INDUSTRIES OF INDIA

PENICILLIN

A Great Inventions of the Century book



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P E N I C I L L I N

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Reference numbers in square brackets resolve in the companion volume, Penicillin: Sources and How They Were Read.

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PART I - THE SUBSTANCE

Chapter 1 - What penicillin is

Penicillin is a small, fragile molecule with an unusual piece of architecture at its heart, and almost everything in this book - the decade it spent forgotten, the wartime crash programme, the industry that grew from it, the resistance that now threatens it - can be traced back to that architecture.

Strip the story to chemistry and penicillin is a dipeptide: two amino-acid-derived halves joined by a peptide bond, the same kind of bond that links the amino acids of every protein in every living thing [C4, C6]. One half derives from the amino acid valine, the other from cysteine - and it is cysteine that brings the sulphur. What makes the molecule extraordinary is how the bond is arranged. Instead of lying in an open chain, the peptide linkage is folded back and locked into a ring of just four atoms - three carbons and a nitrogen - which chemists call a beta-lactam ring. That four-membered ring is fused edge-to-edge to a second, five-membered ring containing sulphur, a thiazolidine. The result is a compact, lumpy molecule, no heavier than a couple of sugar molecules joined together, that nature had apparently never built before: when the Oxford chemists first proposed the four-membered ring in 1943, no such ring had ever been found in a natural product [C4].

Rings of four atoms are uncomfortable. The bond angles in a square of carbon and nitrogen are forced far from the angles those atoms prefer, so the ring is strained, like a bent spring, and a strained ring is a reactive one. The beta-lactam’s carbon-nitrogen bond sits under tension, ready to snap open at the first chemical opportunity. This is the whole secret of penicillin, in both directions. The strain makes the molecule lethal to bacteria, because the bond snaps open inside the active site of an enzyme that is building a bacterial cell wall and jams the machinery permanently, as the next chapter describes. And the same strain makes the molecule hopelessly delicate to handle, because almost anything can snap it open first.

The list of things that destroy penicillin reads like an inventory of an ordinary chemistry laboratory. Acids open the ring; so do alkalis. The molecule survives in water only as a salt and only within a narrow band of neutrality, roughly pH 5 to 8. Heavy-metal ions ruin it, including zinc and cadmium - which mattered when early producers grew the mould in whatever metal vessels were available. Ordinary alcohol reacts with it. So do many common laboratory reagents: thiols, aldehydes, oxidising agents. And certain bacteria carry an enzyme, penicillinase, whose only apparent purpose is to open the beta-lactam ring; that enzyme was identified in 1940, before penicillin had treated a single patient, and it would eventually become the central fact of the antibiotic era [C4, C6]. In 1929 Alexander Fleming could grow his mould in broth and show that the broth killed bacteria, but every attempt to concentrate the active substance destroyed it. “We were bacteriologists - not chemists,” he said later, “and our relatively simple

procedures were unavailing” [C2]. The molecule’s fragility, not any failure of observation, is the main reason thirteen years separated the discovery of penicillin from its first cure.

There was a second complication, and it took the wartime chemists to untangle it: there is no single penicillin. The mould makes a family of molecules that share the same fused-ring nucleus but carry different side chains attached to it, and which one predominates depends on the strain of mould and on what it is fed. By 1945 four natural penicillins had been crystallised and distinguished. The British, working with Fleming’s original strain grown in surface culture, dealt mostly with what they called penicillin I, known in America as F, which carries a five-carbon unsaturated side chain. The Americans, growing their strains on corn steep liquor, produced mainly penicillin II, or G, benzylpenicillin, which carries a phenylacetyl side chain and turned out to be the most useful member of the family; it is still, eight decades later, the penicillin of the world’s essential-medicines lists. Penicillins III and IV - X and K in the American notation - appeared in smaller amounts [C4, C6]. The discovery that the side chain could be swapped while the nucleus kept its power eventually became the foundation of the entire modern penicillin industry, but that belongs to a later chapter.

