newly drafted men was the huge YMCA auditorium and the barracks of the 301st engineers. To the right lay the barracks of the 301st, 302nd, and 303rd infantry divisions, and nearby, those for the field artillery, depot brigade, and machine-gun brigade. Beyond that lay fields for practicing drill and bayoneting skills, and an eight-hundred-bed hospital, also run by the YMCA. In all, the cantonment was capable of housing 30,000 men. But over the next few weeks, as raw recruits arrived from Maine, Rhode Island, Connecticut, New York, Minnesota, and as far south as Florida, the rough wooden barracks would be filled with in excess of 40,000 men, forcing engineers to erect tents for the overflow. In recognition of its importance to the north-eastern military command, the cantonment was named Camp Devens in honour of General Charles Devens, a Boston lawyer turned Civil War commander whose Union troops were the first to occupy Richmond after its fall in 1865. As Roger Batchelder, a propagandist for the War Department, put it, admiring Camp Devens from a hill outside Ayer in December 1917, the cantonment resembled nothing so much as a "huge city of soldiers."[1] What the observer did not say was that Devens also represented an unprecedented immunological experiment. Never before had so many men from so many different walks of life—factory workers and farmhands, machinists and

college graduates—been brought together in such numbers and forced to live cheek by jowl.

Camp Devens was not the only camp to be hastily constructed that summer, nor was it the biggest. In all, draftees destined for the American Expeditionary Force would be sent for training to forty large camps across the United States. Some, such as Camp Funston, built on the site of a former cavalry station at Fort Riley, Kansas, accommodated as many as 55,000 men. Meanwhile, on the opposite side of the Atlantic at Étaples in northern France, the British had constructed an even larger facility. Built on low-lying meadows adjoining the railway line from Boulogne to Paris, Étaples had bunks for up to 100,000 British and Imperial troops and hospital beds for 22,000. In the course of the war, it is estimated that one million soldiers passed through Étaples en route to the Somme and other battlegrounds.

Nor were the facilities at many of these camps always as good as war supporters suggested. Indeed, in many cases mobilization had been so swift that engineers had been unable to complete the construction of hospitals and other medical facilities in time, and barracks were often so drafty that men were forced to huddle around stoves in the evening to keep warm and to sleep in extra layers of clothing at night. Some, such as Batchelder, saw this as a way of toughening recruits and preparing them for the hardships of trench warfare in northern France. "At Ayer it is cold, but … the cold weather is exhilarating; it inures the men who have always lived in hot houses to the out-door life."[2] However, others criticized the War Department for selecting a site so far north, saying it would have been better if Devens had been located in the South where the weather was more hospitable.

In truth, the principal danger was not the cold so much as the overcrowding. By bringing together men from so many different immunological backgrounds and forcing them to live at close quarters for weeks on end, the mobilization greatly increased the risk of communicable diseases being spread from one to another. Wars have always been incubators of disease, of course. What was different in 1917 was the scale of the call-up and the intermixing of men raised in very different ecological settings. In urban areas, where populations are denser, the chances of being exposed to measles or common respiratory pathogens, such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, is far higher and usually occurs in childhood. By contrast, in an era before cars and buses, when children raised in rural areas tended to be educated at primary schools close to their homes, many avoided exposure to measles. Nor would many have been exposed to *Streptococcus pyrogenes* and other haemolyticus bacteria that cause "strep throat." The result was that as the US Army grew from 378,000 in April 1917 to a force of 1.5 million by the turn of 1918 (by the war's end, in November 1918, the combined strength of the US Army and Navy would be 4.7 million), epidemics of measles and pneumonia erupted at camps all along the eastern seaboard, as well as in several southern states.[3]

Prior to the introduction of antibiotics, pneumonia accounted for roughly one-quarter of all deaths in the United States. These pneumonias could be triggered by bacteria, viruses, fungi, or parasites, but by far the largest source of community-acquired outbreaks were pneumococcal bacteria (*Streptococcus pneumoniae*). Under the microscope these pneumococcal bacteria resemble any other streptococcus. However, one of *S. pneumoniae*'s unusual features is that it possesses a polysaccharide (sugar) capsule that protects it from drying out in air or being ingested by phagocytes, one of the immune system's principal cellular defences. Indeed, in moist sputum in a darkened room, pneumococci can survive on surfaces for up to ten days

