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CHAPTER XIV

FROM PASTEUR TO PENICILLIN

> Just think of it. A hundred years ago there were no bacilli, no ptomaine poisoning, no diphtheria, and no appendicitis. Rabies was but little known, and these we owe to medical science. Even such things as psoriasis and parotitis and trypanosomiasis, which are now household names, were known only to the few, and were quite beyond the reach of the great mass of the people.
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> STEPHEN B. LEACOCK, *Literary Lapses* (1910)

MICRO-ORGANISMS

A PATCHWORK OF IDEAS AND INSTITUTIONS, theory and practice, craft and science, involving divided and vying professional factions, medicine has a generally muddled history, infinitely less clear-cut than, say, theoretical physics. But the latter part of the nineteenth century brought one of medicine's few true revolutions: bacteriology. Seemingly resolving age-old controversies over pathogenesis, a new and immensely powerful aetiological doctrine rapidly established itself – one that its apostles prized as the master-key to disease, even to life itself. Moreover, most unusually for medicine, the new disease theories led directly and rapidly to genuinely effective preventive measures and remedies, saving lives on a dramatic scale.

The general thinking behind bacteriology (that disease is due to tiny invasive beings) was far from new; theories of contagion, long proposed for maladies like smallpox and syphilis, maintained that disease entities were passed from the infected party to others; in the case of the pox, sexual intercourse offered the obvious transmission mode. Developing some hints in Galen, Girolamo Fracastoro had written in 1546 of disease seeds (*seminaria contagiosa*) carried by the wind or communicated by contact with infected objects (fomites); and the microscope confirmed the reality of wriggling, squirming 'animalcules'. Yet what grounds did anyone have for thinking that such 'little animals' actually caused disease?

Similar problems attended the putrefaction problem. What made substances go bad, decompose and stink? Why did grubs and mites appear on decaying meat and fruit? Did decay produce the insects (by spontaneous generation) or insects the decay?

By boiling up broth, sealing it in containers and showing that nothing happened, Francesco Redi (1626–98) believed he had proved that maggots did not appear on meat protected against flies, thereby discrediting the theory of spontaneous generation; in *De la génération des vers dans le corps de l'homme* (1699) [On the Generation of Worms in the Human Body], Nicholas Andry also argued that the seeds 'entered the body from without'. But, as so often, there were counter-findings. In 1748 John Needham (1713–81) repeated Redi's experiments; he boiled a meat infusion, corked it, reheated it and, on cooling, identified 'animalcules' in the broth which, he concluded, had appeared spontaneously. Convinced Needham had failed to protect his infusion from the air, Lazzaro Spallanzani maintained that broth, if boiled and hermetically sealed, would keep indefinitely without generating life. With no agreement as to where these 'little animals' came from, their alleged role in disease causation was a mare's nest.

The crucial issues raised were what such 'demonstrations' actually demonstrated (experiments are always open to multiple explanations), and whose experiments should be trusted. There were also metaphysical puzzles. For some, the very idea of 'spontaneous generation' smelt of scandal. It contravened the doctrine that God alone could create life and mocked the natural order, opening the door for whimsy and weirdness in the generation of 'monsters'. Nature, reason taught, was constant and lawlike; hence, was not spontaneous generation as preposterous as centaurs or six-headed cows? Yet certain *philosophes* of materialist leanings, like Diderot, had a soft spot for spontaneous generation precisely for that reason, since it rendered God the Creator otiose while proving that Mother Nature was fertile, creating novel forms as she went along. Spontaneous generation therefore remained a bone of contention, both experimentally and philosophically. The debate had immediate implications for disease aetiology.

Belief in specificity gained ground in nineteenth-century medicine,

thanks to the rise of patho-anatomy. So might not specific animalcules (parasites and bacteria) be responsible for particular diseases? There was no clear-cut evidence for this, partly because of the common assumption that all bacteria were much of a muchness. But that began to be challenged. In 1835, Agostino Bassi (1773–1856), an estate manager from Piedmont who was faced with the devastating silkworm disease, muscarine, argued that the fungus found on dead silkworms contained the cause of the disease; by inoculating healthy silkworms with it he could induce the sickness. Bassi's conclusions inspired Johann Schoenlein of Zürich (1793–1864) to investigate ringworm. He, too, found a fungus in ringworm pustules, concluding in 1839 that it was the cause of the condition.

Putrescence was also being hotly debated, thanks to Liebig's fermentation theories and to cell pathology. Working in Müller's Berlin laboratory, Schwann maintained that yeast cells caused fermentations and showed that heat would destroy the 'infusoria' responsible for putrefaction. Persuaded by Bassi, Jacob Henle (1809–85) claimed in *Pathologische Untersuchungen* (1840) [Pathological Investigations] that infectious diseases were caused by a living agent, probably of a vegetable nature, which acted as a parasite on entering the body: 'the substance of contagion is not only organic but living, and endowed with a life of its own, which has a parasitic relation to the sick body.' Broadly anticipating Koch's postulates, he theorized criteria for testing the pathogenic role of parasites: constant presence of the parasite in the sick, its isolation from foreign admixtures, and reproduction of the specific disease in other animals through the transmission of an isolated parasite.

Splicing together various strands of evidence – clinical, veterinary, epidemiological and zoological – Henle challenged spontaneous generation and miasmatism. A political liberal who, like Virchow, supported the revolutions of 1848, he regarded his findings as a ray of hope, presaging an end to the despairing therapeutic nihilism bedevilling Paris and Vienna; once the causal organisms were found, cures would follow. But his conclusions were slighted as speculative. Liebig's reading of fermentation and putrefaction as chemical not biological processes carried greater weight and chimed with dominant miasmatism and environmentalism. From 1857, however, the controversy was transformed by Louis Pasteur (1822–96).

PASTEUR

Born in the Jura, the son of a tanner who was a veteran of Napoleon's *grande armée*, Pasteur, like all ambitious French lads, went to Paris, getting his education at the École Normale Supérieure. Chemistry was his first love, and from the beginning he displayed the dazzling dexterity that became his trademark, selecting big problems which galvanized his energies, and becoming confident all problems could be solved in the laboratory.

Chemistry led him to biology, through experimentation on tartrates. It was known that tartaric acid (a waste product of wine-making) and racemic acid had identical chemical compositions but different physical properties. The crystals of tartrate compounds were asymmetric; solutions could be produced that rotated polarized light both to the left and the right. Pasteur concluded that such molecular asymmetry fundamentally distinguished living from inanimate things. Thereafter it was the properties of the living that fascinated him. Moving from crystals to life, he began to probe the meanings of micro-organisms, thereby laying the foundations for his abiding 'vitalism': a commitment to the irreducible divide between merely chemical and truly living phenomena. Thereafter his mission was to reveal the workings of biology.

Appointment in 1854 to a university chair at the manufacturing centre of Lille led him to study fermentation: the souring of milk, the alcoholic fermentation of wine and beer, the forming of vinegar. Liebig had stated that fermentation was a chemical process, regarding ferments as unstable chemical products. Pasteur promoted the notion of their specificity: fermentation, he held, was the result of the action of particular living micro-organisms. His new inquiries, continued after his return to Paris to take up a chair, centred on the souring of milk (lactic acid) and on the fermentation of sugar into alcohol; by 1860 he had established the biological (rather than chemical) character of fermentation, showing it required such micro-organisms as brewer's yeast. These organisms could in some cases even live without oxygen, in an atmosphere of carbon dioxide; they were thus 'anaerobic'.

This research programme, probing the specific actions of micro-organisms, blossomed into some of Pasteur's most spectacular demonstrations, designed to refute Félix Pouchet's claim to have established

spontaneous generation by means of critical experiments. The biologist Pouchet (1800–72) was himself no mean experimenter, and his doctrine of spontaneous generation, set out in his *Hétérogénie* (1854) [Heterogenesis], chimed with the reductionist scientific naturalism championed by anticlericals attempting to free science from the supernatural. On grounds both scientific and spiritual, Pasteur, however, discounted the possibility of life arising out of mere matter: *apparent* proofs, such as Pouchet's, merely betrayed shoddy lab techniques, and he devised ingenious counter-experiments to prove the essential role of micro-organisms.

As everyone knew, broth in a flask would go 'bad' and organisms would appear. Were these, as Pouchet claimed, spontaneously generated? Convinced they came from living agents in the atmosphere, Pasteur devised an elegant sequence of experiments. He passed air through a plug of gun-cotton inserted into a glass tube open to the atmosphere outside his laboratory. The gun-cotton was then dissolved and microscopic organisms identical to those present in fermenting liquids were found in the sediment. Evidently the air contained the relevant organisms. Further experiments showed air could be introduced without infecting a sterile infusion, if the air had previously been sufficiently heated. Thus the organisms present in air were alive and could produce putrefaction, but heating killed them. He next showed that an infusion could be sterilized and left indefinitely open to the air provided the flask's neck had a convexity pointing upwards: the *air* could pass up over this swan-neck but the *organisms* were impeded by gravity. Finally, he showed that micro-organisms were not uniformly distributed in the air. Taking numerous sealed flasks containing a sterile infusion, he broke and resealed the neck of each at a range of different altitudes; unlike in Paris, in calm, high mountain air very few of the flasks showed growth.