The common nucleus - the fused beta-lactam and thiazolidine rings with their one free acid group - was given a name when chemists finally isolated it in 1959: 6-aminopenicillanic acid, mercifully shortened to 6-APA. It is worth remembering that string of syllables, because 6-APA is the penicillin story in miniature. A mould makes it; chemists decorate it; factories in a handful of countries produce it by the thousand tonnes; and every penicillin pill ever swallowed, from the first wartime vial to the amoxicillin in a child’s medicine cabinet today, is built on that one small frame [C6, C8].

A word, too, about the name. Fleming coined “penicillin” in 1929 for the antibacterial substance in his mould broth, following the ordinary convention of the day: the word said where the substance came from, the mould genus Penicillium, just as digitalin said Digitalis, the foxglove [C2]. For years the word named a crude broth filtrate of uncertain composition. Only after the wartime chemistry did it come to name a defined molecule - or rather a defined family, the penicillins. The broader word “antibiotic” came later still, from the soil-microbe hunters who followed in penicillin’s wake, and the mould’s own gift has kept its original, modest name throughout: the thing from the Penicillium.

One property of the molecule deserves emphasis before the story begins, because it is easy to miss and everything hangs on it. Penicillin is poisonous to bacteria and almost harmless to us. Fleming’s crude broth could be diluted a thousandfold and still stop staphylococci growing, yet in his blood experiments it did no more damage to human white cells than plain culture medium, and injected into animals it appeared to have no toxicity at all [C2]. This selective toxicity is not a lucky bonus tacked onto the molecule; it is a direct consequence of its target. Penicillin

attacks a piece of chemistry - the building of a cell wall - that bacteria cannot live without and human cells do not possess at all. Paul Ehrlich had spent his career dreaming of a “magic bullet,” a chemical that would kill the microbe and leave the patient untouched [C1]. For thirty years the dream produced almost nothing. The bullet, when it came, came from a mould, and its magic was written in the shape of a strained four-atom ring.

Chapter 2 - How it kills

The first thing anyone saw penicillin do was dissolve living bacteria. On Fleming's contaminated plate in 1928, the staphylococcal colonies near the mould had gone transparent - the cells were not merely checked in their growth but were visibly undergoing lysis, coming apart [C2, C5]. In the series of experiments that followed, Fleming established that his mould broth did three distinct things: it stopped susceptible bacteria multiplying (bacteriostatic), it killed them (bactericidal), and it lysed them (bacteriolytic) [C2]. What it did not do was obvious to him at once, and just as important: it left human white blood cells unharmed at concentrations hundreds of times higher than needed to kill staphylococci. Explaining those facts - why a bacterial cell dies, why it bursts, and why a human cell does not care - took science another thirty years, and the explanation is one of the most satisfying pieces of detective work in twentieth-century biology.

The earliest clue was visual. Watch susceptible bacteria under a microscope as penicillin is added, and they do not simply stop. At low doses they grow into long filaments, cells that elongate but cannot divide; at higher doses they swell, deform and burst [C6]. Whatever penicillin was attacking, it had something to do with cell division and with whatever structure holds a bacterial cell in its shape. That structure is the cell wall, and in the 1940s almost nothing was known about it.

A bacterial cell is a bag of living chemistry under pressure. The cytoplasm inside is concentrated, the world outside usually dilute, so water constantly pushes in; the internal osmotic pressure of a bacterium can reach several atmospheres. What keeps the bag from bursting is the wall - and in particular one enormous molecule, called murein or peptidoglycan, that wraps the entire cell like a net. The net is a fabric of long sugar chains, alternating two amino-sugars (N- acetylglucosamine and N-acetylmuramic acid), with short peptide stubs hanging off every second sugar; the stubs of neighbouring chains are knitted together by cross-links, and it is the cross-linking that turns a stack of threads into a load- bearing fabric. When biochemists finally isolated and analysed walls in the early 1950s, they found this same basic design across the bacterial world, in organisms that otherwise share almost nothing [C6]. The wall is, in effect, the universal bacterial exoskeleton - and it is a structure no human cell possesses. Here, already, lies the answer to Fleming's white-blood-cell puzzle: a drug that sabotages wall construction can wreck a bacterium while passing straight through the biochemistry of its host.