Worldwide, there are more than eighty subtypes of pneumococcal bacteria, each one differing from the others in terms of the constitution of its capsule. For the

most part, these bacteria reside in the nose and throat without causing illness, but if a person's immune system is impaired or compromised by another disease, such as measles or influenza, the bacteria can get the upper hand, triggering potentially fatal lung infections. Typically, such infections begin as an inflammation of the alveoli, the microscopic sacs that absorb oxygen in the lungs. As the bacteria invade the alveoli, they are pursued by leukocytes and other immune cells, as well as fluids containing proteins and enzymes. As the air sacs fill they become "consolidated" with material, making it harder for them to transfer oxygen to the blood. Usually, this consolidation appears in patches surrounding the bronchi—the passages which branch from the bronchus, the tube that carries air from the trachea into the right and left lungs. When this consolidation is localized it is known as bronchopneumonia. However, in more severe infections, this consolidation can spread across entire lobes (the right lung has three, the left two) turning the lungs into a solid, liverlike mass. The effect on lung tissue is dramatic. A healthy lung is spongy and porous and a good conductor of sound. When a doctor listens to the breathing of a healthy patient through a stethoscope he or she should hear very little. By contrast, a congested lung conducts breathing sounds to the wall of the chest, resulting in rattling or cracking sounds known as rales.

In the late Victorian and Edwardian period, pneumonia was perhaps the most feared disease after tuberculosis and nearly always fatal, particularly in the elderly or those whose immune systems were compromised by other diseases. Prominent victims included the ninth president of the United States, William Henry Harrison, who died one month after his inauguration in 1841, and the Confederate general Thomas Jonathan "Stonewall" Jackson, who died of complications of pneumonia eight days after being wounded at the Battle of Chancellorsville in 1863. Another victim was Queen Victoria's grandson, the Duke of Clarence, who suffered a fatal case of double lobar pneumonia after contracting "Russian influenza" at Sandringham in the winter of 1892. Little wonder then that Sir William Osler, the so-called father of modern medicine, dubbed pneumonia the "Captain of the Men of Death."[4]

When contracted in childhood measles usually results in a rash and high fever accompanied by a violent cough and sensitivity to light, but in the case of the camp-acquired measles cases the symptoms were far more severe. The outbreaks produced the highest infection rates the army had seen in ninety-seven years and were often accompanied by an aggressive bronchopneumonia. The result was that between September 1917 and March 1918, more than 30,000 American troops were hospitalized with pneumonia, nearly all as a result of complications of measles, and some 5,700 died. The extent of the outbreaks astonished even battle-hardened doctors, such as Victor Vaughan, the dean of the University of Michigan's School of Medicine and a veteran of the Spanish-American War. "Not a troop train came into Camp Wheeler (near Macon, Georgia) in the fall of 1917 without bringing one to six cases of measles already in the eruptive stage," he wrote. "These men had brought the infection from their homes and had distributed its seed at the state encampment and on the train. No power on earth could stop the spread of measles through a camp under these conditions. Cases developed, from one hundred to five hundred a day, and the infection continued as long as there was susceptible material in the camp."[5]

By the spring of 1918 the War Department was being lambasted by Congress for shipping recruits to training camps before facilities were fully ready and under conditions that failed to meet basic standards of public health, and by July the department had appointed a pneumonia commission to investigate the unusual prevalence of the disease in the large cantonments. The commission read like a future who's who of American medicine, and included Eugenie L. Opie, the future dean of Washington University School of Medicine; Francis G. Blake, who would

go on to become professor of internal medicine at Yale University; and Thomas Rivers, who would become one of the world's leading virologists and director of the Rockefeller University hospital in New York. Assisting them in the surgeon general's office with the rank of commanders were Victor Vaughan and William H. Welch, the dean of the Johns Hopkins School of Medicine and then the most famous pathologist and bacteriologist in America, and Rufus Cole, the first director of the Rockefeller University Hospital and a specialist in pneumococcal disease. Together with his assistant Oswald Avery, Cole would direct laboratory investigations of the pneumonia outbreaks and train medical officers in the correct techniques for culturing the bacteria and making serums and vaccines. Meanwhile, keeping a watch over their endeavours would be Simon Flexner, the head of the Rockefeller Institute and a former student and protégé of Welch.