No fact is theory-free and incontrovertible. All the same, Pasteur's experiments were exceedingly impressive and persuasive, and when, in characteristically French manner, the lab war between Pouchet and Pasteur was officially adjudicated by the Académie des Sciences, the ruling came down decisively on Pasteur's side. (It surely helped that he was a Parisian establishment figure who could play upon conservative and Catholic anxieties that Pouchet's spontaneous generation was the creed of materialists and anticlericals.)

Developing a sense of duty and destiny, Pasteur marched majestically on to tackle the murky relations between micro-organisms, putrefaction and disease, showing that particular ferments were living forms. Continuing his work for the wine industry, he proved that the micro-organism *Mycoderma aceti* was responsible for souring wine and that heating it to 55°C eliminated the problem. Later, he applied the same principle to beer and milk: 'pasteurization' marked a major step towards the purifying of foods. Since it had been argued by Henle and others that fermentation, putrefaction and infection were related, it required no drastic leap for Pasteur to conclude that disease was a vital process, once he was sure the air was teeming with germs. The first disease he attributed to a living organism was *pébrine*, which was devastating the French silkworm industry. He showed it was caused by a communicable living organism (a protozoan), and laid bare its life cycle from moth through egg to chrysalis.

On 19 February 1878 before the French Academy of Medicine, Pasteur argued the case for the germ theory of infection. Later that year, in a joint paper with Jules Joubert (1834–1910) and Charles Chamberland (1851–1908), he spelt out his conviction that micro-organisms were responsible for disease, putrefaction and fermentation; that only particular organisms could produce specific conditions; and that once those organisms were known, prevention would be possible by developing vaccines.

In 1879 he put these ideas to the test in investigations of chicken cholera and anthrax, two diseases extremely destructive to French agriculture. He infected healthy birds with 'stale' cholera-causing microbes, two weeks or more old, and was intrigued to discover that no serious disease followed. Next he injected these same birds, and some others, with a new culture. Whereas the additional birds fell ill, those previously injected remained healthy. Here was the way to protect chickens against cholera – he had succeeded in immunizing the chickens with the weak, old bacteria culture, which afforded protection when he later gave them fresh, strong samples. Pasteur's hunch had paid off, but it was he who said that chance favours the prepared mind.

He then applied the same principle to anthrax, a highly contagious condition commonly affecting cattle and sometimes humans. It was a disease of the lungs, which often afflicted woolsorters, and was conventionally attributed to rural miasmas. Livestock losses were immense, and anthrax was particularly ruinous because it continued to develop in fields from which infected animals had long been excluded.

Fortunately, the groundwork had already been laid. Franz Aloys

Pollender (1800–79) and Casimir Joseph Davaine (1812–82) had observed microscopic bacilli in the blood of cattle which had died of anthrax. Robert Koch (1843–1910), soon to emerge as Pasteur's titanic rival, had also been investigating the disease. Koch had studied medicine at Göttingen under Wöhler and Henle; after serving as a surgeon in the Franco-Prussian War, he took a post as district medical officer (*Kreisphysikus*) in Wollstein, a small town in Posen (modern Poland), avidly pursuing microbiological researches in his backyard laboratory. Anthrax was severe in Posen. Koch found that under certain conditions the rod-shaped anthrax bacilli (*Bacillus anthracis*) formed exceedingly heat-resistant spores (small encysted bodies) in the blood. Neither putrefaction nor heat killed them, and they could later develop into bacilli. The persistence of the disease in fields was thus explained: it was through the spore. Koch's early laboratory work was technically adroit and systematic – the virtues which earned his later fame.

Using Koch's anthrax bacillus, Pasteur experimented with different time periods to find the way to attenuate its effect, and finally succeeded in producing a vaccine. He then staged a characteristically stunning public demonstration. On 5 May 1881 at Pouilly-le-Fort near Melun, he injected 24 sheep, 1 goat and 6 cows with living attenuated vaccine, leaving a similar number of animals uninjected. He gave the test animals a further and stronger injection on 17 May, and then on 31 May all the animals received a virulent anthrax culture. By 2 June, the control sheep and the goat were all dead and the cattle ill, but the vaccinated animals were fine. The experiment was a striking success, suggesting the possibility of preparing vaccines against diseases by attenuating the infective agent. Such demonstrations gave the germ theory a boost, though Pasteur was concerned less with basic microbiological theory than with concrete investigations, solving problems and contributing to prevention and cures.

Aided by Chamberland and Pierre Emile Roux (1853–1933), in 1880 Pasteur moved on to rabies, a disease dreaded since antiquity because its hydrophobic symptoms were so gruesome and death inescapable. His attempt to find the causative microbe was to no avail – not surprisingly, since the virus can be seen only with an electron microscope. Undeterred, he began his search for a vaccine by injecting rabies-riddled spinal cord tissue into rabbits' brains. When rabbit after rabbit had been injected with the same virus, a consistent incubation period of about six days was produced. The virus acting in this way was called

a *virus fixe*. He then injected this fixed virus into the spinal cord, and after death dried them. A cord dried for two weeks became almost non-virulent. In 1884 he made a series of 14 graduated vaccines and set up an experiment with 42 dogs: 23 received 14 injections each, one injection a day, starting with the weakest vaccine and ending with the strongest; the remaining 19 dogs were the controls, receiving no injections. At the end of two weeks, all the dogs were exposed to the rabies virus. None of the 23 immunized got the disease, whereas 13 of the control dogs did. A way had been found to give dogs immunity to rabies; Pasteur later showed that, because the incubation period was lengthy, vaccination worked even if the dogs had been infected for some time.

The moment of truth came on 6 July 1885, when Joseph Meister was brought to his doorstep. Two days before, this nine-year-old boy had been bitten fifteen times by a dog thought to be rabid, and a doctor had told the boy's mother to try Pasteur. He took the risk: he ordered a fourteen-day series of increasingly virulent (and painful) injections, and the boy stayed well. So did a second case treated three months later, a fourteen-year-old shepherd lad, Jean-Baptiste Jupille, from Pasteur's home-district of the Jura, who had been severely bitten as he tried to protect other children from a rabid dog.

These dramatic human interest events, expertly handled by Pasteur who had a flair for publicity and a way of presenting his experiments as more successful and conclusive than they were, captured the world's imagination and vindicated the role of experimental biology. Over the next fifteen months, the vaccine was given to well over two thousand people, and his rabies procedure became standard, with about 20,000 people worldwide being treated during the next decade. Though Pasteur won lavish praise, criticism was levelled as well, on the grounds that he was injecting perhaps perfectly healthy people (not all those bitten by rabid animals develop rabies) with what might prove an unsafe virus. His confidence was posthumously vindicated in 1915, however, when a ten-year study revealed that, of 6000 people bitten by rabid animals, only 0.6 per cent of those vaccinated had died, compared with 16 per cent of the rest.

On a wave of national enthusiasm created by rabies immunization, the Institut Pasteur was set up in 1888, and donations flooded in; appropriately Joseph Meister became the gatekeeper. When Pasteur died eight years later, he was buried in his Institute, consecrated as a shrine to medical science.

KOCH

Pasteur was a wizard, both within the lab and beyond, but bacteriology's consolidation into a scientific discipline was due mainly to Robert Koch (1843–1910) and his team and pupils, whose painstaking microscopic work definitively established the germ concept of disease and systematically developed its potential.

By formalizing the procedures for identifying micro-organisms with particular diseases, and by his insistence upon pure cultures, Koch elevated bacteriology into a regular science, rather as Liebig had normalized organic chemistry and Müller and Ludwig, physiology. Koch's paper on the aetiology of infectious diseases (1879) – a testament to his method and orderliness – launched upon the daunting task of discriminating among bacteria, connecting micro-organisms with particular effects, and settling the old question of whether bacteria were the cause of infection or simply background noise. It also offered an early formulation of what came to be known as Koch's Postulates. Formalized in 1882, these stated that to prove an organism was the cause of any disease, it was necessary to demonstrate

1 That the organism could be discoverable in every instance of the disease;
2 That, extracted from the body, the germ could be produced in a pure culture, maintainable over several microbial generations;
3 That the disease could be reproduced in experimental animals through a pure culture removed by numerous generations from the organisms initially isolated;
4 That the organism could be retrieved from the inoculated animal and cultured anew.