The chemistry of the sabotage was uncovered in stages. In 1949 James Park and his colleagues noticed something odd: staphylococci treated with penicillin accumulated, inside the cell, large amounts of a peculiar set of molecules - uridine nucleotides carrying amino sugars and short peptide chains. Nobody knew what they were. Park and Jack Strominger then made the connection: these accumulating molecules were wall precursors, bricks manufactured inside the cell

that were piling up unused because the construction outside had been halted [C6]. Penicillin was not stopping the brick factory. It was stopping the bricklayers.

Wall construction turns out to be a conveyor belt with three stations. In the cytoplasm, the cell builds the precursor: a sugar backbone with a five-amino-acid peptide tail, ending in a distinctive pair - two D-alanines, mirror-image versions of the ordinary amino acid, a configuration almost never found in human biochemistry. The precursor is then ferried through the cell membrane and bolted onto the end of a growing wall strand. Finally, outside the membrane, an enzyme called a transpeptidase performs the decisive step: it grabs the peptide tail of one strand, clips off the terminal D-alanine, and uses the freed energy of that bond to lash the tail to a neighbouring strand. Cross-link after cross-link, the fabric is sewn tight around the cell. This final sewing step is the only one that needs no fuel - the chemistry of the D-alanine pair itself powers it - and it is exactly here that penicillin strikes [C6].

The mechanism, proposed by Strominger and Donald Tipper in the 1960s and confirmed in detail since, is molecular impersonation. One edge of the penicillin molecule has almost exactly the same shape as the D-alanyl-D-alanine end of a wall strand, and - the crucial refinement - the strained, reactive bond of the beta-lactam ring sits in precisely the position of the bond the transpeptidase normally attacks [C6]. The enzyme takes penicillin for its substrate. It opens the ring as it would open the D-alanine pair - and there the resemblance ends. The opened ring locks the penicillin covalently onto the enzyme’s active site, permanently. A transpeptidase that has grabbed penicillin never lets go and never works again. One molecule of antibiotic, one enzyme molecule dead. This is why vanishingly small concentrations of penicillin kill: it is not a poison that must fill the cell, but a saboteur that needs only to meet its target.

The enzyme targets soon had names and personalities. From 1949 onward, experimenters fed bacteria radioactive penicillin and asked where it went; the answer was always the same few proteins, bound irreversibly, which came to be called penicillin-binding proteins, or PBPs [C6]. Each bacterium keeps a small crew of them - staphylococci manage with four, gut bacilli like E. coli run seven or eight - and they have divided the wall-building work among themselves: one PBP specialises in building the septum that splits a dividing cell in two, others in elongating the wall, others in housekeeping and repair. The division of labour explains the old microscope puzzles. A beta-lactam that preferentially knocks out the septum specialist leaves a cell that can grow but cannot split - hence the filaments. One that knocks out the shape-maintaining enzymes gives swollen, round cells. Different members of the penicillin family have different preferences among the PBPs, which is part of why the later, semi-synthetic penicillins behave differently in the clinic from the original.

Why, though, does a bacterium with a blocked construction crew actually die and burst, rather than merely stop growing? The wall of a living bacterium is not a

finished shell but a building site in perpetual renovation: as the cell grows, wall-dissolving enzymes cut the old fabric to make room, and cross-linking follows behind to close the gaps. Penicillin freezes the sewing but not the cutting. The cell goes on enlarging, the autolytic enzymes go on opening breaches, and with no transpeptidase to repair them the breaches widen until the membrane, unsupported, gives way and the cell spills itself - lysis, exactly as Fleming watched on his plate [C2, C6]. The same logic explains a fact doctors learned early: penicillin kills only bacteria that are actively growing. A dormant cell, building no wall, has no work in progress to sabotage, and can sit out a course of treatment. These “persisters” were already troubling the Oxford clinicians in 1941, and they remain part of the explanation when infections relapse.

Two boundaries of penicillin’s power were visible from the very first plate. Fleming’s broth worked gloriously against the cocci - staphylococci, streptococci, pneumococci - and against the bacilli of diphtheria and anthrax, but it barely touched E. coli, typhoid, cholera or the influenza bacillus [C2, C5]. This is the Gram divide. Gram-positive bacteria wear their murein net thick and exposed on the outside; Gram-negatives hide a thinner net behind a second, outer membrane, a fatty, selectively permeable wrapper that keeps many molecules - including penicillin G - from ever reaching the wall. Much of the later history of the penicillin family is the story of chemists widening this doorway: ampicillin and amoxicillin slipped through it, and the cephalosporins and carbapenems walked further still. And the second boundary was enzymatic: some bacteria manufacture penicillinase, the beta-lactam-snipping enzyme, and simply cut the weapon apart before it can reach its PBPs [C4, C6]. That story - the story of resistance - grew from a 1940 footnote into the defining problem of the antibiotic age, and it has its own part of this book.

