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Chapter 8
Bacteriophage: The virus that revealed DNA

'Professor Max Gottlieb was about to assassinate a guinea pig with anthrax germs, and the bacteriology class were nervous. They had studied the forms of bacteria, they had handled Petri dishes and platinum loops . . . and they had now come to . . . the inoculation of a living animal with a swift disease. These two beady-eyed guinea pigs, chittering in a battery jar, would in two days be stiff and dead.'

This scene, from Sinclair Lewis's 1925 novel *Arrowsmith*, dramatizes the predicament facing the medical profession in the early twentieth century; in all too many cases, they were still better at killing than at curing. Thanks to Louis Pasteur, Robert Koch (with whom the fictional Gottlieb is supposed to have studied) and others, the cause of anthrax was known and its effects could be easily demonstrated:

> The assistant held the guinea pig close; Gottlieb pinched up the skin of the belly and punctured it with a quick down thrust of the hypodermic needle. The pig gave a little jerk, a little squeak, and the co-eds shuddered . . . He said quietly, 'This poor animal will now soon be dead as Moses.' The class glanced at one another uneasily. 'Some of you will think that it does not matter; some of you will think, like Bernard Shaw, that I am an executioner and the more monstrous because I am cool about it; and some of you will not think at all. This difference in philosophy is what makes life interesting.'

In his reference to Shaw, Gottlieb is probably thinking of the preface to *The Doctor's Dilemma*, where Shaw – a staunch anti-vivisectionist – asks rhetorically why 'If a guinea pig may be sacrificed for the sake of the very little that can be learnt from it, shall not a man be sacrificed for the sake of the great deal that can be learnt from him?' Indeed, as Gottlieb is preparing to demonstrate the effects of anthrax, he compares the bright-eyed guinea pig to one of his bored and uninspiring students and asks himself, 'Why should I murder him to teach *Dummköpfe*? It would be better to experiment on that fat young man.'[1]

Medical research in laboratories had made kind, benevolent healers into cold, clinical killers; that, at least, was how some saw the new scientifically trained doctors. Later in the novel, its hero, Martin Arrowsmith, is working as a family doctor in the Midwest when he tries desperately to save the life of a child with diphtheria, but fails. As he stands horrified over the dead child, 'he raged with desire to do the impossible. She could not be dead. He had do something', but there is nothing he can do. 'She is dead? Dead?' demands the child's mother. 'You killed her, with that needle thing! And not even tell us, so we could call the priest!'[2]

Like the real doctors on whom he is based – men like Sinclair Lewis's father, who was a family doctor in Minnesota – Arrowsmith is largely powerless against the microbes. He knows how to locate them, grow them and identify them, but in the 1920s, administering anti-toxins or vaccines was still a hit and miss business. But in Lewis's novel, Arrowsmith makes a remarkable breakthrough: he discovers a bacteria killer, a mysterious entity that causes microbes themselves to get sick and die and uses his discovery to fight a plague. Although he is only partially successful, the novel offers hope that one day real doctors will vanquish real bacteria.

Most of the book's readers probably assumed that the enigmatic bacteria killer was as fictional as Arrowsmith himself, but Lewis was describing the real science of his time, so recent that few scientists and almost no doctors would have heard of it. The bacteria killer's real discoverer believed, like Arrowsmith, that it

was the ultimate weapon in the war against the microbes. It proved to be even more extraordinary: in time it showed us exactly how genes work, what the mysterious 'hereditary material' is, how it is preserved, copied, mutated and passed on. It ultimately helped us to understand – and treat – diseases in ways Martin Arrowsmith could never have imagined, but it would take more than half a century for us to understand what this mysterious bacteria eradicator had to tell us.

Miasmas to microbes

Humankind has been wondering about illness – and cure – for as long as we have been wondering about anything. As we have seen, some ancient Greek doctors believed that, just as the world was made of four elements – earth, air, fire and water – so humans were partially composed of four associated 'humours': black bile, blood, yellow bile and phlegm. As we have seen, major imbalances of the humours could also make us sick, which is why for hundreds of years doctors would treat disease by trying to rebalance the humours.

Although the doctrine of humours had a long career in Western medicine, its proponents had difficulty explaining epidemic diseases. Why, for example, did diseases seem to sweep through cities (and it was more often cities than small towns or villages), affecting thousands of people at once? In the early sixteenth century, when Italian cities suffered outbreaks of fever the citizens attributed them to unfavourable planetary influences; which is why the Italian for 'influence', *influenza*, came to be the name we still use for the disease. However, by the early nineteenth century, astrology had largely given way to two rival theories of infectious disease. One school was convinced that miasmas, airborne poisons such as those generated by decaying animals and plants, caused illness. The Italians had long known that those foolish enough to wander into swamps and marshes often became ill, which they attributed to the bad air, or '*mal aria*', of such places. By the late nineteenth century, it was discovered that the swamp disease was spread by a parasite carried by the mosquitoes who

bred there, but the illness is still called malaria, commemorating the original 'miasmatic' theory.

However, the miasmatic theory had its critics: doctors found that patients who had been nowhere near a marsh or polluted city still came down with diseases that spread rapidly through families and villages. They wondered if these illnesses were caused by some kind of particle, which infected the body and was then spread when the patient touched other people. The theory became known as 'contagionism' (from the Latin, *tingere*, 'to touch'). Some assumed the contagious particles were simply inanimate chemicals, like poisons, but that did not seem to explain how epidemics grew and spread. So other contagionists argued that the particles must be 'animalcules', minute animals, like those the early microscopists had discovered to be swarming in every drop of water. They speculated that perhaps some of these were responsible for illnesses, creating epidemics when they multiplied and spread.

The animalcule version of contagionism got a boost in 1835, when it was shown that muscardine, a disease of silkworms, was caused by a fungus. This was the first time that a living organism had been proved to cause a disease. At about the same time, Theodor Schwann (one of the founders of the cell theory) demonstrated that the crucial process of fermentation was caused by a living organism, yeast, and was not – as had been widely believed – a purely chemical reaction. Pasteur had also investigated fermentation – largely at the insistence of French wine-growers – and he discovered that several of the 'diseases' that spoiled wine and beer were also caused by tiny living things. These were visible under a microscope, and since they looked like little sticks they became known as bacteria (from the Greek for 'little stick'). In 1865 Pasteur was also asked to investigate silkworm diseases, and after five years of tests and experiments he was able to identify two distinct diseases, each caused by a different microscopic creature; these invisible killers were christened 'microbes' or germs and the 'animalcule' version of contagionism became the germ theory of disease.

Pasteur's work encouraged dozens of other scientists across Europe to start microbe-hunting, identifying the once-mysterious causes of sickness. In 1877, Koch published his work on anthrax, which clearly showed that whenever the disease was present, so was the microbe. His critics responded by claiming that the microbes were merely a side-effect of the illness, so Koch grew them on a glass dish in the laboratory and then injected them into healthy animals, which quickly sickened and died (precisely the demonstration Gottlieb performs on his unlucky guinea pig). At much the same time, Pasteur showed that if the microbes were filtered out of the blood of infected animals, the blood could no longer cause anthrax.

Between them, Pasteur and Koch convinced the medical world that microbes caused illness. The publicity that accompanied their successes led to the assumption that every disease must have its own associated microbe, giving birth to a new science – microscopic biology, or microbiology. As universities and medical schools built labs to teach their students how to kill guinea pigs with germs, efforts were made to improve laboratory equipment. For example, as the demand for microscopes boomed, their manufacturers found themselves competing in an increasingly crowded marketplace, so they invested in making their microscopes more and more powerful. At the same time, biologists were improving the techniques used to prepare specimens, such as staining, which made the component parts of the specimen easier to see. And as each new tool revealed more about microbes, the researchers demanded further improvements. Like Calvin Bridges in Morgan's fly room, every lab seemed to have a tinkerer or two, working to improve their tools. The round, flat-bottomed glass dishes that are still used to grow microbes were named after their inventor, Julius Richard Petri, a German bacteriologist who worked with Koch. Also in Koch's lab was a young German doctor, Walther Hesse; one hot summer afternoon he became frustrated by the gelatin on which microbes were grown, because it melted in the heat. Gelatin (derived from animal tissues) was of course also used in cooking, to make jellies set, and Hesse was

intrigued to notice that his wife Angelina's jellies did not melt. When he asked her why, she explained that instead of setting them with gelatin, she used a powder called agar. Agar, which is made from seaweed, had been used in Far Eastern cooking for centuries, and while Angelina had been growing up in New York she had learned about it from a Dutch neighbour who had been born in Java. The more stable agar gel quickly became standard in Koch's lab and is still in use all over the world.

Once they were properly equipped, students – just like those in Arrowsmith's class – were taught what had become known as 'Koch's postulates'. These were the microbe hunters' creed: first, every patient with a particular disease had to be shown to carry the same microbe; then the microbe had to be isolated and grown in the lab, to produce what was called a 'pure culture', free from contamination; and finally, the pure culture had to be capable of producing the disease when it was introduced into a healthy patient (or, more usually, a guinea pig).

That, at least, was the theory. In practice, there were still many more diseases than there were microbes. Smallpox was one of the recalcitrant ailments that resisted Koch's postulates: no one could find a definite microbe that would grow in the lab, or at least, whatever it was that *could* be grown in the lab seemed not produce the disease in healthy subjects. Microbe hunting had become a mature science, confident in its methods and reluctant to accept work that failed to conform to high professional standards; in cases like smallpox, the microbe-hunters became increasingly confident that the only reason they could not find a microbe was that there wasn't one.

By 1890, even Koch had to admit that there were many diseases – including smallpox, rabies and influenza – for which there was no sign of a bacterium. He suggested that some microbes might be too small to be seen. This was a distinct possibility: it had long been realized that no light microscope – however sophisticated and expensive – could ever resolve objects smaller than the wavelength of visible light itself. By the 1890s, microscopes had reached that theoretical limit of visibility and

bacteriologists speculated that some microbes would remain forever beyond their reach. Perhaps these were responsible for the mysterious seemingly microbe-less diseases?

Microbiologists had been using filters to remove microbes from blood for some decades. One early attempt used the placenta of a living guinea pig to filter anthrax bacteria, but for once the hapless guinea pig did not become standard laboratory equipment – unglazed porcelain or plaster filters were soon used instead (and by the 1880s, it had become clear that some bacteria could cross the placental barrier in any case). A whole range of filters were developed and at London's 1884 International Health Exhibition, an array of standardized commercial filters were on display, which could be used for such purposes as making the city's polluted water supply safe enough to drink.