These conditions were mostly able to be fulfilled, though some pathogenic entities, notably viruses, had to be accepted without meeting all the conditions. The thinking behind these rigorous postulates, and their applicability, boosted the dogma of specific aetiology – the idea that a disease has a specific causative agent, with the implication that once this agent has been isolated, it will be possible to control the disease.

In isolating specific bacterial strains, artificial cultivation in liquid media had served Pasteur perfectly well. As superior microscopic techniques revealed the distortions these produced, Koch looked for solid

culturing media, beginning by growing bacteria colonies on a potato slice and later solidifying the standard broth by adding gelatin. This liquefied at body temperature, but that problem was solved by using agar-agar, an extract of Japanese seaweed, to solidify the culture medium on a special dish devised by Richard Julius Petri (1852–1921).

Koch scored his first great triumph on 24 March 1882, in revealing before the Berlin Physiological Society the bacillus causing tuberculosis, *Mycobacterium tuberculosis*, and thus at last settling the vexed question of its aetiology. In the following year, with another cholera pandemic heading Europe's way, he was sent to Egypt to investigate, arriving hard on the heels of a French team headed by Pasteur's colleague, Roux. The latter used the classic Pasteurian method, which was to reproduce the disease in animals and then look for the organism; but the method failed, because cholera affects only humans. Working directly on cholera victims, Koch isolated and identified *Vibrio cholerae* (the comma bacillus) in Alexandria in 1883 and more convincingly the next year in India, showing the bacillus lived in the human intestine and was communicated mainly by polluted water – thus vindicating fully the work of John Snow. He then went on to Calcutta, where he confirmed his findings, and in February 1884 reported his success to the German government, amid tremendous jubilation: first tuberculosis, then cholera!*

Koch became burdened with success, his research declined, and to offset that he turned oracle. The methods he had pioneered proved their worth, however, leading to the rapid discovery, largely by his own pupils, of the micro-organisms responsible for diphtheria, typhoid, pneumonia, gonorrhoea, cerebrospinal meningitis, undulant fever, leprosy, plague, tetanus, syphilis, whooping cough and various other streptococcal and staphylococcal infections.

* Koch's germ theory of cholera was disputed by the Munich hygienist Max von Pettenkofer (1818–1901), who upheld a version of the miasmatic theory and denied the bacillus was the *vera causa* of cholera. He got Koch to send him his cholera vibrios and put them to the test:

> Herr Doctor Pettenkofer presents his compliments to Herr Doctor Professor Koch and thanks him for the flask containing the so-called cholera vibrios, which he was kind enough to send. Herr Doctor Pettenkofer has now drunk the entire contents and is happy to be able to inform Herr Doctor Professor Koch that he remains in his usual good health.

Pettenkofer must have been fortunate enough to possess the high stomach acidity which sometimes neutralizes the vibrios.

Pasteur's dramatic success with the anthrax and rabies vaccines had fuelled expectations of instant therapeutic breakthroughs. All that was needed, it seemed, was that the relevant micro-organism had to be isolated in the laboratory, and an appropriate vaccine would follow as the night the day. In the event, success proved mixed and often completely elusive. Two early developments provided, respectively, a dazzling victory and a dramatic setback.

The triumph was diphtheria, a disease spread through droplet infection and producing fever, sore throat and a hard cough. A leathery membrane forms on the tonsils and palate, blocking the airways and often causing death. Especially in great cities, diphtheria assumed pandemic proportions after 1850. The death rate was high, occasionally being the principal cause of death among children. In New York in the 1870s, over 2000 children a year were dying of it.

In his *Des inflammations spéciales du tissu mugueux* (1826) [Special Inflammations of the Mucous Tissue], Pierre-Fidèle Bretonneau (1778–1862), an early advocate of germ theory, had distinguished it as a specific disease, coining the word *diphtérie* from the Greek for leather (*diphthera*), alluding to the choking tissue produced in the throat. In 1883 Theodor Albrecht Edwin Klebs (1834–1913), a pupil of Virchow, isolated and described its specific organism, the diphtheria bacillus (*Corynebacterium diphtheriae*), a rod-shaped bacterium. Friedrich Loeffler, one of Koch's assistants, then succeeded in cultivating it. (He also discovered the rod-shaped bacillus in healthy children, one of the observations that led to the concept of the carrier.)

Once the cause was known, the bacillus's action in the human system had to be established. Between 1888 and 1890, brilliant laboratory investigations in France by Roux and Alexandre Yersin (1863–1943), and in Germany by Karl Fraenkel (1861–1901), Emil Behring (1854–1917) and his Japanese colleague Shibasaburo Kitasato (1852–1931) resolved the problems. Roux and Yersin showed that the diphtheria bacterium produced a poison which, when inhaled, lodged in the throat or windpipe, generating a poisonous toxin in the blood-stream. This permitted definitive diagnosis.

In December 1890 Fraenkel showed that attenuated cultures of diphtheria bacilli, injected into guinea pigs, produced immunity. Working with Kitasato in Koch's Institute, Behring announced that the blood or serum of an animal rendered immune to diphtheria through the injection of the relevant toxin could be used to treat another animal exposed to the disease. Immune animals could be prepared by challenging them with gradually increasing doses of either bacillus or toxin.

Such a diphtheria antitoxin (a toxin-resisting substance) was first used on a child in a Berlin clinic on 25 December 1891. This dramatic Christmas rescue, outpasteuring Pasteur (how the modern media would have loved it!), proved a success. Serum production began, and its introduction in 1894 into Berlin hospitals brought an instant plunge in diphtheria mortality. Meanwhile in Paris, Roux and Yersin made large-scale serum production possible by using horses as sources of antitoxin. The French serum was introduced into England by Joseph Lister; diphtheria antitoxin came into general use about 1895, and within ten years the mortality rate had dropped to less than half (the epidemic was in any case spontaneously waning).

Especially once the Hungarian Béla Schick (1877–1967) developed the test bearing his name to identify the presence of immunity, large-scale immunization programmes were undertaken. In New York, the death rate had peaked at 785 per 100,000 in 1894; by 1920, it had dipped to under 100. By 1940, with 60 per cent of pre-school children immunized, diphtheria deaths had become a thing of the past.

The campaign brought a famous victory and, because, like rabies, it also involved children, it provided further superb publicity for the new bacteriology. New scientific possibilities had been opened up since – in contrast to Pasteur's live vaccines – it had now been shown that the cell-free serum of immunized animals could kill virulent bacteria, and protection could be transferred via serum from animal to animal. (This suggested that it was not simply the bacterial cell itself that caused disease, but a toxin it yielded.) On this putatively safer basis serum therapy was launched, with the production of antitoxins not just for diphtheria but also for tetanus, plague, cholera and snake bites. Yet serum therapy encountered problems of its own, for antitoxin production was impossible to control, and supplies varied in strength and purity. Occasional deaths of patients receiving antitoxin proved shocking, and serum sickness (fever, rash and joint pains) was a common side-effect. Apart from such practical troubles, profound questions were surfacing about the nature of the body's reactions to micro-organisms and chemicals.

If diphtheria was the dramatic therapeutic success, the dispiriting failure was tuberculosis, potentially the gold medal for the new science. Consumption had become the single largest cause of adult deaths in

the West. Thanks to the Paris school, cases could reliably be clinically diagnosed. Laennec and Bayle had unified the disease, and in 1839 J. L. Schoenlein, professor of medicine at Zürich, named the whole complex 'tuberculosis', since the tubercle seemed to be its anatomical root.

But its cause remained obscure and hotly disputed – was it hereditary, constitutional, environmental, or contagious? The received wisdom was that an 'innate susceptibility' or a 'diathesis' was to blame. Despite an army of 'cures', ranging from blistering to living in cowsheds to inhale the breath of cattle, and the new faith in the sanatorium on the magic mountain, tuberculosis seemed a good justification for therapeutic nihilism: 'I know the colour of that blood! It is arterial blood. I cannot be deceived in that colour. That drop of blood is my death warrant. I must die,' cried John Keats, on first coughing up blood – and how right he was. Some survived for a long time, and some recovered spontaneously; but no realist thought medicine cured the disease.

The idea that tuberculosis was communicable, though mainly rejected, had its advocates. William Budd (1811–80), best known for his work on typhoid fever, argued for contagiousness on the basis of epidemiological studies, and the French physician Jean Antoine Villemin (1827–92) attempted to confirm this by inoculating rabbits and guinea pigs with sufferers' blood, sputum, and secretions – work paralleled in Germany by Virchow's pupil Julius Cohnheim (1839–84). Villemin also argued for cross-contagiousness between humans and cattle, but his work had little immediate impact; attempts to repeat his rabbit experiments were inconclusive, and many mysteries remained. Rebutting Laennec, Virchow maintained that pulmonary and miliary tuberculosis were quite different diseases, though here he perhaps betrayed a chauvinism that killed three birds with one stone: denigrating both Paris and Pasteur, and voicing his perennial scepticism towards bacteriology.