Stand back and the elegance of the design is striking. Penicillin is a shaped charge aimed at the single piece of chemistry every bacterium must run and no human cell runs at all: the cross-linking of a wall. Its toxicity is low not because nature was kind but because its target is absent in us. Its killing is swift not because it poisons the cell but because it turns the cell’s own growth into the instrument of destruction - the bacterium, in a real sense, bursts itself. Every property the clinicians would come to rely on, and every weakness the resistance engineers of the bacterial world would come to exploit, is folded into that one mechanism: the right shape, the right strain, the right place.

Chapter 3 - The enemy

To understand what penicillin did, you have to meet the organisms it met. They were not exotic. The bacteria that made infection the everyday terror of the pre-antibiotic world were ordinary inhabitants of skin, throat, soil and gut - creatures that lived with human beings constantly and killed them opportunistically. Penicillin's achievement was not to defeat a rare plague but to disarm a set of neighbours.

First among them stood the staphylococci and streptococci, the two great families of cocci, and they are the cast of this whole book: it was staphylococci on Fleming's plate, streptococci in the Oxford mice, and both together in Albert Alexander's blood [C1, C2]. The staphylococci - Staphylococcus aureus above all - are creatures of the skin and the wound. They seed boils and abscesses, invade any break in the skin, and, when they reach the blood, seed abscesses through the body: a septicemia that before 1941 was close to a death sentence, as the first penicillin patient illustrates [C1, C11]. The streptococci worked broader territory. Streptococcus pyogenes caused - still causes - the sore throats of every childhood, but in the world before antibiotics it also caused scarlet fever, erysipelas, the childbed fever that killed newly delivered mothers in their own beds, and wound infections that turned a torn uniform or a factory cut into a spreading, killing cellulitis [C10]. The puerperal fever chart in Domagk's Nobel lecture - deaths per hundred thousand live births, year by year through the 1930s - is the streptococcus written as a mortality curve, and the chart bends down only when the first drugs arrive [C10].

Behind the cocci stood the rest of the old enemies. The pneumococcus, Streptococcus pneumoniae, made pneumonia the commonest killer among the infections, filling the lungs of the young and the old; the meningococci and gonococci took the meninges and the genital tract; the diphtheria bacillus strangled children with a membrane of its own making [C2, C5]. And in war, above all, there were the spore-forming bacilli of the soil - the gas-gangrene organisms such as Clostridium septicum, which turned the mud-driven wounds of battlefields into spreading, gas-forming rot [C1]. It is not an accident that the Oxford team's first Lancet paper tested their new substance against exactly three organisms: Streptococcus pyogenes, Staphylococcus aureus and Clostridium septique. That is a battlefield list [C1].

What made these organisms so dangerous was not any single weapon but the arithmetic of unchecked multiplication combined with medicine's inability to intervene inside the body. Once bacteria established themselves in blood or deep tissue, the doctor's armoury narrowed to the patient's own defences - the white cells of Fleming's slide-cell experiment - plus rest, drainage, and surgery where surgery could reach [C2]. The white cells usually won against small invasions; against large ones they lost, and the loss was total. There was no middle

intervention, no way to tip the balance chemically from outside. That was the gap Ehrlich had named and failed to fill, and it is the gap into which penicillin fell [C1].