Filters played an important role in the hunt for ever-smaller microbes. In the 1890s, several European researchers were studying a disease of tobacco plants known as tobacco mosaic disease because it caused the leaves to become mottled with light and dark spots. The disease attacked many valuable crops, so there was considerable interest in finding its cause. In 1898 a Dutch researcher, Martinus Willem Beijerinck, discovered that whatever caused the disease easily passed through a bacterial filter and seemed able to survive indefinitely, spreading from plant to plant, from generation to generation. That ruled out a poison – it would rapidly have become too diluted to have any effect. Whatever caused the infection was reproducing, somehow renewing itself in the infected plants, infecting others, and then repeating the process. Beijerinck did not think it could be any kind of microbe, since it passed through the filters, nor could it be destroyed in any of the ways microbes were usually killed. And no matter how hard he looked with his microscope, Beijerinck could detect nothing.

Beijerinck wondered if the infectious agent was a liquid of some kind and devised an experiment to test the idea. He took a Petri dish covered in agar gel and put infected plant sap on it, leaving it for ten days so that any liquids would diffuse through the agar.

Then he removed the sap and the top layer of agar, which had been in direct contact with it. He then tested the lower, untouched layer of agar: would it still transmit the infection? It did. He concluded that the infectious agent could not be a bacterium or fungus – it must be a liquid or something that dissolved in a liquid.

Pasteur had called the seemingly unidentifiable cause of rabies a virus, and Beijerinck adopted the term. The Romans had first used the word 'virus' to mean anything bitter or unpleasant. By the Middle Ages it had come to mean a poison, and eventually was used to refer to anything that caused infection. The seventeenth-century German Jesuit scholar Anathasius Kircher seems to have been the first to use the word in this sense, when he referred to whatever it was that caused the plague as the *virus pestilens*. By the eighteenth century, 'virus' was regularly used in English to mean an infectious agent; Edward Jenner, one of the founders of vaccination, used it in his classic treatise on smallpox, referring to the substance extracted from the pustules or pocks that characterized such diseases as 'cow-pox virus'. By the early nineteenth century it was used in two senses: it referred to the specific cause of a well-defined disease, but also to any unknown disease-causing agent. By the 1870s and 80s, Pasteur and others were using 'virus' as a general term to refer to all the various kinds of disease-causing microbes. Koch claimed that in discovering the microbe responsible for TB, 'we have the true virus of tuberculosis'.[3]

Yet, however ancient the word's pedigree, there was no escaping the fact that 'virus' effectively meant 'we do not know'. Beijerinck realized that his tobacco mosaic virus could not be a simple chemical like a poison, because it reproduced in the plant; it must be a living infectious fluid, which he simply referred to as 'living infectious fluid', though in Latin (*contagium vivum fluidum*), presumably because that sounded more impressive. His proposal violated the central dogma of the cell theory, that every living thing is made of cells and all cells come from cells; whatever his mysterious *fluidum* was, it did not conform to the dogma. And, despite being alive, it resisted all attempts to grow it outside the

plant: it would only multiply in living, dividing cells. The very novelty of Beijerinck's ideas made them hard to accept, especially his notion of a living thing that could not reproduce itself independently – after all, the ability to reproduce was a key part of what defined life. He was contradicting both cell theory and germ theory, two of the great triumphs of nineteenth-century biology, and, not surprisingly, few were willing to listen to him.

Nevertheless, by the beginning of the twentieth century, science had reached a clear understanding of what viruses were not: they were not blocked by filters; they were not visible under the microscope; and they would not grow in the lab. All very intriguing, but what *were* they?

The bacteria eaters

On the eve of the First World War, the English microbiologist Frederick Twort noticed something rather peculiar about his agar plates. In the middle of his growing colonies of bacteria there were clear patches. He followed procedure: stained and fixed them and put them under the microscope. All the bacteria were dead, nothing but empty carcasses were visible. He investigated further. Whatever was killing the bacteria could pass through a filter and still remain lethal. Twort published an article about his discovery, in which he discussed several theories, including the possibility that he had found a microbe that attacked other microbes. But he was too cautious a scientist to choose between his hypotheses and before he could pursue the problem, the war intervened. Not long after his paper had appeared, Twort joined the British Army Medical Corps and was sent to Salonica (now Thessaloniki), in Northern Greece, where British troops were digging in for one of the long, bloody and largely pointless campaigns that characterized the war. By the time it was over, others were at work on the bacteria-killer and so, as Twort put it, 'I passed on to other work.' His original paper was largely ignored.[4]

While Twort was in the army, a French-Canadian, Félix Hubert d'Hérelle, was one of dozens of researchers who were

trying to answer a deceptively simple question: given that the world was literally swarming with microbes, many of which caused diseases, why were not we all sick all the time? This raised other questions, such as why, when there was an epidemic, did not everyone succumb? One proposed explanation of resistance to disease came from the Russian embryologist Elie Metchnikoff, who observed strange cells in starfish and sponges that were produced in massive numbers when a creature was under attack from potential diseases. The special cells seemed to be able to protect the organism from infection by engulfing and consuming the invaders, so Metchnikoff called them phagocytes ('eating cells'), arguing that they were the basis of the body's natural immunity.

In 1915 d'Hérelle was working at the Pasteur Institute in Paris, studying a patient who was suffering from severe dysentery. He was busy culturing the dysentery bacteria, just as Koch advised, growing them until the test-tubes were cloudy with swarms of thriving microbes. After repeating the experiment several times, d'Hérelle was startled when one morning he found a completely clear test-tube. The bacteria were all dead. Even more surprisingly, he discovered that if a drop of the liquid from the clear tube was put into one full of thriving bacteria, they died too. He had inadvertently rediscovered the phenomenon Twort had first observed. After several years of experiments, in 1917 d'Hérelle announced that whatever killed the bacteria both passed through filters and seemed to get more lethal with successive cultures. That suggested the unknown assassin was growing and multiplying – it was clearly a virus like the one Beijerinck had observed in tobacco, and d'Hérelle christened it 'bacteriophage' ('bacteria eater'; the same word is both the singular and the plural).

D'Hérelle suggested that the bacteriophage virus was nature's defence against bacteria, an idea that had come to him as he had been searching for a microbe that would kill locusts. He had discovered that some locusts were immune to his supposedly lethal microbes; on examining them, he had found in their guts evidence of something that killed bacteria. He began searching for other examples of this phenomenon – his dysentery experiments

being one approach – and was intrigued to discover that the dysentery-killing bacteriophage were much more common in the stools of people who had just been ill than they were in healthy people. That suggested that bacteriophage multiplied to fight off an infection, like Metchnikoff's phagocytes.

D'Hérelle wrote a book about his discovery, which was translated into English as *The Bacteriophage: its role in immunity* (1922). That same year his work was discussed in the *Proceedings* of the Royal Society and he and Twort were invited to address the British Medical Association's annual meeting. News of the discovery spread rapidly: Michigan's Academy of Science, Arts and Letters discussed bacteriophage the following year. Soon, teams were investigating bacteriophage in several countries: Andre Gratia and Simon Flexner in the USA, d'Hérelle in France, and in Belgium the Nobel Prize-winner, Jules Bordet, who led a research team in Brussels.

As the number of researchers working on the bacteria-killer grew, disputes flared up about what it was they were actually studying. No one could even agree on what it should be called: a few used d'Hérelle's term 'bacteriophage', thus implicitly adopting his view that it was indeed a virus (whatever that was), but others disagreed – just as they had disagreed with Beijerinck. One thing that the researchers did agree on was that the mysterious microbe-killer caused bacteria to disintegrate (or undergo 'lysis' in scientific terminology). Bordet – who insisted that the phenomenon was purely chemical, not organic – called it 'transmissible autolysis' ('self-disintegrating that can be passed on', in English). Scientists were well aware that the term they chose to use aligned them with a different camp in a small but increasingly fractious scientific world, so some tried to distance themselves from the debate by adopting deliberately neutral phrases, such as 'the Twort-d'Hérelle phenomenon'.[5]

Bordet was convinced that his 'transmissible autolysis' was – as its name suggested – in some way hereditary, but he was equally sure that bacteriophage was not living – it was purely chemical, something produced by the bacteria themselves. Biochemists had

established that organisms produced substances called enzymes (from the Greek for 'in ferment'), which acted as catalysts, controlling the speed of the body's chemical processes. Perhaps, Bordet speculated, autolysis was caused by a mutation in the bacteria that led them to produce too much of a normally useful enzyme, causing a runaway chemical reaction that eventually killed the bacterium. It might even serve some useful function; perhaps the disintegration killed off undesirable mutants, so as to 'discipline the evolution of the species'.[6] However, this was a very controversial idea. Bacteria had no nucleus and no visible chromosomes, so the idea that they might be subject to the same genetic laws as other organisms seemed unlikely. Indeed, in the early 1920s it was still not clear whether bacteria could even be considered organisms in the usual sense. Yet one of Bordet's colleagues, Andre Gratia, joined the campaign against d'Hérelle's view that bacteriophage were alive. So what if the phenomenon could spread? Gratia sarcastically pointed out that fire spreads and 'reproduces' itself and yet 'fire is not living'. Bubbles appear on the inner surface of a glass of soda water, just like the clear patches that appeared on a dish of infected bacteria, 'yet gas is not a virus'.[7] Gratia took the anti-d'Hérelle line with him to the US, when he joined the Rockefeller Institute in New York.

Standard oil and snake oil

The Rockefeller Institute for Medical Research was only one part of John D. Rockefeller Sr's vast philanthropic empire. Rockefeller had made over $900 million by 1912 (about $80 trillion in today's dollars), mostly in the oil business, yet he was haunted by what he had heard in church as a boy, that it was easier for a camel to pass through the eye of a needle than it was for a rich man to enter the kingdom of heaven. His deeply religious mother had taught him the importance of charity and so Rockefeller began a systematic campaign of giving away his money. His generosity was as legendary as his fortune, and he soon faced a torrent of begging letters from charities. In 1891 he appointed a full-time financial

manager, the Reverend Frederick T. Gates, who took care both of increasing and reducing Rockefeller's fortune, by managing both his investments and his philanthropy.