* * *

While American physicians were worrying about camp-acquired measles and pneumonia cases, medics in the British Army were becoming concerned about another respiratory disease. Labelled "purulent bronchitis" for want of a better term, the disease had broken out at Étaples in the bitterly cold winter of 1917, and by February 156 soldiers were dead. The initial stages resembled ordinary lobar pneumonia—a high fever and the expectoration of blood-streaked sputum. But these symptoms soon gave way to a racing pulse accompanied by the discharge of thick pale yellow dollops of pus, suggesting bronchitis. In half of these cases death from "lung block" followed soon after.

Another striking feature was cyanosis. This condition occurs when a patient becomes breathless because the lungs can no longer transfer oxygen efficiently to the blood and is characterized by a dusky purple-blue discolouration of the face, lips, and ears (it is oxygen that turns blood in the arteries red). However, in the case of the Étaples patients, their breathlessness was so acute that they tore off their bedclothes in distress. At autopsy, the pathologist, William Rolland, was shocked to find a thick, yellowish pus blocking the bronchi. In the larger bronchi, the pus was mixed with air, but when he cut a section through the smaller tubes he wrote, "the pus exudes spontaneously … with little or no admixture of air."[6] This explained why the attempt to relieve patients' symptoms by giving them piped oxygen had been of little use. Étaples was not the only army camp where this peculiar disease appeared. In March 1917 a similar outbreak had occurred at Aldershot, "The Home of the British Army," in southern England. Once again the disease proved fatal to half to those it infected, the signature feature being the exudation of a yellowish pus followed by breathlessness and cyanosis. Of the cyanosed patients, physicians noted, "no treatment that we have been able to devise appears to do any good." To some, the short shallow breathing recalled the "effects of gas poisoning,"[7] but later the bacteriologists and pathologists who examined the Aldershot and Étaples cases became convinced it had been a type of influenza.[8] Flu had long been recognized as a trigger for bronchial infections. During influenza epidemics and the seasonal outbreaks of the disease which occurred every fall and winter, epidemiologists were accustomed to seeing a spike in respiratory deaths, particularly among the very young or elderly sections of the population. But for young adults and those below the age of seventy, flu was considered more of a nuisance than a mortal threat to life, and convalescents were frequently viewed with suspicion.

* * *

We may never know whether the outbreaks at Étaples and Aldershot were flu, but in March 1918 another unusual respiratory outbreak visited a large army camp—this time at Camp Funston in Kansas. Initially, physicians thought they were seeing another wave of camp-acquired pneumonias, but they soon revised their opinion.

The first casualty was supposedly the camp cook. On 4 March, he woke with a splitting headache and aches in his neck and back and reported to the base hospital. Soon, one hundred other members of the 164th Depot Brigade had joined him, and by the third week in March more than 1,200 men were on the sick list, forcing Fort Riley's chief medical officer to requisition a hangar adjacent to the hospital for the overflow. The illness resembled classic influenza: chills followed by high fever, sore throat, headache, and abdominal pains. However, many patients were so incapacitated that they found it impossible to stand up; hence the malady's nickname, "knock-me-down fever." Most of the men recovered within three to five days, but, disturbingly, several went on to develop severe pneumonias. Unlike the pneumonias after measles, which tended to localize in the bronchi, these post-influenzal pneumonias frequently extended to the entire lobe of a lung. In all, such lobar pneumonias had developed in 237 men, roughly one-fifth of those hospitalized, and by May there had been 75 deaths. As Opie and Rivers discovered the following July when the pneumonia commission eventually arrived to conduct an investigation, there were other disturbing features, too: after the initial epidemic had petered out in March there had been further outbreaks in April and May, each one corresponding to the arrival of a new group of draftees.[9] Not only that, but men transferred to camps in the East appeared to carry the disease with them, and when many of these same men joined the American Expeditionary Force and mingled freely with soldiers sailing for Europe, they sparked further outbreaks on board Atlantic troopships. The pattern continued when the transports arrived at Brest, the main disembarkation point for American troops, and disgorged their cargo. "Epidemic of acute infectious fever, nature unknown," reported a medical officer at a US Army hospital in Bordeaux on 15 April. By May, "grippe" had broken out in the French lines and scores of British soldiers at Étaples were sick with PUO—"pyrexia of unknown origin." As at Funston, the initial cases were mild but by June thousands of Allied troops were being hospitalized, and by August alarm was mounting. "These successive outbreaks tended to be progressively more severe both in character and extent, which would speak for an increasing virulence of the causative agent," observed Alan M. Chesney, a medical officer at an AEF artillery training camp in Valdahon.[10]