One more property of the enemy matters for everything after 1945, and Fleming saw it in his first experiments. His 1929 measurements showed a substance with a sharply specific spectrum: on his famous streak plate the sensitive microbes - staphylococci, haemolytic streptococci, the diphtheria and anthrax bacilli - stopped centimetres short of the mould while the typhoid and coli bacilli grew right up to it; his dilution tables add the pneumococcus, the gonococcus and the meningococcus to the sensitive list and the influenza bacillus, the proteus and pyocyaneus forms and the cholera vibrio to the untouched [C2, C5]. In modern terms, penicillin was a Gram-positive drug - devastating against the thick-walled cocci and bacilli whose peptidoglycan armour sits exposed, weak against the Gram-negative organisms that hide their wall behind an outer membrane [C6]. The specificity was a gift and a boundary at once: a gift, because it made penicillin an exquisitely targeted weapon against the commonest killers and even a useful laboratory sieve for isolating the germs it spared; a boundary, because whole classes of infection - typhoid above all - lay outside its reach [C2, C6]. The later chapters of this book are largely the story of medicine pushing at that boundary: wider-spectrum penicillins, new antibiotic families, and the bacteria’s own answering push, resistance. The enemy, it turned out, evolves.

It is worth saying plainly what the enemy cost, because the cost is the reason for everything that follows. Exact numbers belong to the next chapter, but the shape of the burden can be drawn from the organisms themselves: a world in which a rose-thorn scratch could kill a healthy policeman [C11], in which a mother could be delivered safely of a child and dead of childbed fever within the week [C10], in which pneumonia carried off the strong in days, in which every surgical operation ran a gauntlet of sepsis and every battlefield wound was a lottery against gangrene [C1]. That was not the distant past. It was the living memory of the people who built penicillin, and it is why they worked the way they did.

PART II - THE WORLD BEFORE

Chapter 4 - The world before

To feel what penicillin changed, begin in a surgery in, say, 1930. The physician at the bedside is not ignorant and not stupid. He - and it is usually he - can name the organism with confidence, culture it, stain it, tell the family precisely what is killing the patient, and chart its course almost to the day. What he cannot do is stop it. William Osler, the most influential physician in the English-speaking world, had written the creed of that helplessness nearly four decades earlier in his great textbook: pneumonia, he told his readers, “is a self-limited disease, and has its course uninfluenced in any way by medicine” [C36]. This was not despair. It was an honest description of the state of the art, delivered as teaching to generations of doctors: your task is to watch, to support, and to give an accurate prognosis.

The numbers behind the posture were grim, and everyone in medicine knew the worst of them by heart. Pneumonia - the pneumococcal lobar pneumonia of otherwise healthy adults - killed roughly one patient in four, and Osler himself had called it the “Captain of the Men of Death” [C36]. By the 1930s pneumonia was so large and so visible a killer that public-health officials in the United States tried to fight it the way they fought epidemics: with state programs, free laboratory diagnosis, and the one specific therapy that existed, type-specific antipneumococcal horse serum [C36]. The serum worked, after a fashion. Given early and matched to the exact pneumococcus type, it could pull a Type I case-fatality rate down from a baseline near 25 per cent to about 11 per cent; in the best reported hands, at the Rockefeller Institute hospital, mortality fell from more than 25 per cent to 7.5 per cent [C36]. But it was a biological product, not a medicine in any modern sense: expensive to make, typed against dozens of pneumococcal varieties that had first to be identified in each patient, and brewed in horses, so that the cure itself could sicken the patient it saved. A therapy that required a laboratory, a horse and a matched type was never going to be an answer for ordinary practice, and by the end of the 1940s the whole crusade had quietly folded - not because it failed, but because penicillin had made it unnecessary [C36].

What pneumonia was to the medical ward, sepsis was to the surgical one. Surgery in 1930 could be bold in the operating theatre and helpless afterwards: the operation was a triumph of technique, and then the wound bloomed. A deep, suppurating wound was its own country, walled off from everything the doctor could pour into it. When the Oxford team finally had penicillin in hand and sat down in 1941 to explain what made it different, they reached for exactly this failure as their yardstick. The sulphonamides - the best systemic antibacterials then in existence - “seem to have but little beneficial action” on heavily infected wounds, they wrote, and pus itself annulled the sulphonamides’ action in the test tube, while penicillin’s action was unaffected by pus and undiminished even

against massive bacterial inocula [S-H3]. Read their comparison the other way round and it is a precise description of the old world's ceiling: the best drug available retreated precisely where the infection was worst.