Rockefeller's son, John D. Jr, urged his father and Gates to put money into medical research, conscious that there were still few effective treatments available for most diseases. The younger Rockefeller may also have felt a familial guilt that his grandfather, William Avery Rockefeller, had also made his money in oil – snake oil. A self-proclaimed 'Doctor', he charged $25 a time (well over $500 in today's money) for a worthless cancer cure. Whatever their motives, the Rockefellers' philanthropy had in 1901 resulted in the Rockefeller Institute for Medical Research (now Rockefeller University): the family had given it over $50 million by the 1930s.

In 1920 a young scientist called Paul de Kruif arrived at the Rockefeller Institute, eager to become a microbe hunter. He was immediate struck by the Institute's luxurious facilities: 'What a temple of science the Rockefeller Institute was!' he recalled, especially when compared with the medical building at the University of Michigan where he had trained, which stank of rats and guinea pigs; 'at the Rockefeller you did not smell the animals. They were brought to you from a beautiful animal house in the bowels of the Institute by a servant.' The facilities were new and expensive and life was easy: 'Lab servants washed the glassware and cooked the culture medium,' de Kruif reminisced, 'and if you had a well-enough trained technician, he could even do your experiments for you.'[8]

De Kruif knew everyone in the small but flourishing world of bacteriophage. He had visited the Pasteur Institute in Paris during the war, where he had heard of (and may even have met) d'Hérelle. Back in the US, he had studied with Frederick Novy, the first serious American bacteriophage researcher, and the year de Kruif arrived at the Rockefeller Institute, he had met Bordet and shared a lab with Gratia.

However, De Kruif's work at the Rockefeller Institute was not concerned with the enigmatic bacteria-killer, but an apparently

unrelated phenomenon: bacterial impurity. As we have seen, Koch's postulates demanded that a bacteriologist produce a pure colony of the microbes suspected of causing a disease; it was an essential first step, since if there were more than one type of bacteria present, it would remain unclear which one actually caused the illness. The procedures for doing this were well known; de Kruif would have learned them from Novy in a class like the one described in *Arrowsmith.* However, sometimes what appeared to be a pure colony would separate into two types, only one of which proved to be vulnerable to the anti-toxin that ought to have killed it. De Kruif called this puzzling behaviour 'dissociation' and suggested that the bacteria might be undergoing a de Vriesian mutation, forming a new species. His idea was greeted with considerable scepticism by most biologists: the popularity of the Mutation Theory was fading, largely because Morgan's fly researchers were focusing attention on to the Mendelian behaviour of chromosomes.

De Kruif was just one of the many who were trying to understand why bacteria were so changeable. Not only could they radically change their form when watched under a microscope, they seemed able to live off one substance when in one shape, but lose their appetite for it when they changed. Bacteria seemed to be highly adaptable, but were these genuine genetic changes, or was some other mechanism at work? When the early microbe hunters had discovered bacteria they often referred to them as a 'ferment', more like a frothy mix of chemicals than a population of individual organisms. And in the twentieth century, bacteriologists still tended to talk about the properties and behaviour of bacterial 'cultures', as a whole, rather than about the properties of individual, variable bacteria. Even de Kruif, who thought he might be watching the effects of individuals mutating, by calling the phenomenon 'dissociation' was implicitly referring to the behaviour of the culture as a whole, not to the individuals that composed it.

De Kruif had begun his career as a medical student, but as he became increasingly aware of doctors' helplessness in the face of

most diseases, he switched to pure science. The Rockefeller Institute was the obvious place to be; Frederick Gates had assured John D. Rockefeller Sr that, given enough money, science would soon conquer the microbes, major diseases would be cured within years and Rockefeller would find himself a place both in the history books and in paradise. But the promised cures did not arrive and de Kruif began to wonder why. He became increasingly cynical about the medical profession, which he and his fellow researchers were supposed to be serving; he began to suspect that most doctors were only interested in making money.

De Kruif began to think about a new career as a writer. There were more magazines and newspapers in the United States than ever before; by 1910 the country had about 2,600 newspapers, all struggling for circulation and advertising and in desperate need of stories to fill their pages. De Kruif wondered whether he might put his scientific training to use, explaining the latest breakthroughs and discoveries to the general public while unmasking frauds and failures. One evening, at a literary party in New York, he was riding his favourite hobby horse, complaining about the self-interested greed of America's supposedly selfless healers, when he met the historian Harold Stearns. Stearns was amused that someone who worked at the temple of medical science – the Rockefeller Institute – could be so cynical about the contrast between the apparent worthlessness of most medicines and the prestige and wealth of those who dispensed them. He invited de Kruif to contribute a chapter on the state of American medicine to a book he was editing; de Kruif, increasingly tired of research, accepted – on condition that he remain anonymous. When the chapter appeared, the editor of the *Century Magazine* invited de Kruif to expand it into a book, to be serialized first in the magazine.

De Kruif began writing, but when the first instalment of 'Our Medical Men' appeared in the *Century*, it was not his criticisms of doctors that got him into trouble; his byline cost him his job. Despite his insistence on anonymity, he had mentioned his $500 advance to many of his colleagues at the Rockefeller, so when

the article appeared, signed 'K—, MD', his boss, Simon Flexner, had a pretty good idea who was responsible. Flexner summoned de Kruif, to express his outrage that a PhD had apparently passed himself off as an MD, a medical doctor. In fact, de Kruif was mostly innocent: a sub-editor had made the change without his knowledge, but de Kruif had failed to spot the error because he had not troubled to read the proofs the magazine had sent him. He resigned from the Rockefeller before Flexner could fire him and set about inventing an entirely new specialization – he became one of the world's first full-time science writers.

In 1922 de Kruif was researching a piece on fraudulent medications. In a doctor's office he encountered 'a young red-headed man, very tall and slightly stooped, nervous, his face spotty red . . . An unearthly character, not to be forgotten once seen'. This was the novelist Sinclair Lewis, whom de Kruif described as 'the then most famous author in the wide world'.[9] Lewis had just published his second major novel, *Babbitt*, which like its precursor, *Main Street*, had been both a commercial and critical success. He was becoming famous around the world; some British critics acclaimed him as America's Dickens.

Lewis and de Kruif hit it off immediately, not least because of their shared fondness for bootlegged liquor. Lewis was looking for a subject for his new novel and in de Kruif's impassioned attacks on the unscientific state of American medicine, he felt he had found it. The two men shared a desire to see a genuinely scientific medicine come to the aid of honest but largely helpless family doctors (like Lewis's father), who would then be able to drive the cynical snake-oil salesmen out of medicine. Just a few months after their first meeting, Lewis and de Kruif set sail on the SS *Guiana*, bound for the Caribbean, where they planned to set their novel of science and medicine; De Kruif was going to provide a solid scientific basis for Lewis's writing skills and practised imagination.[10]

De Kruif had been a fan of H.G. Wells's novels ever since his student days and was impressed by the way Wells's fiction had

always been rooted in real science, some of which Wells had learned directly from Darwin's disciple, Thomas Huxley. As de Kruif and Lewis discussed possible real scientific topics that might be comparably dramatic, de Kruif suggested that their fictional hero, Martin Arrowsmith, might fight a Caribbean plague using bacteriophage. Few in the medical world knew of d'Hérelle's work and its potential therapeutic uses, and practically no one in the wider world would have heard of it, yet here was a real science that, if d'Hérelle was right, could vanquish the microbes that made human life so precarious.

According to de Kruif's (not altogether reliable) memoirs, the two men were soon on fire with this idea; they worked hard every day, drank equally hard every night, and explored each Caribbean island they visited, unaccountably wearing pith helmets (apparently so that they would look British). The collaborators had brought with them a trunk-load of medical books, maps and letters of introduction to various island doctors and administrators. From Lewis's surviving notes, it is clear that de Kruif gave him a fairly intensive course in microbiology during their voyage; his notebooks are full of technical details of lab protocols and techniques, together with sketches of scientific equipment. De Kruif acknowledged that Lewis 'never tried to make do with phoney movie science . . . He kept teaching me to let myself go to dramatize real science'.[11]

Lewis put de Kruif to work writing a brief scientific biography of each character in the novel. Arrowsmith's mentor, Max Gottlieb, was a composite of Jacques Loeb (who also worked at the Rockefeller Institute) and de Kruif's old teacher Frederick Novy. For Arrowsmith himself, Lewis drew on several of de Kruif's colleagues and indeed on de Kruif himself. By the end of the voyage, they had the skeleton of the book and all the scientific background Lewis would need. When the novel appeared, in 1925, it was a sensational triumph; Lewis won the Nobel Prize for Literature in 1930, largely on the strength of it.

Arrowsmith was widely reviewed and praised. *Science* reviewed it in its section on 'Scientific Books'. The magazine was

delighted that it was not only 'a novel of the first rank', but had 'a scientist for its main character'. *Science* even suggested that the novel's publication was 'an added bit of evidence of a certain shift in our civilization shown by the growing interest of the layman in scientific matters', a shift that was taking place because the scientific 'High Priests' had finally 'taken off their false whiskers and have given Mr. Average Citizen a peep at the ceremonies going on inside the Temples'. The journal congratulated Lewis, not merely for showing 'no small amount of courage' in making a scientist his hero, but for describing his researches, 'clearly and intelligently, without yielding to the temptation to write down to the technical knowledge of a novel reading public'.

De Kruif's contribution to the novel was acknowledged by Lewis (although not to the extent that de Kruif wanted), and *Science*'s reviewer observed that 'much of the verisimilitude of the action and characters' was undoubtedly the result of de Kruif's efforts. After praising aspects of the novel ranging from the convincing idea of laboratory life to Lewis's satirical sense of humour, the review urged that 'Every medical student who feels vague rumblings of scientific curiosity or the urge for pure research, should read it.'[12] This advice seems to have been widely followed: *Arrowsmith* was one of the first novels to feature a scientist as a hero and many idealistic young people were inspired by it – and by de Kruif's next book, *The Microbe Hunters* (1926) – to follow medical or scientific careers.

One result of *Arrowsmith*'s success was that bacteriophage became a popular topic for journalists. Before the novel's appearance, only two short pieces relating to the phenomenon had appeared in English in the non-specialist press. But soon, bacteriophage were written about so regularly that the *Lancet* was tetchily complaining about 'The musical comedy spirit which reduces 'bacteriophage' to its final syllable'.[13] The magazine's complaint was in vain. Within a year the term 'phage' was so common that it had been used in the *Encyclopaedia Britannica*; it has remained in use ever since.