Koch made the dramatic breakthrough. Having cultured a specific microbe apparently associated with tuberculosis, in 1882 he provided solid evidence from animal experiments, conformable with his 'postulates', that the tubercle bacillus was the specific cause of the disease. Then, after years of travelling and official duties connected with his prestigious Institute for the Study of Infectious Diseases, he began to work in the laboratory again, with great intensity and secrecy, perhaps feeling the need to eclipse Pasteur with one great therapeutic coup. In August 1890 all was revealed in a speech before the Tenth International Congress of Medicine in Berlin: Koch had found a substance which

arrested the growth of the tubercle bacillus in the test-tube and in living bodies, referring to his agent, which he called 'tuberculin', as a 'remedy' and thus leading the world to believe he had a TB cure.

Dazzling publicity followed, and Koch was fêted. Before tuberculin's efficacy and safety had been evaluated, the Kaiser personally conferred upon him the medal of the Grand Cross of the Red Eagle, and he received the freedom of the city of Berlin. Despite Germany's law prohibiting 'secret medicines', Koch avoided disclosing the nature of tuberculin. Sent to Berlin to report for the press, Arthur Conan Doyle (1859–1930) paid a call on Koch's son-in-law and found his office knee-deep in letters begging for the miraculous remedy; the whole business was like Lourdes.

Within a year thousands had received tuberculin treatment, without system or controls. It seemed to help some patients in the first stages of lupus (tuberculosis of the skin), but experience quickly showed that tuberculin was useless or even dangerous for patients with pulmonary tuberculosis. The fiasco brought a violent backlash, with denunciations of Koch and his secret remedy. A study prepared for the German government found little evidence to justify the claims made for tuberculin. Koch was rumoured to have sold his 'secret' to a drug company for a million marks, to help finance his divorce and remarriage.

In a paper published in January 1891, Koch at last revealed the nature of his remedy: tuberculin was nothing but a glycerine extract of tubercle bacilli. He was accused of divulging the great secret only when it had become obvious that tuberculin was financially worthless. He disappeared to Egypt with his young bride, leaving his underlings to cope with the débâcle.

To the end of his life, he continued to express the hope that an improved form of tuberculin would serve as an immunizing agent or cure. He was mistaken, though it did prove to have a use – not as a cure but as a diagnostic aid in the detection of early, presymptomatic tuberculosis. In the heroic tradition of the time, Koch had tested tuberculin on himself: his strong reaction indicated that, like most of his contemporaries, he had not escaped a 'touch of tuberculosis'; and what he had stumbled upon was the complex immunological phenomenon now called delayed-type hypersensitivity. The tuberculin test was put into service, and microbiology laboratories were able to help the physician monitor the patient's status by analysing throat cultures or sputum samples.

Koch made a further blunder: he wielded his authority to scotch Villemin's case that bovine and human tuberculosis were very similar. Human tuberculosis, Koch insisted, could not be transmitted to cattle, nor could bovine tuberculosis be communicated to humans. In this he was wrong, and only when his mistake was undone could it be recognized that transmission of tuberculosis from cattle to humans was a serious problem. This led to measures to purify milk through pasteurization and tuberculin tests. His latest biographer has concluded that Koch 'ended his career as an imperious and authoritarian father figure whose influence on bacteriology and medicine was so strong as to be downright dangerous'.

Despite the tuberculin débâcle, the search continued for ways of immunizing against tuberculosis. Attempts to protect individuals by injecting them with tubercle bacilli, killed or treated, had no success until a new method was developed by Albert Calmette (1863–1933), of the Pasteur Institute, and his collaborator Jean Marie Guérin (1872–1961). From 1906 they used living bacilli from a bovine strain of the tubercle bacillus so attenuated as to have lost their disease-producing properties while retaining their protective reaction. The vaccine was given the name BCG (Bacille-Calmette-Guérin); it was first used for inoculating calves and then, from 1924, after delays caused by the First World War, was extended to humans. By 1928 it had been successfully given to 116,000 French children, though its efficacy remained controversial. With medicine thoroughly tainted with nationalism, Germany declined to approve BCG, as did the USA; in Britain its uptake was dilatory, but it was used successfully in Scandinavia, where it markedly reduced the death rate. After the Second World War, the BCG vaccine was central to a huge Danish Red Cross vaccination programme in war-devastated Europe.

The great infectious diseases were targeted by the new bacteriology with mixed success: discovery of the infective agent by no means always led to effective therapies. Nevertheless, in the twenty-one golden years between 1879 and 1900 the micro-organisms responsible for major diseases were being discovered at the phenomenal rate of one a year. Typhoid was one.

By 1837 the distinction between typhoid fever and typhus fever had been established, and the typhoid micro-organism was isolated in 1884 by Koch's pupil, Georg Gaffky (1850–1918). Immunization against typhoid was introduced by Almroth Wright (1861–1947) in 1897, but its efficacy was disputed by the statistician Karl Pearson (1857–1936) and only a fraction of the British troops received it during the Boer War; in South Africa 13,000 men were lost to typhoid as against 8000 battle deaths. Controversy raged until a special anti-typhoid commission reported favourably in 1913; the army then adopted a policy of vaccinating all soldiers sent abroad. The results were dramatic: whereas in the Boer War typhoid incidence was around 10 per cent with a mortality of 14.6 per 1000, in the Great War incidence was down to 2 per cent, with a minuscule death rate. Because of the presence of paratyphoid fever on the eastern fronts, killed cultures of paratyphoid bacilli A and B were added to the vaccine, so that it became known as T.A.B.

Another success, proved by the First World War, came with tetanus. This extremely dangerous disease (the death-rate is above 40 per cent) is caused by tetanospasmin, a toxin secreted by the bacterium *Clostridium tetani* which lives in the soil. The bacillus enters the body through agricultural cuts and battlefield wounds, and the toxin travels along nerve fibres towards the spinal cord. Sweating and headaches are followed by increasingly severe muscular spasms in the head and neck (lockjaw). Though known to Hippocrates, nothing could be done until the bacteriological era. The tetanus bacillus was discovered, like so many others, in the 1880s. Arthur Nicolaier (1862–1942) produced it in mice by inoculating them with garden earth; Kitasato grew it in a pure culture in Koch's laboratory in 1889, leading to the production of antitoxin. (He also found it grew when deprived of oxygen, an early example of the anaerobic bacteria group, discovered in 1861 by Pasteur.) Tetanus became a serious problem at the outset of the 1914–18 war, when the bacillus entered the body through gaping shell wounds. From 1915 practically every wounded soldier received antitoxin, and tetanus was dramatically reduced.

Some progress was also made with plague. The bacillus was discovered independently by Kitasato and Yersin during the Hong Kong epidemic in 1894. The Swiss-born Yersin had studied in Paris, becoming Roux's assistant and publishing papers with him on diphtheria before leaving to satisfy his wanderlust in the Far East. He returned to bacteriology, but in the colonial context, going to Hong Kong to investigate the plague epidemic spreading from China.

In June 1894, more or less simultaneously with Kitasato, Yersin isolated the plague bacillus now known as *Yersinia pestis*, reproducing the disease experimentally in healthy rats and transmitting it from rat to rat. 'The plague', he wrote dryly, 'is contagious and inoculable. The rat probably is the principal vector and one of the most promising prophylactic measures would be extermination of rats.' It had long been observed that outbreaks of a deadly disease among vermin preceded outbreaks of plague in humans; these epizootics which preceded epidemics finally became recognized as being due to the plague bacillus, conveyed via the *Xenopsylla cheopis* flea.

Exploiting this discovery, however, posed further problems. Bacteriologically, plague differs from diphtheria in that the organisms, instead of remaining localized, multiply rapidly throughout the body. The filtrate of a culture of plague bacilli was not very toxic and so conferred no immunity. The first vaccine made from killed cultures of plague bacilli came from the Russian, Waldemar Haffkine (1860–1930), an ex-pupil of Pasteur working in British government service in India, one of the world's plague centres. Its success was rather limited, and nothing helped much before antibiotics.

A significant breakthrough in understanding and management also followed with undulant fever, a disease involving fever, with muscle and joint pains. Many of the British sick and wounded in the Crimean War, shipped to Malta to recover, had contracted this condition. In 1887 Major David Bruce (1855–1931) isolated the causative organism in 'Malta fever'. The organism was of the spherical or coccus type, being called *Micrococcus melitensis* (from *Melita*, Latin for Malta). Goats were found to be highly susceptible, excreting the organism in their milk, and a ban on drinking goats' milk produced a dramatic fall in the disease. Ten years later the Norwegian Bernhard Bang (1848–1932) independently described a very small bacillus found to cause contagious abortion in cattle. This *Bacillus abortus* also caused an obscure and persistent condition in humans; named undulant fever, it was common in the Mediterranean. In 1918 it was concluded that Bruce's *Micrococcus melitensis* and Bang's *Bacillus abortus* were identical. A new name *Brucella abortus* was coined in Bruce's honour, and the diseases caused by them became *Brucellosis* – another triumph for British terminological imperialism. The health gains following this discovery were limited; the British garrison on Malta was protected from contaminated milk, but no efforts were made to reduce the incidence of *Brucellosis* among the local population.