Chesney's was a rare example of concern. In the summer of 1918 no one had experienced a pandemic of influenza for twenty-eight years. Compared to typhus, a deadly blood-borne disease spread by lice that lived in soldiers' clothing, or the septicaemia that bred in gunshot and shrapnel wounds, influenza was a trifling infection from the point of view of army medical officers. Civilian physicians regarded flu with similar disdain, particularly the British, who had long considered influenza a suspect Italian word for a bad cold or catarrh.[fn1] Besides, after nearly five years of brutal trench warfare which had already claimed the lives of tens of thousands of Europeans, and with two million Allied troops now dug in in northern France and Flanders, officers had more pressing issues on their minds. "Quite 1/3 of the Batt. and about 30 officers are smitten with the Spanish Flu," the poet Wilfred Owen informed his mother, Susan, disdainfully in a letter from a British Army camp in Scarborough, North Yorkshire, in June. "The thing is much too common for me to take part in. I have quite decided not to! Imagine the work that falls on unaffected officers."[11]

Owen was wrong to be so complacent. Between the summer of 1918 and the spring of 1919, tens of thousands of soldiers and millions of civilians would be

mown down by Spanish flu (so-called because Spain was the only country not to censor reports of the spreading epidemic) as the disease ricocheted between America and northern Europe before engulfing the entire globe. In the United States alone, some 675,000 Americans would perish in the successive waves of flu; in France, perhaps as many as 400,000; in Britain, 228,000. Worldwide, the death toll from the Spanish flu pandemic has been estimated at 50 million—five times as many as died in the fighting in World War One and 10 million more than AIDS has killed in thirty years.

One reason Owen and others were so relaxed about influenza was that in 1918 medical scientists were confident that they knew how the disease was transmitted. After all, in 1892 Richard Pfeiffer, the son-in-law of Robert Koch, the German "father" of bacteriology, had announced that he had identified the disease's "exciting cause," a tiny Gram-negative bacterium he dubbed *Bacillus influenzae*. Pfeiffer's "discovery" came at the height of the so-called Russian influenza pandemic and made headline news around the world, fuelling expectations that it would only be a matter of time before scientists trained in German laboratory techniques had produced a vaccine. Never mind that other researchers were not always able to isolate "Pfeiffer's bacillus," as the bacterium was popularly known, from the throat washings and bronchial expectorations of influenza patients. Or that it was notoriously difficult to cultivate the bacteria on artificial media and it often took several attempts to grow colonies of sufficient size that the small, spherical, and colourless bodies could be visualized through a microscope using special dyes. Or that despite inoculating monkeys with the bacillus, Pfeiffer and his Berlin colleague, Shibashuro Kitasato, had so far been unable to transfer the disease, thereby failing the test of Koch's fourth postulate.[12] As far as most medical authorities were concerned, Pfeiffer's bacillus *was* the aetiological agent of influenza and that was that. Rare was the man of science who dared to challenge the authority of Koch and his disciples by expressing unease at the failure to find the bacillus in each and every case of influenza.

Perhaps that explains why, on arriving at Camp Funston in July, Opie, Blake, and Rivers had ignored the fact that researchers had failed to find *Bacillus influenzae* in 77 per cent of the pneumonia cases, or that the bacillus had also been isolated from the mouths of one-third of the healthy men, i.e., those who had *not* shown any signs or symptoms of influenza.[fn2] Instead, they tried to make sense of the higher pneumonia attack rates observed among African American draftees from Louisiana and Mississippi, an incidence they attributed to racial differences between white and "coloured" troops. This was despite observing that the units that had suffered most severely from post-influenzal pneumonias were the ones that were new to the camp and had only been at Fort Riley for three to six months, and that a greater proportion of the African American draftees came from rural areas.[13] For the most part, the survey was dull, repetitive work and Blake soon found himself longing for a change of scene. As he complained to his wife on 9 August, "No letter from my beloved for two days. No cool days, no cool nights, no drinks, no movies, no dances, no club, no pretty women, no shower bath, no poker, no people, no fun, no joy, no nothing save heat and blistering sun and scorching winds and sweat and dust and thirst and long and stifling nights and working all hours and lonesomeness and general hell—that's Fort Riley, Kansas."[14]

Very soon Opie, Blake, and Rivers would get orders to leave Kansas, only to be thrust into a far worse hell when they found themselves in the midst of a raging epidemic of influenza and pneumonia at Camp Pike, Arkansas. They were spared the worst hell of all, however.