What is life?

The popular American magazine *Science Monthly* discussed the question 'Do Bacteria have Disease?' a year after *Arrowsmith* appeared. The article noted that, despite all the interest in phage, there was still considerable debate about what viruses actually were. Scientists had tried to measure them by passing them through smaller and smaller filters until they were finally caught. Based on these tests, they were estimated to be about 1,000 times smaller than a bacterium. That was far too small to be observed through even the most powerful microscope, but there was a second reason for concern: could something that small possibly be living? If the measurements were right, viruses such as bacteriophage were not much bigger than a single protein molecule and, as *Science Monthly* put it, that 'seems to leave us in a dilemma'. Since it was assumed that proteins were the fundamental units of life, 'is it possible to have living organisms smaller than the protein molecule!'[14]

The possibility that proteins were the basis of life had made them the focus of intense study among biochemists, who were not only sceptical that something as tiny as phage could be alive, but were also unwilling to see such an interesting and potentially important phenomenon fall into the domain of their rivals in bacteriology. Biochemists were convinced that phage were protein molecules, and since the study of proteins was part of biochemistry, phage therefore 'belonged' to the biochemists.

Leading the protein research at the Rockefeller Institute was John H. Northrop, who had proved that enzymes were proteins (he and two colleagues would win the Nobel Prize in 1946 for this work). He also investigated the way enzymes catalysed reactions, building on the earlier work of J.B.S. Haldane and others. Northrop's team discovered that the speed at which chemical reactions proceeded within the body was controlled by the concentration of the enzyme – the greater the enzyme concentration, the faster the reaction. With this discovery in mind, Northrop turned his attention to phage, which had been found to consist almost entirely of protein. If, as Bordet and others claimed, the

phage phenomenon was simply a chemical reaction, researchers would expect it also to depend on simple measurable quantities, such as the concentration of phage. Opponents of the living virus theory argued that the bacteria burst as a result of purely chemical changes within the cell: osmotic pressure drew in water until the bacterium disintegrated. If they were right, the phage were something entirely lifeless produced by the bacterium itself.

To test these ideas, Northrop's co-worker, Alfred Krueger, developed a method for estimating the amount of bacteria and phage in a culture, treating them as if they were enzyme and substrate (the substance on which an enzyme acts). His experiments revealed that the concentration of phage was indeed the crucial factor in whether or not the bacteria disintegrated – and that suggested that phage did indeed act like enzymes and so fell within the territory of the biochemists rather than that of the bacteriologists. It was also significant that viruses like phage and tobacco mosaic virus (which was also being worked on at Rockefeller) could be crystallized, just like any other protein. That seemed a most unlikely property for a living creature, but it might explain why viruses had some 'life-like' properties since, of course, crystals grow without being alive. Perhaps viruses were some kind of self-catalysing enzyme: they began a reaction that in turn produced more of the virus; since the virus itself catalysed the reaction, as the concentration of virus rose, the reaction accelerated, producing yet more virus. This idea explained the multiplication of the virus and the apparent runaway nature of the reaction, ending in the bacterium's disintegration.

Part of Northrop's argument that viruses were purely chemical was the principle of Occam's Razor. This is (perhaps surprisingly for what has become a scientific precept) named after a medieval Franciscan friar, William of Occam. He proposed that '*Pluralitas non est ponenda sine neccesitate*' ('multiple entities should not be assumed unnecessarily'); in other words, if a simple explanation will do, there is no reason to look for a more complicated one. Scientists have often suggested using Occam's Razor to decide between rival theories: if a simple theory explains the facts, it

should be preferred to a more complicated one. The principle does not, of course, assume that nature *is* in fact simple, merely that it makes sense to avoid further complexities unless it becomes unavoidable – usually as a result of some experiment or observation that cannot be explained by the simplest theory. In Northrop's view, the biologists were making matters unnecessarily complicated. They were far too prone to assume that there was something mysterious, almost mystical, about 'life', which made them reluctant to fully accept the implications of the fact that living things were built out of simple chemicals and their life processes were based on straightforward chemical reactions. This was not, of course, a new argument – it has probably been going on in various forms ever since we first evolved the ability to ask the deceptively simple question: what is life?

For those with an interest in this issue, viruses such as bacteriophage posed provocative questions, but scientists were also interested in the practical problems they presented. When Emory L. Ellis completed his PhD in biochemistry at the California Institute of Technology (Caltech) in 1934, he began a post-doctoral project on viruses, trying to investigate if and how they were involved in causing cancer. He decided to work on phage, which might seem an odd choice, since there was no evidence that they cause cancer and he was not particularly interested in bacteria. What Ellis wanted to understand was the role viruses play in cancers – first in animals, but eventually in people. However, testing viruses on animals 'required a large animal colony, with all its attendant problems and expense'.[15] So Ellis abandoned the mice he had been working with and switched to phage. Ellis and his wife, Marion, visited Pasadena's sewage treatment plant to gather samples of untreated effluent. They found the sewage full of different kinds of phage, many of which seemed specialized to attack particular types of bacteria.

Ellis chose to work on a phage that preyed on *Escheria coli* (usually known simply as *E. coli*). This is a very common bacterium (every one of us has millions in our guts) and one of Morgan's students (the Morgan Drosophila team had now moved

from Columbia to Caltech) happened to be working on it, so he had plenty to spare. Ellis was careful to choose a phage that was not too lethal – so that the clear areas it produced when it had killed the bacteria (known as plaques) were fairly small – he was able to get about fifty of them on a single Petri dish. (D'Hérelle had first hit on the idea of counting plaques as a way of calculating how many phage were present.)

Not only were phage small and cheap, they were fast. Testing viruses on animals involved waiting for them to get sick, which could take days or weeks, whereas it only took a few hours to complete a phage experiment (Ellis would later help reduce this to just two hours). 'Clearly, then,' he decided, 'bacteriophage was by far the best material from these points of view.'[16] He hoped that his small, fast, cheap phage would enable him to understand the basic biology of viruses, as a first step towards understanding the hypothetical role of viruses in cancer. The phage were to be used as a model organism, just as the USDA had kept guinea pigs as model farm animals, allowing costly large-scale experiments to be done in miniature; the phage were to be used rather like a scale model of a plane that is tested in a wind-tunnel before an expensive prototype is built.

As he was busy working with his phage one morning, Ellis was interrupted by a visitor, Max Delbrück, a German physicist who was looking for a paradox that would reveal new laws of physics. Yet he had not wandered into the wrong lab; he was hoping Ellis's phage might be able to help him.

In 1935 Max Delbrück had been a nineteen-year-old student in Berlin when he had sat alongside Albert Einstein and Max Planck to hear Werner Heisenberg present quantum theory for the first time. He later admitted that he had understood very little of what Heisenberg said that day, but he had grasped enough to realize that he was present at the birth of something extraordinary – an entirely new understanding of the atom, of matter itself. The following year, Delbrück joined Heisenberg to study at the University of Göttingen. He had planned to be an astronomer, but was soon completely absorbed by the new quantum physics.

In the late nineteenth century, physicists had discovered much about the atoms, which the ancient Greeks had first hypothesized as the basic components from which everything was made. It was clear that these once-hypothetical entities definitely existed, but it was also becoming apparent that the atoms physicists had identified were not in fact the fundamental entities the Greeks had imagined. As new phenomena such as X-rays and other kinds of radiation were explored, it became clear that atoms consisted of even smaller particles, such as electrons and protons. And as these new, sub-atomic particles were investigated it became clear that they were not simply very tiny versions of the billiard balls and planets whose behaviour was described by the laws of classical physics. In this new realm of the unimaginably small, those laws ceased to operate and new, strange ones took over. It became apparent, for example, that energy, instead of flowing smoothly and continuously, came in discrete packets, called quanta. Only some quantum states were stable and electrons seemed to jump between them, jerking – inexplicably and discontinuously – from one to another. Another puzzle was that ordinary light took on a paradoxical quality: sometimes it behaved in ways that could only be explained by assuming that it was a wave, while at other times its behaviour made it clear that it was made of particles. The deeper the physicists investigated, the more mysteries they unearthed. Heisenberg, Niels Bohr and Erwin Schrödinger eventually resolved these paradoxes by wrapping them in mathematics. It was impossible to picture these implausible phenomena that were sometimes waves and sometimes particles, and appeared either to be nowhere or to be in more than one place, until experiment actually tried to pin them down. But the maths worked and it worked brilliantly.

Inspired by the excitement of quantum physics, Delbrück went to Copenhagen for a year to study with Bohr, the brilliant Danish physicist who had won the Nobel Prize in 1922 for his work on atomic structure. Delbrück recalled that Bohr 'incessantly worked and reworked his ideas on the deeper meaning of quantum mechanics'. At the heart of these was the principle of com-

plementarity, which states that it is impossible to describe all the aspects of any situation in atomic physics in a way that produces a single coherent picture. Each kind of experiment can only furnish one kind of information and the different experiments are mutually exclusive, so cannot be used to establish a complete picture. This was what Heisenberg summed up as his famous uncertainty principle – there seemed to be absolute limits on what we could know. Some interpreted Heisenberg's maths to mean that sub-atomic particles simply lacked fixed, knowable properties; a view that came as a shock to some physicists. Einstein rejected this approach on principle and remained convinced to the end of his life that quantum physics would eventually be replaced by an even newer physics that would combine quantum ideas with some of the knowable, stable reality of classical physics. But Bohr was entirely comfortable with the new indeterminacy, convinced that it was a major step forward.[17]

Of all Bohr's ideas, the one that most inspired Delbrück was the thought that complementarity might apply to all of science, including biology. Delbrück remembered Bohr repeatedly asking 'whether this new dialectic would not be important also in other aspects of science'? Perhaps biologists' failure to understand the nature of life resulted from a similar kind of mutual exclusion: 'you could look at a living organism either as a living organism or as a jumble of molecules', but not both. Some kinds of experiments revealed 'where the molecules are', but quite different ones were needed to 'tell you how the animal behaves'.[18] Part of Bohr's argument was that the atomic structure of an organism could not be investigated without killing it first, but perhaps living matter had genuinely unique properties – such as the power of replication – that were lost when it died. In which case, the traditional methods of biology, such as dissection, were doomed; if Bohr was right, biology needed to follow the same path as physics – to go smaller, to search for the real, fundamental 'sub-atomic particles' of life. When these were examined, perhaps paradoxes like those of the quantum world would emerge, and resolving them might reveal new scientific laws that would explain the mysterious

properties of life. In effect, biology might hold the key to the next step forward in physics.