Though by any criteria bacteriology had a dazzling string of successes to its credit, certain diseases proved refractory. One was scarlet fever, a dreadful killer of infants throughout the nineteenth century. Streptococci were first isolated from the blood of scarlet fever patients by Edward Klein (1844–1925) in 1887, but he was unable to reproduce the disease in animals. And while streptococci could be recovered from the throats of scarlet-fever patients, the next steps – showing, following Koch's postulates, that the bacterium was the true cause of the disease and then producing a vaccine – were stymied. The streptococcus was found to be pathogenic for various laboratory animals, but on injection it hardly ever produced typical scarlet fever.

In 1924, George (1881–1967) and Gladys Dick (1881–1963), at the University of Chicago, identified haemolytic streptococcus as the causal agent and succeeded in infecting volunteers after swabbing their throats with a culture obtained from scarlet fever patients; they also established a test for immunity (the Dick test). But, as with many other communicable diseases, what brought its decline was not a therapeutic breakthrough but a healthier environment and improving patient resistance.

DEBATES OVER IMMUNITY

Whereas Pasteur developed attenuated live vaccines, German researchers pioneered serum therapy. They turned their attention from cellular to so-called 'humoral' immunity once it was shown that animals could be made immune to the toxins produced by diphtheria and tetanus bacilli, thanks to injections of immune serum. Opposing their view that a bactericidal property resided in the serum, a counter-theory was developed by Élie [Ilya Ilyich] Metchnikoff (1845–1916), the Russian pathologist appointed in 1887 as sub-director of the Pasteur Institute. This dispute became the scientific expression of Franco–German and Russo–Japanese rivalries.

How did the body develop immunity to protect itself against organisms? Recognition had been growing from the mid nineteenth century that normal blood could destroy bacteria, but little was understood of how that happened: Pasteur preferred vaccines to theories. In 1884 Metchnikoff observed a phenomenon which suggested a cellular theory of immunity and resistance. He saw amoeba-like cells in water fleas and other lower organisms 'ingesting' foreign substances like fungi. These

cells, he concluded, might be similar to the pus cells in the inflammatory response of higher organisms. Microscopic observations on animals infected with various micro-organisms, including the anthrax bacillus, revealed white blood cells attacking and appearing to digest these disease germs, 'fighting infection' like soldiers. Pasteur gave Metchnikoff's ideas his nod, while Koch and most German bacteriologists demurred; Koch even suggested that white blood cells might be more like a fifth column through which germs spread into the organism. Metchnikoff's cellular immunity theories became connected with the French school, and chemical theories with the German view that germ wars were waged less by the blood cells than by the serum.

Metchnikoff styled the cells which ingested micro-organisms 'phagocytes' (from the Greek *phagein*, to eat, and *kutos*, cell). Macrophages was his name for the large mononuclear cells of the blood and tissues which ingested foreign particles; microphages were the leucocytes of the blood, active in ingesting micro-organisms. In what became the cellular (phagocytic) theory of immunity, he showed that one special kind of macrophage, the white cell (granulocyte), ate bacteria, and also that the body's supply of such cells multiplied when infection struck. His views constitute perhaps the first model of immune response.

The alternative serum or humoral theory viewed infections as caused by bacilli-produced toxins; filtrates of these, containing no organisms, caused disease when injected into animals, the bacillus producing its effects through exotoxins in the filtrate. But the serum of treated animals equally acquired the property of neutralizing toxin: Behring and Kitasato called this property 'antitoxic'.

By 1890 scientists had thus identified both a cellular and a serum system. Koch's tuberculin work pointed to a third – a group of smaller, light-staining white cells different from Metchnikoff's larger, dark-staining white granulocytes. These became known as lymphocytes. The body thus appeared to have an immune system made up of various elements which worked by combining forces. This possibility was strengthened in 1895 when two Belgian biologists, Joseph Denys and Joseph Leclef, modified Metchnikoff's views. The Russian held that the leucocytes from an animal immunized against a certain organism actively engulfed that organism (phagocytosis). Working with streptococci, they showed that, if the leucocytes from a treated animal were placed in immune serum, the resultant phagocytosis was exceptionally active.

These ideas were developed further by Almroth Wright, director of the Institute of Pathology at St Mary's Hospital in London, a larger-than-life figure caricatured on stage as Sir Colenso Ridgeon in George Bernard Shaw's *The Doctor's Dilemma*. Wright held that the action of both normal and immune serum was due to the presence of certain substances which promoted phagocytosis. Likening these to a sauce making the bacteria more tasty for the leucoctyes, he called them opsonins (Greek, *opsonein*, to prepare food), these being antibodies facilitating phagocytosis. The level of opsonic activity could be seen as a measure of a patient's defences against bacterial infection – hence the slogan Shaw put into Ridgeon's mouth: 'Stimulate the phagocytes!' The Englishman's work on opsonins appeared to marry the chemical (German) and cellular (French) theories of immunity, though his limitless faith in immunization ('the physician of the future will be an immunizer' he predicted) proved unjustified.

All such antigen-antibody reactions (as they were later called) had certain features in common, protecting the individual against bacterial poisons. But it was found that comparable reactions could occur which were harmful rather than preservative. With diphtheria antitoxin treatment, some patients developed serum sickness (fever, nettle rash, muscle and joint pain), something first studied in Vienna by Clemens von Pirquet (1874–1929), and his assistant Béla Schick. Examining reactions to substances such as pollen, von Pirquet decided they were due to antigen-antibody reactions and coined the term 'allergy' to indicate the hypersensitive state producing abnormal reactions to certain foreign substances. Allergic reactions had been known since the Greeks; John Bostock (1773–1846) had coined the term 'summer catarrh' (hay fever), and John Elliotson (1791–1868) identified pollen as the agent; but the cause of such reactions had remained mysterious.

Bacteriological investigations of resistance and immunity also brought to light the baffling question of the carrier. Experience showed that the diphtheria bacillus sometimes persisted in the throats of convalescent patients; in 1900 a case was reported of a healthy individual passing typhoid bacillus in his urine, and some persons convalescing from enteric fever still excreted the organism, forming a worrying source of further infection. It was soon realized that some carriers could excrete it for many years, the most notorious being the Irish-born 'Typhoid Mary' who, though well herself, infected many people in New York with enteric fever between 1900 and 1907. The mechanisms of immunity

were evidently more complicated than anyone had surmised, and early military images of gunning down 'invading' micro-organic pathogens obviously needed refinement.

CHEMOTHERAPY

Chemical theories of response were systematized by Paul Ehrlich (1854–1915), from 1899 director of the Royal Prussian Institute for Experimental Therapy in Frankfurt-am-Main. A truly seminal thinker, Ehrlich had a personal interest in these matters, since he had discovered tubercle bacilli in his sputum, had tried Koch's tuberculin therapy and had spent a year in Egypt convalescing. He drove immunity investigations one stage further by developing chemotherapy, pinning his faith on the creation of artificial antibodies.

Treatment by natural drugs, above all herbs, goes back to the dawn of medicine; experience showed that certain substances had therapeutic properties. Paracelsus had proclaimed specific remedies for specific diseases, and Sydenham had hoped that one day every disease would have its own remedy, on the model of the Peruvian bark for malaria. From time to time new medications had been hit upon, as with the Revd Edmund Stone's discovery of willow bark, which was the first stage on the road to aspirin.*

As shown in Chapter 11, the study of *materia medica* developed during the nineteenth century into laboratory-based pharmacology. Meanwhile drugs research and manufacturing became inseparably linked. The booming chemical industry developed pharmaceutical

* That road was long. In 1826 two Italians found that willow bark's active ingredient was salicin, and three years later a French chemist obtained it in pure form. Meanwhile the Swiss pharmacist Johann S. F. Pagenstecher began extracting a substance from meadowsweet (*Spirea ulmaria*, a pain reliever well-known to folk medicine), which led to the German chemist Karl Jacob Löwig (1803–90) obtaining the acid later known as salicylic acid. Its molecular structure was ascertained in 1853 by Karl Friedrich Gerhardt (1816–56), a Montpellier chemistry professor, who tried to eliminate its severe side-effect: the painful irritation of the stomach-lining. In time Felix Hoffman (1868–1946) came up with acetylsalicylic acid, found to be not only a painkiller but anti-inflammatory and anti-pyretic. In 1899, a new name was invented for the drug: aspirin. The following year, the German Bayer drug company took out patents on it and it became their best-selling product, indeed the most popular drug of all time; in the United States, over 10,000 tons of aspirin are used annually.

divisions, often as a sideline of the thriving dyestuffs business. In Britain W. H. Perkin (1838–1907) isolated mauve (aniline purple) from coal tar in 1856, but it was German entrepreneurs who excelled in exploiting dyes and organic chemistry.