* * *

In August 1918, Clifton Skillings, a 23-year-old farmer from Ripley, Maine, boarded a southbound Boston train. Like thousands of other American men of fighting age, Skillings had received his draft papers a few weeks earlier and had now been ordered to report for duty to Camp Devens. Alighting at Ayer, he fell into step with other draftees dressed in their Sunday best and began striding toward the camp, with a trooper on horseback leading the way. To the eyes of the Boston men, Ayer was a "hick town."[15] Whether Skillings thought it so he does not say, but to judge by his letters and his postcards he did not care particularly for the food. "We have your beans at noon but they are not like the beans you get at home," he complained to his family on 24 August. "It makes me think of mixing up dog food." Skillings immediately fell in with a group from Skowhegan, Maine, but was amazed to learn that the camp included men from midwestern states such as Minnesota. "There is a good many thousand men in this campground. It seems awful funny to see nothing but men … I wish you folks could come in & look around." Four weeks later the size of the camp and the quality of food is the least of his concerns, however. "Lots of the boys are sick and in the hospital," he wrote home on 23 September. "It is a disease. Some [thing] like the Gripp … I don't think I will get it."[16]

It's not known where the fall wave of influenza originated. It could have been incubating in America over the summer, but more likely it was introduced by troops returning from Europe. From an ecological point of view, northern France was a vast biological experiment—a place where large masses of men from two continents converged and mingled freely with men from a host of other nations, including Indian soldiers from the Punjab, African regiments from Nigeria and Sierra Leone, Chinese "coolies," and Indochinese labourers from Vietnam, Laos, and Cambodia. One theory is that the second wave began with an outbreak at a coaling station in Sierra Leone at the end of August, from whence it spread rapidly to other West African countries and to Europe via British naval vessels.[17] Another is that the bug was already in Europe, hence the pre-pandemic waves recorded in Copenhagen and other northern European cities in July.[18]

In the United States, the second wave had first announced itself toward the end of August at Commonwealth Pier in Boston, one of the main entry points for returning AEF troops, when several sailors were suddenly taken ill. By 29 August, fifty had been transferred to the Chelsea Naval Hospital, where they came under the care of Lieutenant Commander Milton Rosenau, a former director of the US Public Health Service's Hygienic Laboratory and a member of Harvard Medical School. Rosenau isolated the sailors in an effort to contain the outbreak, but by early September US naval stations in Newport, Rhode Island, and New London, Connecticut, were also reporting significant numbers of flu cases.[19] At around the same time, Devens saw an increase in pneumonia cases. Then, on 7 September, a soldier from Company B, 42nd infantry, was admitted to the base hospital with "epidemic meningitis." In fact, his symptoms—runny nose, sore throat, and inflammation of the nasal passages—were consistent with influenza, and when the following day twelve more men from the same company fell ill with similar symptoms, doctors had no hesitation in labelling it a "mild" form of Spanish influenza.[20] It would not remain mild for long.

When a parasitic organism meets a susceptible host for the first time, it triggers an arms race between the pathogen and the host's immune system. Having never encountered the pathogen before, the immune system is initially blindsided and takes time to mobilize its defences and launch a counterattack. With nothing to stop it, the pathogen tears through the host's tissue, invading cells and multiplying at will. At this stage, the parasite resembles a child having a tantrum. With no one

and nothing to discipline it, its tantrum can easily escalate and its behaviour can become increasingly virulent. Eventually, in the most extreme cases of all, its rage may become all-consuming. This is usually bad news for the host. From a Darwinian point of view, however, the parasite does not want to kill its host; its primary objective is to survive long enough to escape and infect a new susceptible. In other words, the death of the host is a bad strategy for a parasite, an "accident" of biology if you will. A far better survival strategy over the long term is to evolve in the other direction, toward avirulence, resulting in an infection that is mild or barely detectable in the host. But in order for that to happen, the immune system must first find a way of taming the parasite.