Having absorbed Bohr's thought-provoking vision, Delbrück returned to Berlin, where he met Nikolai Vladimirovich Timoféeff-Ressovsky, one of the Russian biologists who had become a Drosophila geneticist as a result of encountering Hermann Muller on the latter's first visit to the USSR. Like Timoféeff-Ressovsky and his collaborators, Delbrück soon became strongly influenced by Muller's ideas. For a physicist, perhaps the most interesting aspect of Muller's work was that in 1926 he had used X-rays to produce artificial mutations in Drosophila (work for which he would eventually win the Nobel Prize). This proved extremely useful to biologists, who could now generate mutations more or less to order, instead of waiting for them to arise accidentally. They could not control what kinds of mutations were caused – they were still random – but they appeared so quickly that it became much easier to find those that were interesting or useful. The X-ray experiments helped accelerate the pace of chromosome mapping but, even more crucially, they persuaded many scientists that genes really did exist; if they could be affected by X-rays, they had to be real, physical entities with definite properties. This was another important step in replacing Mendel's *Anlagen* with definite physical entities, open to full investigation.

For someone with Delbrück's background, Muller's X-ray work opened up an intriguing possibility: perhaps genes were in some ways like atoms. Both were stable – genes could be passed on from generation to generation – but genes (like atoms) could be destabilized, mutated by a burst of energy. Perhaps the heritable mutations produced by X-rays were caused by a gene being 'flipped' into a new stable state, analogous to an electron being flipped from one stable quantum state to another? If so, genes might prove to be the true elements of life, the real biological atoms, so investigating them could perhaps reveal the new paradoxes – and thus the new laws of physics – that Bohr and Delbrück were hoping for.

Delbrück, Timoféeff-Ressovsky and Karl Günter Zimmer collaborated on a joint paper, which became known as the Green Paper (simply because that was the colour of the cover on the copies they sent out). It suggested why genes were usually unchanging but also why they could be changed by radiation: genes were stable chemical molecules, but the energy of radiation was enough to rearrange their constituent atoms into new forms. The Green Paper connected physics and biology in the most direct way.

During the 1930s, many scientists were keen to connect physics and biology, for a variety of reasons. Biology had always been rather a poor relation to more rigorous and prestigious sciences such as chemistry and, in particular, physics. One reason why biologists were interested in establishing new connections between the so-called 'hard' sciences and their softer cousins, the life sciences, was that they hoped to enjoy some of the prestige – and funding – of their physicist colleagues. They were supported in this ambition by some of the physicists and chemists themselves, who – perhaps for the first time – wanted to associate themselves with the life sciences precisely because they were sciences of *life*. As we have seen, biochemists emerged from the First World War as the discoverers of vitamins, savers of lives; chemists as the discoverers of the poison gas that had maimed and killed so many. However unfair the characterization, the hard sciences had begun to be seen as sciences of death. By the 1930s, it seemed to some that an unholy alliance of physicists and chemists had unleashed new technologies of killing on the world: in 1937, as fascist aeroplanes bombed defenceless civilians in the ancient Basque city of Guernica, many wondered what new horrors science might have in store for them. Meanwhile, biologists were unravelling the basic principles of life, such as respiration and digestion – at worst, this knowledge was harmless, at best, it could save lives, free humanity from disease, even conquer death itself.

Biology benefited from the unease that had begun to surround the physical sciences. In the 1930s, thanks in large part to the

Rockefeller Foundation's money, biologists were tackling a new problem, investigating the shape of large, complex molecules such as proteins in order to see how they worked. Protein structure began to be seen by many as 'the problem of life', the key to understanding life itself. Traditional biochemistry did not seem to be making much headway in solving it, so gradually in the 1930s a new discipline began to take over. It used new tools, such as X-ray crystallography, and in 1938 it acquired a new name, 'molecular biology'. The name was coined by Warren Weaver, director of Rockefeller's Natural Sciences Division. He defined the field as the 'biology of molecules' or as 'sub-cellular biology', shifting from the cell itself as the object of study to a more fundamental level of analysis. Weaver made an explicit analogy with the sub-atomic world of the quantum physicists; to make headway, biology had to go deeper by going smaller.

Weaver was an engineer with no biological background; his sense that biology was the 'science of the future' was shaped by biologists writing in the press, describing their ambitions to control life and conquer disease. However, there seemed little evidence to support these grand claims, and Weaver's view was that biology still seemed to be 'lacking laws and beyond rational analysis'.[19] The Rockefeller Foundation's response would be a healthy injection of cash and physics – and especially of new technology. That, Weaver believed, would enable biologists to establish the laws of their field, make rapid progress and save a civilization threatened by fascism, communism and a global economic depression.

It is debatable whether Weaver and those who shared his views were really shaping biology's new direction, or simply jumping on to a bandwagon that was already gathering pace. Probably both, but the new money certainly allowed – and encouraged – biologists to adopt the exciting – but expensive – new technologies which the physicists had created and apply them to biological problems. In addition to generating mutations, X-rays could also be used to reveal chemical structures, using the process of X-ray crystallography. This technique relied on the fact that when a

substance crystallizes, all its molecules are arranged into a regular, evenly spaced structure. That means that, in some important respects, the crystal is like a single giant molecule. When a beam of X-rays is shone through it, the beam is scattered and the scattering pattern can be detected using photographic film. This may be easier to understand by imagining shining a torch into a box. Inside the box is a chandelier, but the chandelier is out of sight; all that is visible is the pattern that the light makes when it is refracted on to the wall beyond the box. Using the laws of optics, the design of the chandelier can be deduced from the pattern on the wall. The same principle is used in X-ray crystallography – the pattern the X-rays make when they are scattered by the latticework of molecules within the crystal can be used to deduce the shape of an individual molecule.

X-ray crystallography was first used to investigate the structure of simple, inorganic compounds, such as diamond, but, using the rules thus developed, biochemists realized that it was possible to apply the technique to a range of much larger, more complex organic molecules, such as proteins. One of the results of such investigations was the realization that the three-dimensional shape of these molecules had a direct connection to the way the molecule behaved, the way it was able to perform its chemical – and ultimately its biological – function.

In 1935, the same year that the Green Paper appeared, one of Northrop's colleagues at the Rockefeller Institute, Wendell Stanley, managed to produce crystals of the tobacco mosaic virus (TMV) and announced that a virus was simply a protein molecule. His announcement caused a sensation: Delbrück was one of hundreds of biologists excited by an experiment which seemed to bring the properties of proteins, supposedly life's fundamental building blocks, firmly into the terrain of physics. In 1937 Delbrück was invited to apply for a Rockefeller Institute fellowship in molecular biology and went to Caltech to work with Morgan and his relocated fly boys.

As work on tobacco mosaic virus and similar plant viruses proceeded, it became clear that they belonged to a small group of

proteins whose chemical structure included traces of phosphorus. Fifty years earlier, chemical analysis had shown that chromosomes were also made from this kind of protein, which – because chromosomes were found in the nucleus of a cell – had been named 'nuclein'. But in the early twentieth century the name gave way to 'nucleoprotein'; the fact that it could be crystallized allowed teams of researchers to use X-rays to start probing its structure, in the expectation that the precise shape of the molecule would reveal how it worked.

Muller was one of many scientists intrigued by the discovery that viruses were made of the same stuff as chromosomes. He had been interested in viruses – and phage in particular – for some time. Back in 1922 he had wondered whether bacteriophage 'were really genes, fundamentally like our chromosome genes'? If they were, that 'would give us an entirely new angle from which to attack the gene problem'. And it now appeared that phage might be something very like naked genes, genes that had somehow got outside cells and were able to survive on their own. Muller acknowledged that 'it would be rash to call them genes, and yet at present we must confess that there is no distinction known between genes and them'. That opened up the possibility that 'we may be able to grind genes in a mortar and cook them in a beaker after all'.[20]

The crystallization of tobacco mosaic virus seemed to confirm Muller's view: if viruses were not genes, they were so similar that they could provide the ideal tool for investigating the mechanism of inheritance. When Delbrück went to America, he was already interested in phage and viruses, wondering if phage might be naked genes, and if genes were the elements of life. When he arrived at Caltech, he found Morgan's group waiting to welcome him: the fly boys were very interested in collaborating with physicists – largely thanks to Muller's X-ray work – but few of them could understand the maths of Delbrück's Green Paper. One of his first tasks upon arrival in Pasadena was to explain it to them.

The Phage Group

While the fly boys got to grips with his maths, Delbrück tried to master Drosophila genetics, but remembered spending his first few months at Caltech struggling – and failing – to understand the fly's genetic complexities. By this time, fly studies had become a mature field, with its own terminology and literature: engaging with it entailed reading a vast number of academic books and papers, as well as mastering all the practical aspects of the fly business. Delbrück later admitted that he 'did not make much progress in reading these forbidding-looking papers . . . I just did not get any grasp of it'.[21] He decided that the flies were too much for him and in any case, to a physicist, they seemed both too large and too complex. Physicists had often found that the first step in solving a problem was to simplify it, strip it down to the most basic possible components; working on Drosophila was like trying to deduce the essential principles of quantum physics from vast, problematic molecules like proteins. Delbrück wanted a biological equivalent to the hydrogen atom – one proton, one electron, no complications.

Before leaving Europe for the United States, Delbrück had already been vaguely aware that viruses might be interesting to work on. En route to Caltech in 1937, he had visited Wendell Stanley at the Rockefeller Institute labs, but was disappointed to find that even tobacco mosaic virus seemed too complex for the kind of simple experiments he had had in mind. When the Caltech flies got too much for him, Delbrück took a holiday and went camping. On his return, he discovered that he had missed a seminar on phage, given by Emory Ellis. 'I was unhappy that I had missed it,' Delbrück remembered, 'and went down to ask him afterwards what it was all about. I had vaguely heard about viruses and bacteriophages . . . I had sort of the vaguest of notions that viruses might be an interesting experimental object.'[22] This was what had led him to Ellis's lab.