Drug production became industrialized, with many of the companies appearing that later dominated the field. In 1858 E. R. Squibb opened a laboratory to supply medicines to the US army. Benefiting from the Civil War, his firm expanded rapidly, producing pure ether and chloroform, and using steam power for pulverizing drugs. The Eli Lilly Company was founded in Indianapolis in 1876; Merck and Company, a branch of a leading German chemical firm, opened in the United States in 1891; Parke, Davis & Company, formed in 1867, established one of the earliest research institutes in 1902.

Technological advances helped the drugs firms. Mass-production of sugar-coated pills started in France, being refined in 1866 by William R. Warner, a Philadelphia manufacturer who also began production of small pills (parvules). The gelatin capsule was developed, being brought into general use about 1875 by Parke Davis. Capsules not only made medicine easier to swallow, they ensured a precise dose. Mechanization also made the tablet possible. A tablet-compression machine was introduced in England by William Brockedon in 1843 and in the USA by Jacob Denton in 1864.

Henry Wellcome (1853–1936) was born in Wisconsin, the son of a travelling Second Adventist minister. Inspired by a doctor uncle, he went into pharmacy, sweated as a travelling salesman (peddling pills, not salvation), and hitched up in his mid twenties with Silas Burroughs (1846–1895), who had the capital Wellcome lacked. Burroughs was the first American to bring medicines to Britain in mass-produced, machine-made tablets. Setting up in Holborn, Burroughs, Wellcome and Co. procured the British patent for the process, inventing 'Tabloid' as their trade-mark (the term's application to newspapers came much later).

Developing its research side, the pharmaceutical industry joined hands with academic pharmacology, whose institutional development followed the familiar German path. Institutes, notably those at Dorpat and Bonn, produced research schools employing chemists and physiologists. By 1900, pharmaceutical manufacturers were turning discoveries made in university laboratories to profit. Such cooperation between science and commerce was not always plain-sailing: industrial patenting

and profit-seeking potentially clashed with the ideals of open scientific inquiry. When John Jacob Abel (1857–1938) and some academic colleagues established the American Society for Pharmacology and Experimental Therapeutics (1908), they excluded anyone in the permanent employ of a drug firm.

Wellcome ran into similar problems in Britain when he sought registration for animal experimentation at his Wellcome Physiological Research Laboratories, set up in 1894. Although he maintained his laboratories were independent of his drug firm, they were financed out of company profits and in practice linked with the manufacturing side. With the backing of key members of the British medical establishment, however, he obtained the necessary Home Office authority for animal experiments, and other British pharmaceutical firms followed, as animals were used to raise antitoxins and test products.

The symbiosis between science and industry was closest in Germany: Ehrlich's Frankfurt Institute research laboratories had ties with the Hoechst and Farbwerke Cassella companies. In his quest for chemical cures, Ehrlich thus had a long tradition of pharmaceutical developments and microbiological investigations to draw on. His vision lay squarely within the framework of the new bacteriology, taking the idea of natural antibodies and transferring it to synthetic drugs. The idea had been already present in his doctoral thesis, which held that specific chemicals could interact with particular tissues, cells or microbial agents. Systematically exploring the range of dyes manufactured by the German chemical industry – dyes were evidently promising because, as histological staining made clear, their action was specific, staining some tissues and not others – Ehrlich was intrigued by the molecular (stereochemical) aspects of physiological and pharmacological events. Above all, he believed chemical structures were crucial to the actions of biologically active compounds, and that they could not affect a cell without being attached to it: *corpora non agunt nisi fixata* (substances do not react unless they become fixed) was one of his adages. A 'receptor' was a structure that received a dye. If there were dye receptors, why not drug receptors? Ehrlich began looking for substances fixed by microbes but not by the human host.

His first contributions to immunity theory came in the 1890s. Pondering how tetanus antitoxin actually worked, he advanced a series of significant hypotheses. Each molecule of toxin combined with a particular, invariant amount of antitoxin; the toxin-antitoxin connection involved groups of atoms fitting together like a key in a lock; tetanus

toxin became bound to the cells of the central nervous system, attaching itself to the chemical 'side-chains' on the cell protoplasm, thereby blocking their physiological function. This blockage led the cell to produce fresh side-chains to compensate for what was blocked. These were the antibodies produced by toxin action.

Ehrlich's side-chain, or chemical affinity, theory was based on the assumption that the union of toxin and antitoxin was chemical in nature, involving agents specifically toxic for particular bacteria, which would have no effect on the host. An antibody in the blood, produced in response to a certain micro-organism, was specific for that organism and highly effective in killing it, but harmless to the host. Antibodies (nature's remedies) were magic bullets which flew straight to their mark and injured nothing else. The challenge was thus to find chemical equivalents tailormade for a particular organism and non-injurious to its host. Chemotherapy would be the discovery of synthetic chemical substances acting specifically on disease-producing micro-organisms.

Guided by this model of antigen-antibody reactions, Ehrlich set out to find agents specifically bound to and toxic for particular bacteria. In 1891, with quinine's action in mind, he treated malaria with methylene blue, one of the aniline dyes – the first instance of Ehrlichian chemotherapy; the results, he thought, were promising. The next targets for his new chemotherapy were the trypanosomes, the causative agents of sleeping sickness. For this he tried a drug called atoxyl and similar arsenical compounds. This was quite effective, but caused neurological damage and blindness by way of side-effects.

Next he turned to syphilis. That disease had seemingly become more virulent again in the nineteenth century; certainly it was a disease of the famous, including Baudelaire and Nietzsche, the myth being popular among the *avant garde* that it contributed to genius, providing drive and restless energy. Many writers were positively exalted at getting poxed (or were good at putting a brave face on it). 'For five weeks I have been taking mercury and potassium iodine and I feel very well on it,' boasted Guy de Maupassant in 1877:

> My hair is beginning to grow again and the hair on my arse is sprouting. I've got the pox! At last! Not the contemptible clap . . . no – no – the great pox, the one Francis I died of. The majestic pox . . . and I'm proud of it, by thunder. I don't have to worry about catching it any more, and I screw the street whores and trollops, and afterwards I say to them, 'I've got the pox'.

The natural history of syphilis had been clarified. In 1837 Philippe Ricord (1800–1889) established the specificity of syphilis and gonorrhoea through a series of experimental inoculations from syphilitic chancres. He also differentiated primary, secondary and late syphilis, the three stages of infection. In 1879 the German bacteriologist Albert Neisser (1855–1916) identified the gonococcus causing gonorrhoea, and in 1905, the protozoan parasite causing syphilis was discovered by Fritz Schaudinn (1871–1906) and Erich Hoffman (1868–1959); found in chancres, this spiralling threadlike single-celled organism was named the *Spirochaeta pallida* (since renamed the *Treponema pallidum*). Diagnostic screening was made possible in 1906 when August von Wassermann (1866–1925) developed a specific blood test. Despite these substantial advances in knowledge, no therapeutic advances had been made upon the wretched mercury, in use since the sixteenth century. Arsenical compounds such as atoxyl were mildly effective but injurious.

Seeking a chemical cure, by 1907 Ehrlich had synthesized and tested over 600 arsenical compounds. He took out a patent on Number 606, but went no further. In 1909 the Japanese bacteriologist Sahachiro Hata (1873–1938) began work as his assistant and retested the whole series of synthetic preparations for their action on the *Treponema*. It became clear that 606 was very active. After two physicians had volunteered as guineapigs, Ehrlich's collaborators began intramuscular injections of 606 on some of their most hopeless patients, and were surprised at the improvements engendered by a single injection. By September 1910 about 10,000 syphilitics had been treated with Preparation 606, by then named Salvarsan. It transformed syphilis treatment, especially once it was used in the modified form of Neo-Salvarsan (1914), now called neoarsphenamine. This represented a considerable advance, but it was toxic and still required many painful injections into the bloodstream over a long period before a cure was complete – the 'magic bullet' didn't cure syphilis 'like magic'.