It did not take long for the infection to spread from the 42nd infantry to adjacent barracks, and when it did, the flu was nothing like the "mild" spring wave. It was explosive. By 10 September more than five hundred men had been admitted to the base hospital at Devens. Within four days, those numbers had tripled, and on 15 September a further 705 were admitted. The next three days were the worst, however. On 16 September medical orderlies had to find beds for a further 1,189 men and the following day beds for 2,200 more. The pneumonia cases began to mount soon afterward, but they were nothing like the bronchopneumonias associated with measles. Instead, they resembled more severe versions of the lobar pneumonias that had developed in some of the flu cases at Camp Funston in the spring. "These men start with what appears to be an ordinary attack of *La Grippe* or Influenza, and when brought to the Hosp. they very rapidly develop the most vicious type of Pneumonia that has ever been seen," recalled a Scottish physician named Roy, who was present when pneumonia ripped through the wards. "Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the coloured men from the white …. One could stand it to see, one, two or twenty men die, but to see these poor devils dropping like flies … is horrible."[21]

As the writer John Barry noted in his book *The Great Influenza*, in 1918 these cyanoses were so extreme that victims' entire bodies would take on a dark purple hue, sparking "rumours that the disease was not influenza, but the Black Death."[22] British Army medical officers, many, like Welch and Vaughan, experienced civilian physicians and pathologists who had taken military commissions at the outset of war, were similarly impressed by these cyanotic cases and, struck by the resemblance to the cyanoses seen at Étaples and Aldershot in the winter of 1917, commissioned an artist from the Royal Academy to paint patients in the last throes of illness. The artist labelled the final stage "heliotrope cyanosis" after the deep blue flowers of the same name beloved by English gardeners.[23]

As concerns about measles and pneumonia had grown over the summer, the surgeon general's office in Washington had kept Welch, Vaughan and Cole busy. They were sent to make an inspection of Camp Wheeler, near Macon, Georgia, and other camps in the South. On leaving Macon in early September, Welch had suggested they stop at the Mountain Meadows Inn, a fashionable retreat in Asheville, North Carolina. A portly man famous for his love of cigars and gourmet dining, Welch was now in his late sixties and, except for a strip of white around the ears, almost completely bald. To offset the absence of hair on top, he sported a fashionable goatee and moustache, which were also white. To some this gave him the appearance of an elder statesmen—an impression underscored by his reputation for being an aloof and distracted teacher. But that was the older Welch. In his youth his imagination had been fired by reports from Germany of the advances being made in the understanding of disease processes using the

colonies of the bacillus, the next step was to stain it with an appropriate dye, wash it with alcohol, then stain it again with a contrasting dye (Gram-positive bacteria retain crystal violet stains, whereas *B. influenzae* and other Gram-negative bacteria, such as mycobacteria, require red counterstains).[32] Such stains could also be applied directly to slides smeared with sputum from influenza cases. However, a more precise and conclusive method was to prepare pure cultures of the bacillus by inoculating mice with sputum from flu patients and then growing the bacteria from fluids taken from the mice and reintroduced to the blood agar media.

Like other researchers, Avery at first found it difficult to grow Pfeiffer's bacillus from the sputum and bronchial expectorations of flu victims, so, to increase his chances, he refined his methods, adding acids to his agar culture medium and substituting defibrinated blood for untreated blood (other researchers heated the blood or filtered and dried it to separate the haemoglobin from the fibrin). Gradually, as Avery perfected his techniques, he was able to find the bacillus more and more frequently, until he was able to tell Welch it was present in twenty-two of thirty dead soldiers examined at Devens. Wolbach's results were even more definitive: he had found the bacillus in every case he examined at Brigham Hospital. That was enough for Welch, Cole, and Vaughan. "It is established that the influenza at Camp Devens is caused by the bacillus of Pfeiffer," they wired the surgeon general on 27 September.[33]

* * *

In fact, influenza is a viral infection. *B. influenzae* is merely a fellow traveller. Like other bacteria commonly found in the mouths, throats, and lungs of influenza patients, it is not the primary cause of the disease, though it may play a role in secondary infections.[34] However, in the fall of 1918 no one knew this, though some researchers had begun to suspect it. Instead, failure to cultivate *B. influenzae* reflected badly on researchers, not the theory of bacterial causation. Indeed, so dominant was the scientific view that influenza was a bacterial infection that, rather than doubt Pfeiffer's claim, scientists chose to doubt their instruments and methods. If the bacillus could not be cultivated on the first attempt, they needed to improve their culture medium, refine their dyes, and try again.