Blood poisoning was the terror that needed no hospital at all. A scratch, a thorn, a nick from a razor, an insect bite scratched raw - any of these could admit the staphylococci that everyone carries on their skin, and once in the blood they seeded abscesses as they went: in the lungs, the bones, the heart's valves. Septicaemia of this kind was close to a death sentence, and it killed the young as readily as the old [C1, C11]. The first patient ever to receive systemic penicillin would be a policeman whose illness had begun with a sore at the corner of his mouth, and whose case record - staphylococcal septicaemia, sulphapyridine given without improvement - reads like thousands of others of its time [S-H3]. Every family had its own version of that story, and every doctor had watched it unfold.

Childbed and barracks had their own well-known patterns, and the names of the diseases carried the fear in plain words: puerperal fever for the mothers who sickened within days of delivery, erysipelas for the spreading streptococcal fire under the skin, gas gangrene for the wounds that gassed and blackened. When deaths from puerperal fever are plotted year by year through the 1930s, the line runs high and flat until the first antibacterial drugs arrive - a mortality curve that only bends when chemistry finally enters the fight [C10]. Hospitals amplified as well as housed the danger: a maternity ward or an open surgical ward could pass a streptococcus from bed to bed faster than any treatment could follow.

None of this means that pre-antibiotic medicine was passive or empty. It was, within its limits, ingenious - and its two great traditions, the antisepsis that fought microbes on surfaces and in wounds and the search for internal remedies that could reach them in the blood, were both old, serious and, by the 1930s, newly armed. Antiseptic surgery had made the operation itself survivable. Serum therapy and antitoxins had given doctors their first specific victories. And in 1935 the sulphonamides had arrived, the first chemicals that could cure a systemic bacterial infection from inside the body, and for a few years it seemed the problem might be solved by dyes and their colourless offspring. Those weapons - what they could do, and the exact points at which they stopped - are the subject of the next chapter, because penicillin's meaning is inseparable from them. The new drug did not enter a world with no defences. It entered a world whose defences failed precisely where it mattered most: in the deep wound, in the blood, in the lung of a strong adult struck down in a week.

Chapter 5 - The first weapons

Medicine did not meet the germ empty-handed. By the time penicillin arrived, three generations of weapons had been built against bacterial infection, and each one teaches something about why the fourth changed everything. The first was antisepsis: kill the germ on the way in. The second was the biologicals: recruit the body's own defences. The third was the sulfa drugs: chemistry's first real victories inside the body. Penicillin's ancestors were honourable, limited, and - this is the part usually forgotten - increasingly confident. The 1930s did not feel like a dark age to the doctors living through them.

The antiseptic idea was the oldest, and by 1914 it was in trouble. The chemicals that sterilised instruments and swabbed skin - phenol and its descendants - were indiscriminate poisons, and the First World War's deep, filthy wounds exposed them. Fleming, who served in the Royal Army Medical Corps research laboratory at Boulogne under Almroth Wright, spent the war watching antiseptics fail in exactly the wounds that needed them most, and he carried the problem home [C2, C13]. In 1924 he devised what he considered the best experiment he ever did, and it is worth describing because it states the whole case against the old weapons in one slide. Human blood kills the common cocci - but take the white cells out and the killing stops. Fleming infected blood with a measured few thousand staphylococci in a capillary cell and watched the survivors grow out as countable colonies; then he added phenol at a strength too weak to touch the bacteria. Every coccus grew. The antiseptic had not helped the blood fight the germ; it had destroyed the white cells that do the fighting [C2]. He tested, by his own account, every chemical used as an antibacterial agent, and they all behaved the same way: at some concentration they killed the patient's defences and let the bacteria through [C2]. That experiment is the benchmark the rest of this book is measured against. A true antibacterial drug has to be more poisonous to the germ than to the host, inside the host. Nothing in the antiseptic cabinet cleared that bar.

The second tradition aimed higher by aiming narrower: not poison, but specificity. Paul Ehrlich coined both the ambition and the field - a "magic bullet" that would kill the microbe and leave the host unaltered, found by planned chemical synthesis, derivative after derivative, tested one by one; he called the approach chemotherapy [C1]. His triumph was real: arsphenamine - Salvarsan, compound 606 - introduced in 1910 with its successor Neosalvarsan, transformed the treatment of syphilis [C1]. And then, for twenty years, nothing. Salvarsan and Neosalvarsan remained the only chemotherapy for bacterial infection; despite exhaustive searching, no second magic bullet was found [C1]. By the early 1930s, Ehrlich's vision had gone quiet, and the respectable money in infection medicine was on the biologicals - antitoxins, sera and vaccines that armed the patient's own immunity [C1, C6]. These worked where they existed, but they existed for few diseases, they were expensive biological products rather than shelf-stable

chemicals, and they could not be generalised. The wound infections, the puerperal fevers, the pneumonias of ordinary practice waited for something else.