Once Salvarsan was discovered, would not other chemical magic bullets follow rapidly? Though plausible, that hope proved wrong. Many compounds, including some new synthetic dyes, were tried against the common bacterial diseases (the cocci and bacilli), but without success. Chemotherapy came to seem, after all, an impossible dream. Well into the twentieth century, for most infections there were no effective therapies; ancient and useless remedies like emetics were still prescribed; as late as the 1920s, the professor of applied pharmacology at Harvard,

H. W. Haggard (1891–1959), confessed that medicine could 'do little to repair damage from diseases'. The only effective chemotherapeutic substances, as distinct from painkilling drugs like morphine, were mercury, and Salvarsan and its variants, antimony for schistosomiasis, and quinine. Quinine's action was still little understood; it was thought to have a selective affinity for malaria parasites in the blood, but in laboratory experiments it was hardly active in killing the malaria parasite. This suggested that the action was not a direct destruction of the parasites but a change produced in the body tissues inhibiting further parasite development. The situation changed, however, in 1935, when Gerhard Domagk (1895–1964) published his experiments with Prontosil.

Searching, like Ehrlich, for chemical remedies, Domagk devoted his early years to testing the therapeutic potential of metal-based compounds – gold, tin, antimony and arsenic. None worked: their antibacterial actions were too weak or their toxic side-effects too strong. In 1927 he was appointed research director of I. G. Farbenindustrie, the chemical company which had absorbed such familiar names as Bayer and Hoechst. Since his firm's main products were azo dyes used for colouring textiles, he decided, like Ehrlich, to see whether they had any negative effect on streptococci, organisms that produce infections including erysipelas, tonsillitis, scarlet fever and rheumatism. In 1932 he found that one azo compound, Prontosil red, a brilliant red dye, cured mice injected with a lethal dose of haemolytic streptococci. Domagk successfully treated his own daughter with it for a streptococcal infection.

Scientists at the Pasteur Institute in Paris obtained Prontosil samples for investigation. Synthesizing the drug, they verified Domagk's results, and found it worked when the compound split into two parts within the body, and that one of the two parts, later called sulphanilamide, was largely responsible for Prontosil's 'bacteriostatic' action – that is, it did not *kill* bacteria but prevented them from multiplying in the host, thus allowing the host's immune system to destroy them.

Domagk went into production with his new drug. As it could not be patented (Prontosil was basically sulphonamide, which had been synthesized back in 1907), it became readily available. At Queen Charlotte's Maternity Hospital in London, Leonard Colebrook (1883–1967) used it to treat puerperal fever and found it was a 'miracle drug', slashing mortality from 20 to 4.7 per cent – and at last realizing Semmelweis's dream.

Though effective against streptococci, Prontosil was little use

against pneumococcal infections, and scientists began to look for comparable drugs. In 1938, a British team, led by A. J. Ewins (1882–1958) of May and Baker, developed M&B 693 (sulfadiazine 693, later called sulphapyridine), which worked well against pneumococci and was even better than sulphanilamide against streptococci. M&B achieved fame when it saved the life of Winston Churchill, seriously ill with pneumonia at a critical stage of the Second World War.

All these compounds were bacteriostatic, affecting the bacterial metabolism and preventing its multiplication in the host, thereby permitting natural body defences to succeed against the invader. As well as puerperal fever, the new drugs checked the pathogens in erysipelas, mastoiditis, meningitis, and some urinary diseases, including gonorrhoea: sulphanilamide could dispose of a case of gonorrhoea in just five days. Domagk was awarded the Nobel Prize in 1939, but Hitler disapproved of such things and had Domagk detained by the Gestapo to prevent his going to receive it (he received it in 1947).

These new 'sulpha drugs' began to be prescribed in vast quantities: by 1941, 1700 tons were given to ten million Americans. However, deaths were reported, and strains of sulpha-resistant streptococci appeared. Controls over pharmaceuticals were then minimal, and experience showed that the sulphonamides had their dangers and could also become ineffectual. They nevertheless represented a major step towards the control of bacterial diseases, and their development spurred research into other anti-microbial agents.

ANTIBIOTICS AND THE DRUGS REVOLUTION

Pasteurian bacteriology opened up the vision of biological (as distinct from chemical) agents being deployed to destroy bacteria. But what sort of biological agents might prove effective? Folklore suggested that fungi might be antibacterial: popular medicine widely recommended mould for treating wounds or cuts. But clear observations of antibacterial action came later, notably by Pasteur in 1877: while anthrax bacilli rapidly multiplied in sterile urine, the addition of 'common bacteria' halted their development. In 1885, the Italian Arnaldo Cantani (1837–93) painted the throat of a tubercular child with bacterial strains and reported that the bacteria in his mixture displaced tubercle bacilli while reducing fever. He stated the principle of bacterial antagonism: one

infective pathogen would drive out another, a notion chiming with popular Darwinian notions of the struggle for existence.

The condition in which 'one creature destroys the life of another to preserve his own' was called 'antibiosis' by Paul Vuillemin (1861–1932). He termed the killer or active agent the 'antibiote'. In due course the word antibiotic (meaning destructive of life) was brought in by Selman Waksman (1888–1973). The first antibiotic to be described was penicillin, a natural by-product from moulds of the genus *Penicillium*. It was brought to light through the work of Alexander Fleming (1888–1955), a Scottish bacteriologist at St Mary's Hospital, London.

During the First World War, Fleming had been working on wounds and resistance to infection, demonstrating that the harsh chemical antiseptics used to cleanse wounds damaged natural defences and failed to destroy the bacteria responsible for infection. He was therefore receptive to the phenomenon of lysis, then under investigation. Exploring staphylococci in 1915, Frederick Twort (1877–1950) noticed that in some cultures the microbial colonies tended to disappear. He filtered some of these, and found a few drops poured over a staphylococcus culture produced degeneration. In 1917, working with cultures obtained from dysenteric patients, Felix d'Hérelle (1873–1949) found that the diluted filtrate produced lysis (dissolving) of the organisms in a broth-culture of the dysentery bacillus. He called the lytic agent the *bacteriophage* (or simply *phage*, meaning eater). Such experiments tended to suggest that lytic agents, generally found in the intestinal tract, were most active against one particular bacterial species or related types, having no effect on others.

Aware of these developments, Fleming's mind was receptive to the first of his discoveries, made in November 1921, when he identified the enzyme lysozyme, a component of tears and mucous fluids. This arose from accidental contamination of a culture of nasal mucus by a previously undescribed organism; it happened to be uniquely sensitive to the lytic action of the enzyme in the mucus, and Fleming observed its colonies being dissolved. The enzyme, which he called 'lysozyme', while it did not kill harmful bacteria, was clearly part of the body's defence system. Sceptical about chemotherapy – once infection entered the body, he believed, it was the body which would have to contain it – Fleming regarded lysozyme in a different light, belonging as it did to that class of substances which bodies themselves produced against outside intrusions.

Fleming's identification of penicillin came six years after the lysozyme discovery, in August 1928. He had been working on staphylococci, the pathogens responsible for boils, carbuncles, abscesses, pneumonia and septicaemia. Returning from holiday, he found that a mould which had appeared on a staphyloccus culture left in a petri dish in his St Mary's lab seemed to have destroyed the staphylococcus colonies. In a paper published in 1929 he identified the mould as *Penicillium rubrum* (actually it was *Penicillium notatum*). While the penicillin strongly affected such Gram-positive* bacteria as staphylococci, streptococci, gonococci, meningococci, diphtheria bacillus and pneumococci, it had no toxic effect on healthy tissues and did not impede leucocytic (white cell) defence functions. This weighed heavily with Fleming in view of his general opinions on wound treatment; penicillin appeared not just strong but safe. Yet it had no effect on Gram-negative bacteria, including those responsible for cholera and bubonic plague; it was hard to produce and very unstable, and thus did not seem clinically promising. Fleming did nothing, and the scientific community paid little heed.

Ten years later, however, a team of young Oxford scientists, led by the Australian Howard Florey (1898–1968), head of the Dunn School of Pathology, and including the ebullient biochemist Ernst Chain (1906–79), a refugee from Nazi Germany, launched a research project on microbial antagonisms. Combing the scientific literature for antibacterial substances, Chain found Fleming's report, and the team began to grow *P. notatum*, soon encountering the difficulties involved in isolating the active ingredient from the liquid the mould produced – only one part in two million was pure penicillin. Another biochemist in the team, Norman Heatley (b. 1911), devised improved production techniques. They continued purifying the drug and began testing. On 25 May 1940 they inoculated eight mice with fatal streptococci doses, and four were then given penicillin. By next morning, all had died except the four treated mice.

Florey seized upon the drug's potential; his department went into production, using, in best Heath-Robinson manner, milk churns, lemonade bottles, bedpans and a bath tub until they thought they had enough to try it on a patient – a policeman near death from staphylococcal septicaemia following a scratch while pruning his roses. There was, in

* The bacteriologist J. M. C. Gram (1853–1938) devised a method for differentiating different sorts of micro-organisms, using a stain.

fact, so little available that his urine was collected to recycle as much of the drug as possible. By the fourth day, he had improved remarkably, but then the penicillin ran out and he died.