Anomalies are a common occurrence in science. No two experiments are ever exactly alike, but by refining methods and sharing tools and technologies, scientists are broadly able to reproduce each other's observations and findings, thereby arriving at a consensus that this or that interpretation of the world is correct. That is how knowledge emerges and a particular paradigm comes to be adopted. However, there is no such thing as absolute certainty in science. Paradigms are constantly being refined by new observations and, if enough anomalies are found, faith in the paradigm may be undermined and a new one may come to supplant it. Indeed, the best scientists welcome anomalies and uncertainty as this is the way scientific knowledge advances.

When Pfeiffer first put forward his claim for the aetiological role of his bacillus, the science of bacteriology and the germ-theory paradigm (one germ, one disease) was in the ascendancy. With the invention of improved achromatic lenses and better culture-staining techniques, by the late 1880s Robert Koch and Louis Pasteur had brought a series of hitherto hard-to-detect germs into view. These included not only such landmark bacteria as the bacilli of fowl cholera and tuberculosis, but streptococcus and staphylococcus. In short order, their discoveries paved the way for the development of serums and bacterial vaccines against diseases such as cholera, typhoid and plague, and by the eve of World War I, Avery and Cole were using the same methods to develop vaccines for pneumococcal pneumonias.

When Pfeiffer made his announcement in 1892, it raised hopes that it would not be long before bacteriology had also delivered a vaccine for influenza. But from the beginning, Pfeiffer's claim was dogged by doubts and anomalous observations. The first problem was that Pfeiffer had failed to find *B. influenzae* in the majority of clinical cases he had examined in Berlin during the Russian influenza epidemic. Second, as noted previously, he had been unable to reproduce the disease in monkeys inoculated with pure cultures of the bacillus (Pfeiffer does not specify what type of monkey he used, but his failure may have been because many monkeys are a poor refractory species for human influenzas).[35] Soon afterwards, Edward Klein, a Vienna-trained histologist and author of the leading British textbook on bacteriology, succeeded in isolating the bacillus from a series of patients admitted to hospitals in London during the same epidemic of Russian flu. However, Klein also noted finding "crowds" of other bacteria in sputum cultures and observed that as the condition of influenza patients improved, it became progressively more difficult to find Pfeiffer's bacillus in the colonies on the agar plating medium used to grow bacteria. Finally, Klein noted that *B. influenzae* had also been isolated from patients suffering diseases *other than* influenza.

After 1892, the Russian influenza epidemic abated and it was no longer possible to conduct bacteriological exams of influenza patients. Now and then there would be a resurgence of Russian flu, however, and investigators would attempt to culture the bacillus from the sputum and lung secretions of convalescents. Sometimes these efforts succeeded, but just as often they did not. For instance, in 1906 David J. Davis, from the Memorial Institute for Infectious Disease in Chicago, reported being able to isolate the bacillus in only three of seventeen cases of influenza. By contrast he had found the bacillus in all but five of sixty-one cases of whooping cough. The following year, W. D'Este Emery, clinical pathologist at King's College London, noted that *B. influenzae* grew more readily in culture in the presence of other respiratory bacteria and seemed to be more virulent for animals in the presence of killed streptococci, leading him to speculate that Pfeiffer's bacillus might, for the most part, be a "harmless saprophyte" and that it required other respiratory pathogens to make it pathogenic.[36]

With the emergence of Spanish flu in 1918, researchers were able to resume their investigations. Again, the results were mixed, and again the anomalies cast doubt on Pfeiffer's claim. By the summer, concerns had reached such a pitch that a special meeting was convened at the Munich Medical Union. Summarizing the debate, *The Lancet* wrote that "Pfeiffer's bacillus has been found but exceptionally," and that if any bacteria had a claim to be the cause of influenza it should be the far more common streptococci and pneumococci.[37] Britain's Royal College of Physicians concurred, arguing that there was "insufficient evidence" for Pfeiffer's claim, though it was happy to allow that the bacillus played an important secondary role in fatal respiratory complications of influenza.[38] In other words, the aetiological role of *B. influenzae* might be open to question, but the bacterial paradigm was not. However, this paradigm was now facing a serious challenge from another quarter.