Delbrück found Ellis eager to show him his phage experiments and he was impressed by what he saw. Despite starting out with no knowledge of microbiology or viruses, and using some very

primitive equipment, Ellis had mastered the basics of phage farming: growing *E. coli*; letting the phage attack them; and measuring the results. Delbrück was 'absolutely overwhelmed that there were such very simple procedures with which you could visualize individual virus particles'. At last, here was some biology that was as clean and simple as physics, which produced clear-cut, mathematical results. Phage seemed to Delbrück to have the potential to be biology's hydrogen atoms – the simplest possible example of life's ability to reproduce. And he decided to work with them until they provided the paradox he was after. 'This seemed to me just beyond my wildest dreams,' Delbrück remembered; finally he could do 'simple experiments on something like atoms in biology'.[23] Delbrück and Ellis agreed to work on phage together.

Delbrück was convinced that phage were not simply a chemical phenomenon, but were genuinely alive; they reproduced and grew like other organisms. He had to believe this if they were to be usable as models for more complex living organisms, but the idea that viruses were alive remained a minority view in the 1930s. The work of the Rockefeller Institute's protein chemists had persuaded most biologists that viruses, like phage, were some kind of enzyme, not an organism at all.

Northrop was sure that even if *some* viruses were alive, phage and tobacco mosaic virus were purely chemical – they were just too small and simple. Stanley had originally agreed with him, but – like Beijerinck before him – had decided that tobacco mosaic virus must be more than a chemical because it was impossible to produce except in living cells, a requirement that simple chemicals did not share. That was also part of what persuaded Delbrück that phage were living viruses; they only multiplied in the presence of living cells. They were also highly specific to their host – the phage that attacked *E. coli* did not attack other bacteria – and that pattern had been found in other animal and plant viruses. Also, phage were roughly the same size as other viruses and – most importantly of all – they were made of the same stuff, nucleoprotein.

As the arguments about what phage were continued, Delbrück concentrated on finding collaborators. He had originally decided to treat the bacterial cell as a black box, not to be opened because that would disturb the living system. His idea was simply to treat the number of phage that infected the bacterium as an 'input' and the number that were released when the cell disintegrated as an 'output' . He reasoned that such a simple approach would enable him to produce a mathematical equation that precisely described phage reproduction. Phage were, as he put it, 'a fine playground for serious children to ask ambitious questions'.[24] He had originally assumed that the project would take only a few months and he would be able to announce the 'secret of life' before his Rockefeller fellowship expired. Like many physicists, he soon realized that he had underestimated the complexity of biological problems: it took him two years simply to devise a reliable way of counting phage.

Long before he had discovered the secret of life, Delbrück's Rockefeller money ran out. He had to take a job as a physicist because there still was not much interest in the kind of hybrid 'biophysics' that he had begun with phage. Soon after, Delbrück met the Italian biologist Salvador Luria, who had heard of Muller's X-ray mutation work in Rome. Luria had also come across the Green Paper and Delbrück's physics-based concept of the gene. Luria soon had to leave the University of Rome; he came from a Jewish family and was forced out of his job by Italy's fascist government in 1938. He went to Paris for a while, but as German troops advanced on the city in 1940, Luria fled on a bicycle, eventually managing to leave Europe, via Spain and Portugal, for New York.

Delbrück realized immediately that this Italian refugee was the colleague he was looking for: Luria was a microbiologist; he had post-doctoral experience of physics, and he was already working on phage. Delbrück and Luria had both discovered that some bacteria were immune to phage attack, so they decided to tackle the central question of whether or not bacteria really had genes by finding out if phage-resistance was in fact a genetic mutation.

Many bacteriologists believed microbes had no genes (in part because bacteria have no nuclei), and that they must evolve in some kind of Lamarckian fashion, since they could apparently, for example, acquire phage resistance so rapidly once they were attacked.

One evening, Luria was considering this question as he watched his colleagues playing the slot machines at a club. The sporadic clatter of winning coins cascading from the machines set him thinking about randomness and probability. If the bacteria underwent genuine mutations, these must arise at random and as a result, the percentage of phage-resistant bacteria that grew on any given Petri dish would also be random. However, if the bacteria developed resistance in response to the attacking phage, the percentage of the resistant type should always be proportional to the number of phage. Luria did the experiments and Delbrück did the maths, and the numbers of resistant bacteria were indeed random. In 1943, they produced a jointly authored paper that convinced their colleagues that bacteria do indeed have genes, which behave in much the way as fly genes. (As we shall see in a later chapter, it was eventually realized that bacteria belong to an entirely separate kingdom of living things that lack a nucleus but do nevertheless have genes like those in other organisms.)

During their work, Delbrück and Luria had come across papers by Alfred Hershey that interested them. Luria met Hershey when he gave a paper at Washington University, in St Louis, Missouri, where Hershey worked on bacteriology. Hershey was also impressed by the potential of phage genetics and so what became known as the Phage Group was born. Delbrück, Luria and Hershey would add a new strand to molecular biology by providing a new tool – bacteriophage – with which to tackle some of its most important questions.

In 1944 molecular biology received an unexpected contribution from a physicist, in the shape of a little book with the ambitious title: *What is Life?* Its author was Erwin Schrödinger, one of the founders of quantum physics, who had come across Delbrück's Green Paper and been inspired by it. Schrödinger

believed that fully working out Delbrück's concept of the gene would indeed 'involve hitherto unknown "other laws of physics" which, however, once they have been revealed, will form just as integral a part of this science' as the existing laws. Schrödinger suggested that genes might consist of some kind of irregular (or 'aperiodic') crystal made up of several molecules that had the same number of atoms, but were arranged in different ways, that would give them different chemical properties (such molecules are known as isomers). He commented that 'the number of atoms in such a structure need not be very large, to produce an almost unlimited number of possible arrangements. For illustration, think of the Morse code. The two different signs of dot and dash in well ordered groups of not more than four allow of more than thirty different specifications.'[25] Schrödinger's choice of metaphor – that genes might be like codes – was to profoundly shape the way genetics developed after the Second World War.

Molecular biology also received an unexpected boost from the tragedy of the atomic bombing of Japan in 1945. Many argued that the bombs saved more people than they killed by bringing the war to a speedy end, but some young physicists were more persuaded by Robert Oppenheimer's assessment that 'the physicists have known sin, and this is a knowledge which they cannot lose'.[26] As direct military investment in physics of every kind increased to unprecedented levels, some of those who read Schrödinger's book were inspired to abandon what increasingly seemed to be the death-dealing science of bomb-making for the new field of molecular biology.

As the Phage Group's work progressed, it soon became clear that even these three exceptionally brilliant men were not going to discover the secret of life in a few months. So Delbrück set out to recruit disillusioned physicists. He organized annual phage meetings and, once he became a biology professor on his return to Caltech, took on graduate students who went out to spread the word about phage. The year after *What is Life?* appeared, Delbrück began teaching a summer course at Cold Spring Harbor Laboratory to instruct newcomers in the basics of phage.

The courses continued on an annual basis for twenty-six years and – as we will see – many of the twentieth century's most influential biologists graduated from Delbrück's Phage Course.

Although Delbrück later recalled that 'the phage group was not much of a group', its members communicated with each other constantly and that was vital to its success: the open spirit of sharing information and results was one of many borrowings from physics. Delbrück acknowledged that this aspect of the group's approach was 'copied straight from Copenhagen and the circle around Bohr', where 'the first principle had to be openness. That you tell each other what you are doing and thinking.'[27] Like Bohr's lab, the Phage Group enjoyed an atmosphere of amiable impertinence, at the centre of which was Delbrück, always delighted to talk to everyone and anyone. The many temporary workers who passed through Caltech and the annual summer phage course took Delbrück's methods and techniques with them, but they also tended to adopt his doctrine of openness and pass it on to their own colleagues and students. In 1944 a newsletter was established, the *Phage Information Service*, which, like the *Drosophila* newsletter it was modelled on, soon became a vital tool for the pioneers of phage genetics. Rapid communication of results was seen as vital, and Delbrück would declare 'pipette-free days' when everyone had to leave their benches and write up their results for publication. Once published and shared, openness led to rapid progress: a proliferation of interesting new results resulted in lots of publications, which in turn recruited numerous graduate students, and they, in turn, increased the attention being paid to phage and raised the profile of the phage researchers. The Phage Group's success meant that its philosophy and methods would be copied by many of the geneticists who followed them.

Another significant way in which physics influenced the new genetics was the drive for standardization. In the early days of phage each research group had its own strains, which had usually been procured from sewage farms or similar sites. To Delbrück, this was comparable to every physics lab using its own set of weights and measures, or its own definitions of acceleration and

force. Such disorder dissipated many of the benefits of co-operation, since it made it harder to compare one lab's results with another's. So he used his rapidly growing influence in the new field to enforce what became known as the 'Phage Treaty': any researcher who wished to be part of the developing phage network had to agree to work on one or more of a specific set of seven 'well-behaved' phages (the T series) that infected one specific strain of *E. coli*. Once every researcher was working on the same phage and using the standard techniques they had learned on the Cold Spring Harbor phage courses, it became possible to treat all the different Phage Groups scattered around the world as if they were one, big cooperating team. It was almost as if the phage themselves bound the groups together and made the cooperation possible.

As this scattered team worked on their viruses, they gradually became convinced that both bacteria and viruses do indeed have genes and that they behave in a standard Mendelian fashion, much like those of Drosophila. However, the central question remained unanswered: what were genes and how did they actually work? It gradually became clear that phage did not in fact feed on or consume bacteria; what the virus did was to take control of the bacteria's own cellular machinery, the equipment necessary for reproduction – that was why they could not be grown on a Petri dish, but needed living bacterial cells to duplicate themselves. Somehow phage hijacked the bacterium's reproductive apparatus so that the cell no longer reproduced itself, but produced phage instead. Delbrück and others could now explain the time lag between the phage attack and the death of the bacterium: that was the period during which a new generation of phage was developing – once there were too many for the bacterium to contain, it ruptured and died, releasing the new phage. This pattern strongly suggested that each phage contained some kind of template for making more phage, but what was the template composed of and where was it?

One important clue came from one of the expensive tools microbiology had acquired from physics, the electron microscope.