Something else arrived in 1935, from an unlikely quarter: the dye industry. At the Bayer laboratories of I.G. Farben, Gerhard Domagk had been testing azo dyes - sulphonamide-containing compounds synthesised by his chemist colleagues - against streptococcal infections in mice, work he published in 1935 under the deliberately modest title “A contribution to the chemotherapy of bacterial infections” [C10]. The red dye Prontosil cured streptococcal infections in animals and then in patients, and the medical world, after years of nothing, suddenly had a chemical that cured [C10]. The French dissection came within months: Tréfouël, Nitti, Bovet and their colleagues at the Pasteur Institute showed that the dye was a delivery vehicle, and that the colourless active core - 4-aminobenzenesulphonamide, plain sulfanilamide, the very starting material the Bayer chemists had built their dyes from - was therapeutically active as such [C10]. A simple, colourless compound turned out to be a systemic antibacterial, and it could be made by anyone. The dye houses and the drug houses of three continents piled in; a family of sulfa drugs followed, each tuned by chemistry, and the late 1930s saw the first golden age of antibacterial therapy. Domagk’s own lecture preserves the evidence of impact that matters most - the chart of deaths from puerperal fever, childbed fever, bending sharply down through the sulfa years [C10].

Two shadows from that golden age belong in the record, because they anticipate everything that follows in this book. The first is resistance. The sulfas worked brilliantly against gonorrhoea - for a while the papers spoke of a “lightning cure” - and then, within a few years, their efficacy against it declined so far that the phrase disappeared [C10]. Bacteria answered the first antibiotic age almost as soon as it opened. The second shadow is what happens when a miracle molecule meets an unregulated market. In 1937 an American company, wanting a liquid sulfanilamide for children, dissolved the drug in diethylene glycol - antifreeze - and sold it as Elixir Sulfanilamide; more than a hundred people, many of them children, died of kidney failure, and the scandal forced the 1938 Food, Drug, and Cosmetic Act through Congress, founding the modern era of drug regulation [C9]. The drug was fine; the business around it killed. Neither shadow would leave the antibiotic story: the germs would always answer, and the money would always need watching.

The sulfa drugs, for all their limits - a narrow-ish range, real toxicity, germs that learned to shrug them off - did one thing above all: they changed what doctors believed was possible [C2]. Fleming said it directly: it was after the introduction of the sulphonamides had completely changed the medical mind about chemotherapy that the world came back to his mould [C2]. The stage was set. What it still lacked was a substance that could pass Fleming’s slide-cell test - more antibacterial than antileucocytic - and cure the infections the sulfas could

not reach. That substance had been sitting in a London culture collection for a decade.

PART III - THE DISCOVERY

Chapter 6 - Alexander Fleming

The man who found penicillin was not looking for it, and said so, repeatedly, for the rest of his life. “Penicillin started as a chance observation,” he told the Nobel audience in 1945. “My only merit is that I did not neglect the observation and that I pursued the subject as a bacteriologist” [C2]. It was a characteristically dry piece of self-assessment, and it was exactly true. But the observation landed on the one bench in the world where it was likely to be pursued, because Alexander Fleming had spent twenty years preparing, without knowing it, to receive it.

He was born in 1881 at Lochfield, a farm near Darvel in Ayrshire, in the Scottish lowlands, and came to medicine by a roundabout road: country schools, the Polytechnic in London, four years as a clerk in a shipping office, and only then, in his twenties, St Mary’s Hospital Medical School [C13]. He qualified with distinction in 1906 and never really left St Mary’s. The institution that shaped him was not the medical school proper but the Inoculation Department of Sir Almroth Wright, a domineering, brilliant advocate of vaccine therapy - the idea that the body’s own defences, properly provoked, could be taught to cure infection. Wright’s laboratory attracted a particular kind of researcher: sceptical of established doctrine, fascinated by the blood’s own antibacterial powers, and fluent in a quantitative, measurement-first style of bacteriology. Fleming became, in time, the department’s most original experimentalist [C13, C1].