If Koch was the German father of bacteriology, then Louis Pasteur was its French parent or, as one writer puts it, microbiology's "lynchpin."[39] In his first biological paper, published in 1857 at the age of 35, Pasteur, then a relatively unknown French chemist working in Lille, boldly formulated what he called the germ theory of fermentation—namely, that each particular type of fermentation is caused by a specific kind of microbe. In the same paper he suggested that this theory could be generalized into a specific microbial aetiology of disease and, later, a general biological principle captured by his phrase, "Life is the germ, and

the germ is life." However, in his own lifetime Pasteur's fame rested on a famous set of public experiments conducted two decades later, in which he isolated the bacteria of anthrax and chicken cholera and, using basic chemical techniques (heat or exposure to oxygen), weakened the microbes to the point where they lost their virulence. Next, he demonstrated that these weakened strains could confer protection to animals challenged with fully virulent versions of the same bacteria. In so doing, Pasteur opened up a whole new branch of microbiology: the study of immunology. Pasteur realized that weak or attenuated microbes stimulated the host (sheep in the case of anthrax; chickens in the case of cholera) to produce substances (antibodies) that protected them against challenge with more virulent, disease-causing microbes. Eight years later, in 1885, Pasteur conducted an even more astounding microbiological experiment by applying the same principles to the rabies virus. Taking the spinal cord from a rabid dog, he injected the diseased material into a rabbit, and, when the rabbit fell ill, repeated the procedure with another rabbit. By passaging the virus in rabbits every few days, he was able to heighten its virulence for rabbits, but reduce its virulence for dogs. Next, he went a stage further and removed the spinal cord of a dead rabbit and dried it for fourteen days. This new attenuated virus no longer caused disease in dogs at all. Instead, it immunized them against challenge with fully virulent rabies. Next, Pasteur staged a daring public demonstration by administering his vaccine to a nine-year-old boy, Joseph Meister, who had been bitten in fourteen places by a rabid dog. Meister made a rapid recovery, prompting banner headlines. Other than smallpox, this was the first successful immunization with a virus vaccine, and within a few months Pasteur was inundated with requests from victims of rabid animal attacks from Smolensk to Seville. However, perhaps the most remarkable aspect of Pasteur's breakthrough in retrospect is that he developed the vaccine without being able to see the rabies virus or having much idea what a virus was. The reason is that rabies, like other viruses, is too small to be seen through an optical microscope (it measures 150 nanometres, or 0.15 micrometres, and requires magnifications ten thousand times greater than were available in Pasteur's day). But although Pasteur could not visualize the virus or cultivate it in the laboratory, he could intuit its existence by excluding microbes that he *could* grow and see, i.e., bacteria. Indeed, in 1892, the same year that Pfeiffer had claimed that a bacillus was the cause of influenza, the Russian botanist Dmitry Ivanovski had shown that tobacco mosaic disease was caused by an unseen agent that passed through porcelain filters with pores too small to admit bacteria. By the turn of the century, these filters, known as Chamberland filters after their inventor Charles Chamberland, were being manufactured and used in research laboratories in Europe and elsewhere, leading to the identification of a variety of "filter passing" agents, including the agents of foot and mouth disease of cattle, bovine pleuropneumonia, rabbit myxomatosis and African horse sickness. Then, in 1902, a commission headed by US Army Surgeon Walter Reed identified the first filter-passing human disease, yellow fever.[40] At the Pasteur Institute in Paris, these agents were referred to as "*virus filtrants*"—"filter-passing viruses."

After his death in 1885, Pasteur's disciples, such as Emile Roux and Roux's star pupil Charles Nicolle, continued these investigations. Dividing his time between biomedical research and administrative duties—it was Roux who created the Pasteur Institute—by 1902 Roux had identified ten diseases that he believed were due to filter-passing viruses. The same year, he persuaded Nicolle to join the Pasteur Institute in Tunis. Though greatly attracted by literature, Nicolle had bowed to the wish of his physician father and studied medicine, but while practicing in Rouen had suffered a hearing loss that prevented him from effectively using a stethoscope—an accident that may have persuaded him to concentrate on bacteriology instead and accept the position in North Africa. Nicolle quickly

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