Recognizing that his laboratory could not produce enough, Florey approached British pharmaceutical companies, but they were too busy supplying wartime needs; so in July 1941 he went to the United States, enlisting aid at the Northern Regional Research Laboratory in Peoria, Illinois. There Heatley, working with Andrew J. Moyer (1899–1959), increased the penicillin yield thirty-four-fold (they made it in beer vats), and three American pharmaceutical companies went into production.

By 1943, British drug companies too had begun to mass-produce penicillin and, in May, Florey travelled to North Africa to perform tests on war wounds. The success was extraordinary. By D-Day in June 1944, enough was available to allow unlimited treatment of allied servicemen. In 1945, Fleming, Florey and Chain shared the Nobel Prize – Heatley received nothing. He was made to wait until 1990 for his reward: an honorary MD from Oxford University.

Penicillin proved highly effective against most types of pus-forming cocci, and against the pneumococcus, gonococcus, meningococcus and diphtheria bacillus, the bacilli of anthrax and tetanus and syphilis. Pre-penicillin, the pneumonia fatality rate was around 30 per cent; it dropped to around 6 per cent, and pneumonia, once the old man's friend, ceased to be a major source of death.

Research continued on the antagonism between fungi and moulds and harmful bacteria, but with sporadic success. In 1927 René Dubos (1901–81) had gone to the Rockefeller Institute Hospital in New York to conduct research on antibacterial agents in the soil. In 1939, with Rollin Hotchkiss, he isolated a crystalline antibiotic, tyrothricin, from a culture media of the soil organism *Bacillus brevis*. Tyrothricin proved active against a range of important bacteria but too toxic for the treatment of infection in humans. These observations, however, were suggestive, and they gave a major impetus to the development of more effective antibiotics.

In 1940 Selman Waksman (1888–1973), a Russian who had migrated to the United States and become a distinguished soil microbiologist, isolated an antibiotic called actinomycin. Though impressively lethal to bacteria, it proved so toxic that it was not tried clinically; however, it convinced Waksman that he was on the right trail. In 1944 he

discovered another species of this fungus, to which the name *Streptomyces griseus* was later given. From this he isolated the antibiotic streptomycin, which proved active against the tubercle bacillus, and its toxicity was relatively low. Use of streptomycin rapidly led, however, to resistant strains and it was found more effective when used in combination with para-amino-salycylic acid (PAS).

In 1950 testing began on a third anti-tuberculous agent, developed by Squibb and Hoffman-La Roche in the United States. This was isonicotinic acid hydrazide, or isoniazid. Like streptomycin, it was prone to resistance, but the shortcomings of these anti-tuberculosis drugs were minimized after 1953 by combination into a single long-term chemotherapy. Tuberculosis had been steadily declining over the previous century; antibiotics delivered the final blow.

The long anticipated therapeutic revolution had eventually arrived. A flow of new drugs of many kinds followed from the 1950s, including the first effective psychopharmacological substances. Some proved extremely valuable, others marginal, and a few positively dangerous. One of the most successful, or at least adaptable to many purposes, has been cortisone, isolated in the Mayo Clinic in the 1930s and put to use with spectacular success after the war, initially for rheumatoid arthritis and other inflammatory conditions. 'If the word "miraculous" may ever be used in referring to the effects of a remedy,' claimed Lord Horder (1871–1955), 'it could surely be excused here.' Arthritis sufferers, long bedridden, were able to get up and walk. Yet it had strong side-effects: ugly skin disorders, heart disease and stomach ulcers sometimes occurred; patients became obese and highly susceptible to certain infections. Clearly, hormonal treatments could disturb the body's homeostatic balance.

Drugs finally began to appear against viral conditions. For centuries the term 'virus' (from the Latin for 'slime' or 'poisonous juice') had signified a poison produced by living beings and causing infectious disease. But viruses understood as specific entities emerged as great enigmas out of bacteriological experimentation. Isolation of them became much easier from 1884, when Chamberland made a filter with pores small enough to hold back bacteria but large enough to allow viruses to pass through.

In 1886 Adolf Eduard Mayer (1843–1942) discovered that tobacco mosaic disease could be transmitted to healthy plants by inoculating them with extracts of sap from the leaves of diseased plants. Mayer

filtered the sap and demonstrated that the filtrate was still infectious. In 1897 Martinus Willem Beijerinck (1851–1931), seeking the microorganism responsible for tobacco mosaic disease, discovered that the disease was apparently transmitted by a fluid after it had passed through a 'bacteria-tight' filter. Concluding that the toxin was in the form of an infectious fluid, he introduced the term 'filterable virus' to refer to a cell-free filtrate as a cause of disease. Although few bacteriologists gave much credence to his notion of life in a fluid form, the discovery of the filterable virus attracted considerable attention. In 1901 James Carroll (1854–1907) reported that filterable virus caused yellow fever in humans, shifting the study from botany to virology, and freeing biology from the dogma of the cell.

Viral diseases were successively identified, for instance poliomyelitis, first clinically described at the end of the eighteenth century, while Simon Flexner succeeded in producing paralysis in monkeys with virus derived from infected nasal secretion. Vaccines for viral diseases followed, a key figure being the American John Enders (1897–1985). Growing viruses in animal tissues with Thomas H. Weller (b. 1915) and Frederick C. Robbins (b. 1916) at the Children's Hospital in Boston, by March 1948 Enders had grown mumps viruses in chicken-broth cultures, and by 1949 polio virus on human tissue. Enders next turned his attention to a measles vaccine, tested in 1960 and licensed in 1963. By 1974, it was judged to have saved 2400 lives in the US alone.

While vaccines had success, drug treatments against viruses proved difficult to develop, since viruses are intracellular parasites, with an intimate association with the host chemical solution. Only since the 1970s has progress been made, first with acyclovir, potent against herpes zoster (shingles), cold sores, and other herpes infections. In cells infected with the herpes virus, acyclovir is converted to a metabolic blocking agent, thereby largely overcoming the old and plaguing problem of toxicity to the host. Other viruses have been less amenable; influenza viruses continue to be a hazard, since they mutate rapidly.

Up to the 1960s new drugs could be launched without strict safety requirements. As laws became more stringent, requiring lengthy and exacting testing, the pace of innovation slowed. That may in some measure explain why the late twentieth century brought no new drugs whose impact could compare with the sulpha drugs or penicillin. Yet in the wider perspective the twentieth-century transformation appears impressive: effective vaccines were developed against smallpox, measles,

mumps, typhoid fever, rubella (German measles), diphtheria, tetanus, yellow fever, pertussis (whooping cough), and poliomyelitis, and successful drugs against many bacterial conditions, some viral infections, and numerous metabolic disorders.

'I will lift up mine eyes unto the pills', sang the journalist Malcolm Muggeridge in 1962, doubtless tongue in cheek. 'Almost everyone takes them, from the humble aspirin to the multi-coloured, king-sized three deckers, which put you to sleep, wake you up, stimulate and soothe you all in one. It is an age of pills.' He was right. Whereas before 1900 the physicians' pharmacy was largely a magazine of blank cartridges, many effective drugs have been introduced: antibiotics, antihypertensives, anti-arrhythmics, anti-emetics, anti-depressants and anti-convulsants; steroids against arthritis, bronchodilators, diuretics, healers of stomach and duodenal ulcers, endocrine regulators and replacements, drugs against parkinsonism and cytotoxic drugs against cancers.

Disasters happened too. Introduced as a safe sleeping tablet, Thalidomide was withdrawn in 1961 after causing horrendous foetal defects in over 5000 babies. Other tragedies and scandals came to light only later. For instance, beginning in the 1940s, the synthetic oestrogen diethylstilbesterol (DES) was given to women to prevent miscarriage and subsequently to prevent pregnancy. Some early studies showed that it was ineffective and, moreover, caused foetal abnormalities in animals, but these findings were ignored. Even after 1971, when it was discovered that DES caused a rare form of vaginal cancer in 'DES daughters' as well as other reproductive problems, it continued to be prescribed in the United States as a 'morning-after' pill. It was also used as a growth stimulant in livestock and, despite being known as carcinogenic from the 1960s, the influential US agricultural lobby stood behind DES.

In the century from Pasteur to penicillin one of the ancient dreams of medicine came true. Reliable knowledge was finally attained of what caused major sicknesses, on the basis of which both preventions and cures were developed. In the general euphoria created by the microbe hunters and their champions, some of the wider conditions of life contained within the evolutionary struggle were easily disregarded, the prospects of killing off diseases being too precious to ignore. In retrospect, far from the bacteriological and antibiotic paradigms then adopted

becoming the basis for the progress of all future medicine, the period between Pasteur and Fleming may one day be nostalgically recalled as an anomalous, if fortunate, exception to medicine's sisyphean strife.