In the early 1930s, novel technologies, especially the cathode ray tube (the heart of the traditional television set), had made it possible to build microscopes that 'illuminated' objects with beams of electrons instead of beams of light. Because the wavelength of an electron beam was much shorter, the new microscopes allowed scientists to observe much smaller objects – several hundred times smaller – than had been possible with even the best light microscopes. The first electron microscopes were built in Germany in the mid-1930s, and when news of them reached America, some scientists thought the miraculous machine might be a Nazi hoax. But it was not. Soon, American companies like RCA were manufacturing them and, in an attempt to stimulate the market, started to investigate new applications. In 1940, RCA offered a $3,000 grant for exploring biological applications; it was won by a researcher called Thomas Anderson, one of the first American electron microscopists.

In 1941 Luria approached Anderson to see if he could take electron microscope photos of phage to see how big they really were. Anderson thought it possible, though Luria had first to apply for security clearance (the Rockefeller Institute's lab was involved in classified defence work at the time). Their first attempts failed, because the solutions of phage were not sufficiently concentrated, but by March 1942 Luria had managed to increase the concentration enough for successful pictures to be made; they revealed phage to be shaped something like tadpoles with a distinct head and tail. The fact that phage had such a relatively complex anatomy added support to the argument that they were really alive. The other intriguing aspect of the early pictures was that they all showed the phage with their heads directed towards the bacterium, as if they were swimming towards it, like sperm towards an egg. (It took Anderson eleven years to demonstrate conclusively what he had long suspected, that this arrangement was in fact simply an accidental result of the way the specimens were prepared.) The sperm-like appearance suggested that phage infection might be something akin to fertilization. Even more intriguingly, the electron microscope photos seemed

to show that the phage did not actually penetrate the bacterium, instead they remained immediately outside it – and yet somehow they were still able to transfer their reproductive templates into the bacterium.

Chemical analysis had confirmed that phage consisted of nothing more than a protein coat surrounding a core of a nucleoprotein called deoxyribonucleic acid, or DNA. Presumably one or the other provided the template for producing new phage, but which? In the 1940s, several researchers had proposed that the still-enigmatic template was composed of DNA, but this claim was greeted with considerable scepticism; DNA seemed such a small, simple chemical compared with the relatively vast protein molecules. Despite his preference for a simple system to experiment on, Delbrück went so far as to reject DNA as a 'stupid' molecule, much too simple to provide the basis for building a complete new organism.[28] However, in 1952, Hershey and his colleague Martha Chase made use of another technology from physics, radioactive labelling, to reveal what the templates were made of. They took advantage of the fact that the proteins which made up the phage's coat contained sulphur but no phosphorus, while the DNA contained phosphorus but no sulphur. They labelled some phage with radioactive isotopes of each chemical and then infected bacteria with their labelled phage. Their analysis showed that the protein coat remained outside the bacterium, while all the DNA in fact entered the cell. The bacterium's protein-synthesizing equipment was hijacked by the phage's DNA to make new phage, each containing a copy of the original phage's DNA. Thanks to phage, the picture was now complete: genes were DNA.

As is well known, the year after Hershey and Chase's work, two researchers in Cambridge – James Watson (a graduate of the phage course) and Francis Crick – worked out the chemical structure of DNA. Their announcement of the famous double helix was made possible by the work of many other people: Rosalind Franklin and Maurice Wilkins at King's College London had done the X-ray crystallography which had suggested the helical

form; Erwin Chargaff had performed the chemical analysis that showed that there were always equal amounts of the four key constituents that made up DNA: equal amounts of the bases adenine (A) and thymine (T), on the one hand, and of guanine (G) and cytosine (C) on the other. These exact matches proved crucial to understanding how the two strands of the double helix were attached to each other, and how it was possible for DNA to accurately copy itself; adenine always pairs with thymine, and guanine with cytosine, so that each strand of the helix is a complementary copy of the other. Phage and the Phage Group had provided the crucial evidence that phage and bacteria actually possessed genes – thanks to Hershey and Delbrück's experiments on phage resistance; they then demonstrated that those genes were composed of DNA. None of that diminishes Watson and Crick's achievement, but it is a useful reminder that – like any brilliant theoreticians – they could not have done it on their own.

Medical phage

The discovery of DNA's role in heredity made modern genetics possible, but it had some unexpected, even paradoxical effects. One might assume that Delbrück would have been delighted that 'his' phage programme had led to Watson and Crick's triumph, but in fact DNA was to prove the ultimate disappointment for him. Once the structure of DNA had been worked out, it became clear that it copied itself through a simple chemical process: it demanded no new laws of physics. Delbrück lost interest in phage, handing over the programme to his younger colleagues, and took up new biological challenges, still searching for the paradox that would generate radical new theories, but never finding it.

Another irony is that Felix d'Hérelle never played any part in the phage genetics revolution. He spent five years at Yale University, trying but failing to interest American doctors in the possibility of phage therapy, using phage to treat illness by attacking the bacteria that caused the disease. In 1933 he accepted an invitation to join a Soviet phage research institute in Tiflis

(Tbilisi). The economic depression in the West was forcing Yale to cut its funding for d'Hérelle's work (he had even made up the shortfall in his department's budget out of his own pocket). Meanwhile his Soviet counterparts received substantial state support, not least because the USSR was still suffering regular outbreaks of epidemic diseases such as cholera. In Soviet Union, he found himself, for the first time in his life, treated as a scientific star and surrounded by attentive, well-trained staff and servants (he even had a chauffeur), and all the modern facilities he could imagine. But – fortunately, as it turned out – he also maintained a private lab in Paris and spent every summer there. Although he was not a communist, d'Hérelle found the intellectual climate attractive: his neo-Lamarckian views on bacterial inheritance fitted in well with the prevailing Soviet dogma of Lysenkoism.

D'Hérelle was also disillusioned by the callous helplessness of the democracies in the face of the Depression and hoped that the USSR might be more active and organized in working to improve the lives of its citizens. He argued that it was crucial in studying disease to observe the 'natural host', humans:

> Because all illnesses studied by significant authors were 'artificial' illnesses (neither the rabbit nor the guinea pig are affected by cholera or typhus in the natural environment) they have bearing only when talking about the artificial illness and not at all practical for application to real, natural illnesses which occur in humans . . .[29]

He hoped that the resources of the USSR would finally allow progress to be made, especially as he saw it as a state run on rational principles which was thus unfettered by what he perceived as the prejudice against his ideas which had held back phage therapy elsewhere. He was to be disappointed. In 1937, the director of the Tiflis institute was arrested and shot; although he was largely uninterested in politics, he had somehow made an enemy of Lavrenty Beria, the head of Stalin's secret police. D'Hérelle was in Paris when he heard the news; he never returned

to the USSR. However, the use of phage therapy remained widespread in the USSR and in other Eastern Bloc nations; it remained so after the war and many successes were claimed for it. D'Hérelle survived the war and the German occupation, and in 1947 received the belated recognition of being invited to lecture on phage at the Pasteur Institute, where he was presented with its medal (despite some opposition from within the institute). He never became interested in molecular biology and clung to his neo-Lamarckian beliefs until his death in 1949.

One might also have thought that the unravelling of how phage reproduced would finally have settled the argument about whether or not they were alive, but – perhaps surprisingly – Northrop and some of the protein chemists were still not persuaded. Northrop stuck to his guns, which could look like inflexible stubbornness, but is really a good example of how some scientific answers depend on the questions asked. Approaching phage as a chemist, using a chemist's tools and a chemist's understanding, they look chemical; but if you tackle them from a biologist's point of view, they seem biological. In a sense, both Northrop and Delbrück were right, and they were both wrong; some aspects of the way phage reproduce turn out to be very like the ways cells normally make proteins, which are in turn very like simple catalysis. Whether or not viruses can really be considered to be living is still an open question: it all depends on what is meant by 'living'.

The successes of the Phage Group inspired many geneticists to look for other small, simple, fast-breeding organisms that could accelerate their research. Meanwhile, working in a field alongside the phage workers at Cold Spring Harbor was a geneticist who wanted to slow things down, to take a large, complex, slow-breeding organism and adapt her work to its pace; her name was Barbara McClintock and she built her reputation by working on one the Americas oldest, most important crops, corn.

38. J.B.S. Haldane to S. Wright, [5 July 1919]: S. Wright, 'Series II: Correspondence'.
39. John Maynard Smith, quoted in M.B. Adams, 'Last Judgment: The visionary biology of J.B.S. Haldane', *Journal of the History of Biology*, 2001: 457–91: 477. Haldane's sister Naomi also remembered them both as 'clumsy and accident-prone': N. Mitchison, 'Beginnings', in *Haldane and modern biology*: 300.
40. S. Wright to J.B.S. Haldane, [31 March1948]: J. Haldane, 'Box 20: Scientific Correspondence' (Haldane Collection: Library Services, University College, London).
41. S. Wright, 'Birth and Family (Series III: Biographical and autobiographical materials)'.
42. J. Cain, 'Interviews with Professor Robert E. Sloan', 1996 http://www.ucl.ac.uk/sts/cain/projects/sloan/
43. Dobzhansky, 1947. Quoted in G. Allen, *Life Science in the Twentieth Century* (Cambridge University Press, 1978): 142.
44. W.E. Castle and H. MacCurdy, *Selection and Cross-breeding in Relation to the Inheritance of Coat-pigments in Rats and Guinea-Pigs*: 3.
45. S. Wright to J.B.S. Haldane, [8 June1934]: S. Wright, 'Series II: Correspondence'.

Chapter 8: Bacteriophage: The virus that revealed DNA

For **viruses** and their discovery, see: S.S. Hughes, *The virus: a history of the concept* (Heinemann Educational, 1977); A.P. Waterson and L. Wilkinson, *An introduction to the history of virology* (Cambridge University Press, 1978).

My account of **Felix d'Hérelle** and **the history of bacteriophage** relies on the work of William Summers, in particular: 'From culture as organism to organism as cell: Historical origins of bacterial genetics', *Journal of the History of Biology*, 1991: 171–90; 'How Bacteriophage Came to Be Used by the Phage Group', *Journal of the History of Biology*, 1993: 255–67;

and *Félix d'Herelle and the origins of molecular biology* (Yale University Press, 1999).

For more about ***Arrowsmith* and its influence**, see: P. de Kruif, *The Sweeping Wind, A Memoir* (Harcourt, Brace & World, Inc., 1962); W.C. Summers, 'On the origins of the science in "Arrowsmith": Paul de Kruif, Felix d'Hérelle and Phage', *Journal of the history of medicine and allied sciences*, 1991: 315–32.

Details about **Max Delbrück and the Phage Group** come from: T.F. Anderson, 'Electron Microscopy of Phages', in *Phage and the origins of molecular biology* (Cold Spring Harbor Laboratory of Quantitative Biology, 1966); E.L. Ellis, 'Bacteriophage: one-step growth', in *Phage and the origins of molecular biology* (Cold Spring Harbor Laboratory of Quantitative Biology, 1966); C. Harding, 'Max Delbrück (oral history interview, July 14–September 11, 1978)' (Archives, California Institute Of Technology, 1978, http://resolver.caltech.edu/CaltechOH:OH_Delbruck_M); W. Hayes, 'Max Delbrück and the birth of molecular biology', *Social Research*, 1984: 641–73; E.P. Fischer and C. Lipson, *Thinking about science: Max Delbrück and the origins of molecular biology* (W. W. Norton & Company, 1988); W. Beese, 'Max Delbrück: A physicist in biology', in *World views and scientific discipline formation* (Kluwer Academic Publishers, 1991); T. Helvoort, 'The controversy between John H. Northrop and Max Delbrück on the formation of bacteriophage: Bacterial synthesis or autonomous multiplication?', *Annals of Science*, 1992: 545–75; G. Bertani, 'Salvador Edward Luria', *Genetics*, 1992: 1–4.

My ideas about the **importance of phage** and related issues are particularly indebted to the work of Lily E. Kay, especially: 'Conceptual models and analytical tools: The biology of physicist Max Delbrück', *Journal of the History of Biology*, 1985: 207–46; 'Quanta of life: atomic physics and the reincarnation of phage', *History and philosophy of the life sciences*, 1992: 3–21; and *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford University Press, 2000).

For the rise of **molecular biology**, see: R.C. Olby, *The path to the double helix* (Macmillan, 1974); P.G. Abir-Am, 'The discourse of physical power and biological knowledge in the 1930s: a reappraisal

of the Rockefeller Foundations "policy" in molecular biology', *Social Studies of Science*, 1982: 341–82; N. Rasmussen, *Picture Control: The Electron Microscope and the Transformation of Biology in America, 1940–1960* (Stanford University Press, 1997); P.G. Abir-Am, 'The Molecular Transformation of Twentieth-Century Biology', in *Companion to Science in the Twentieth Century* (Routledge, 2003).

Notes

1. S. Lewis, *Arrowsmith* (1925; Harcourt, Brace & World, Inc., 1952): 35–7.
2. ibid.: 166.
3. S.S. Hughes, *The virus: a history of the concept* (Heinemann Educational, 1977): 49, 109–12.
4. W.C. Summers, 'On the origins of the science in "Arrowsmith": Paul de Kruif, Felix d'Hérelle and Phage', *Journal of the history of medicine and allied sciences*, 1991: 315–32: 319; A.P. Waterson and L. Wilkinson, *An introduction to the history of virology* (Cambridge University Press, 1978): 87–8.
5. T. Helvoort, 'The controversy between John H. Northrop and Max Delbrück on the formation of bacteriophage: Bacterial synthesis or autonomous multiplication?', *Annals of Science*, 1992: 545–75; A.P. Waterson and L. Wilkinson, *An introduction to the history of virology*: 86.
6. A.P. Waterson and L. Wilkinson, *An introduction to the history of virology*: 91.
7. L.E. Kay, 'Quanta of life: atomic physics and the reincarnation of phage', *History and philosophy of the life sciences*, 1992: 3–21: 9–10.
8. P. de Kruif, *The Sweeping Wind, A Memoir* (Harcourt, Brace & World, Inc., 1962): 13–14.
9. ibid.: 60–61.
10. ibid.: 93; W.C. Summers, 'On the origins of the science in "Arrowsmith": Paul de Kruif, Felix d'Hérelle and Phage': 317; B.G. Spayd, 'Introduction', in S. Lewis, *Arrowsmith*: xv.
11. P. de Kruif, *The Sweeping Wind, A Memoir*: 96; W.C. Summers, 'On the origins of the science in "Arrowsmith": Paul de Kruif, Felix d'Hérelle and Phage': 317; B.G. Spayd, 'Introduction', in S. Lewis, *Arrowsmith*: xv.
12. T.J. LeBlanc, '"Arrowsmith" (review)', *Science*, 1925: 632–4.
13. *Lancet*, 1 August 1925, 234/2.
14. J.E. Greaves, 'Do Bacteria have Disease?', *Scientific Monthly*, 1926: 123–5: 124.
15. E.L. Ellis, 'Bacteriophage: one-step growth', in *Phage and the origins of molecular biology*, Cold Spring Harbor Laboratory of Quantitative Biology: 55.
16. W. Hayes, 'Max Delbrück and the birth of molecular biology', *Social Research*, 1984: 641–73: 648; E.L. Ellis, 'Bacteriophage: one-step growth': 55; W.C. Summers, 'How Bacteriophage Came to Be Used by the Phage Group', *Journal of the History of Biology*, 1993: 255–67: 258–9.
17. Delbrück interview: C. Harding, 'Max Delbrück (oral history interview, July 14–September 11, 1978)' (Archives, California Institute of Technology, 1978, http://resolver.caltech.edu/CaltechOH:OH_Delbruck_M.
18. ibid.; L.E. Kay, 'Quanta of life: atomic physics and the reincarnation of phage': 4.
19. Quoted in P.G. Abir-Am, 'The discourse of physical power and biological knowledge in the 1930s: a reappraisal of the Rockefeller Foundation's "policy" in molecular biology', *Social Studies of Science*, 1982: 341–82: 350.
20. H.J. Muller, 'Variations due to change in the individual gene', *American Naturalist*, 1922, 56: 48–9. Quoted in W.C. Summers, 'How Bacteriophage Came to Be Used by the Phage Group': 262.
21. Delbrück interview: C. Harding, 'Max Delbrück (oral history interview, July 14–September 11, 1978)'.
22. ibid.
23. ibid.
24. Quoted in L.E. Kay, 'Quanta of life: atomic physics and the reincarnation of phage': 11.
25. W. Hayes, 'Max Delbrück and the birth of molecular biology': 653–4.

26. J. Robert Oppenheimer, Lecture at MIT, 25 November 1947; 'Physics in the Contemporary World', *Bulletin of the Atomic Scientists*, Vol. IV, No. 3, March 1948: 66.
27. W. Hayes, 'Max Delbrück and the birth of molecular biology': 654.
28. Quoted in E.M. Witkin, 'Chances and Choices: Cold Spring Harbor, 1944–1955', *Annual Review of Microbiology*, 2002: 1–15: 14.
29. W.C. Summers, *Félix d'Herelle and the origins of molecular biology* (Yale University Press, 1999): 167–8.

Chapter 9: *Zea mays*: Incorrigible corn

Some of the **original scientific papers** referred to in this chapter include: G.H. Shull, 'A study in heredity (review of Johannsen, W., 1903)', *Botanical Gazette*, 1904: 314–15; W.E. Castle and H. MacCurdy, *Selection and Cross-breeding in Relation to the Inheritance of Coat-pigments in Rats and Guinea-Pigs* (Carnegie Institution of Washington, 1907); G. H. Shull, 'The Composition of a field of Maize', in *Report of the meeting held at Washington, D.C., January 28–30, 1908, and for the year ending January 12, 1908* (Kohn & Polloock, 1908); E.M. East, 'A Mendelian Interpretation of Variation that is Apparently Continuous', *American Naturalist*, 1910: 65–82; B. McClintock, 'Introduction to *The Discovery and Characterization of Transposable Elements*', in *The dynamic genome: Barbara McClintock's ideas in the century of genetics* (Cold Spring Harbor Laboratory Press, 1992).

For the **history of corn**, see: P.C. Mangelsdorf, *Corn: its origin, evolution, and improvement* (Harvard University Press, 1974); N.P. Hardeman, *Shucks, shocks, and hominy blocks: corn as a way of life in pioneer America* (Louisiana State University Press, 1981); J.B. Longone, *Mother maize and king corn: the persistence of corn in the American ethos* (William L. Clements Library University of Michigan, 1986); B. Fussell, 'Translating maize into corn: The transformation of America's native grain'. *Social Research*, 1999: 41–65.

For **Kellogg and cornflakes**, see: J.H. Kellogg, 'Plain facts for old and young: embracing the natural history and hygiene of organic life' (Electronic Text Center, University of Virginia Library, 1877 (1999), http://etext.lib.virginia.edu); J. Money, *The Destroying Angel: Sex, fitness & food in the legacy of degeneracy theory, Graham Crackers, Kellogg's Corn Flakes & American Health History* (Prometheus Books, 1985).

The story of **hybrid corn** and of **early maize genetics** is told in: P. de Kruif, *Hunger fighters* (Jonathan Cape, 1929); H.P. Riley, 'George Harrison Shull', *Bulletin of the Torrey Botanical Club*, 1955: 243–8; D.B. Paul and B.A. Kimmelman, 'Mendel in America: Theory and Practice, 1900–1919', in *The American Development of Biology* (University of Pennsylvania Press, 1988); D.K. Fitzgerald, *Business of Breeding: Hybrid Corn in Illinois, 1890–1940* (Cornell University Press, 1990); B. Kimmelman, 'Organisms and Interests in Scientific Research: R.A. Emerson's claims for the unique contributions of agricultural genetics', in *The Right tools for the job: at work in twentieth-century life sciences* (Princeton University Press, 1992); M.H. Rhoades, 'The Early Years of Maize Genetics', in *The dynamic genome: Barbara McClintock's ideas in the century of genetics* (Cold Spring Harbor Laboratory Press, 1992).

The main sources for **Barbara McClintock's life and work** are: E.F. Keller, *A feeling for the organism: the life and work of Barbara McClintock* (W.H. Freeman, 1983); H.B. Creighton, 'Recollections of Barbara McClintock's Cornell Years', in *The dynamic genome: Barbara McClintock's ideas in the century of genetics* (Cold Spring Harbor Laboratory Press, 1992); N. Fedoroff, 'Maize Transposable Elements: A Story in Four Parts', in *The dynamic genome: Barbara McClintock's ideas in the century of genetics* (Cold Spring Harbor Laboratory Press, 1992); N.C. Comfort, 'The real point is control: the reception of Barbara McClintock's controlling elements', *Journal of the history of biology*, 1999: 133–62; N.C. Comfort, *The Tangled Field: Barbara McClintock's Search for the Patterns of Genetic Control* (Harvard University Press, 2001).