The First World War gave his interests a sharp edge. He served through it as a captain in the Army Medical Corps, mentioned in dispatches, and spent it confronting the gap between what antiseptics promised and what they did in real wounds [C13]. The standard antiseptics of the day were blunt poisons, and Fleming’s suspicion, hardened into a research programme, was that they poisoned the patient’s defences as readily as the invader. After the war he set himself a precise question: could there exist an antibacterial substance that was not toxic to animal tissues? The question required a way to measure the two kinds of killing side by side, and in 1924 he devised what he later called probably the best experiment he ever did. Normal human blood kills staphylococci briskly; Fleming showed that the killing is done by the white cells, and that adding the antiseptic phenol at a concentration that barely touches bacteria - one part in six hundred - destroyed the leucocytes and let the cocci grow out freely. The most trusted weapon of wound medicine was disarming the patient [C2]. Everything that followed in Fleming’s career hangs on that experiment: he now had both a motive (find something more antibacterial than antileucocytic) and an assay to detect it.

The first answer came from his own nose. In 1921, suffering from a cold, Fleming cultured his nasal secretions and noticed that something in them dissolved bacteria outright. He tracked the effect through tears, saliva and egg white, and named the responsible enzyme lysozyme [C2, C6]. Lysozyme was a genuine discovery - the first known antibacterial enzyme of the human body, and Florey

and Chain would later work out its chemistry and mode of action - but as a medicine it disappointed: the microbes it lysed most powerfully were harmless ones [C2]. What mattered for the future was the toolkit. Hunting lysozyme had taught Fleming how to spot lysis on a crowded plate, how to streak microbes across a plate to map an inhibitor's spectrum, and how to titrate antibacterial strength in blood and body fluids. Seven years later, when a mould appeared on one of his plates and dissolved the staphylococci around it, he recognised instantly what he was looking at, because he had seen its weaker twin before.

His working style deserves a paragraph, because it explains both the discovery and its limits. Fleming was a plate-and-broth bacteriologist of extraordinary patience and an almost playful inventiveness. He developed a way of growing pigment-producing bacteria on paper discs so their colours bloomed against the white, and he used it to stage bacterial antagonisms like tableaux - one microbe's growth cut short at the edge of another's invisible reach [C2]. Colleagues came to regard these productions as clever tricks rather than the beginnings of therapeutics; Fleming himself, recalling the years when penicillin interested almost nobody, wrote of "what everyone at one time thought was merely one of my toys" [C2]. He was quiet, sparing with words, and happiest at the bench. And he kept things. The original contaminated plate survived. So did the mould, which he subcultured, preserved and posted to anyone who asked for it, for more than a decade, in the hope that someone with better chemistry would make something of it. Oxford asked in the early 1930s, for an unrelated reason - George Dreyer wanted to test whether a bacteriophage explained the mould's effect - and the strain was still sitting in Oxford's collection when Ernst Chain went looking for it [C1].

The part Fleming could not play was chemist, and he knew it. His 1929 paper suggested plainly enough, in its conclusions, that penicillin "may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes" [C5], and he made a few tentative attempts to use his crude broths clinically. But the trials were few, the supply was unstable, and the results, by his own account, were favourable but nothing miraculous [C2]. He was not a practising clinician with wards full of candidates, and the broth lost its activity almost as fast as it was made. "I was convinced," he said later, "that some day when it could be concentrated and rendered more stable it would be used for the treatment of infections" [C2] - which is a precise description of the problem he could not solve and the Oxford team would. He was elected to the Royal Society in 1943, knighted in 1944, and after the war the world buried him in honours: some thirty honorary degrees, the rectorship of Edinburgh University, the American Medal for Merit, and, when he died in March 1955, burial in St Paul's Cathedral [C13]. The fame, when it came, came in a form he had not sought and could not control, and it flattened his story into a solo miracle at the expense of the men who turned his mould into a medicine. That distortion - who made it and

what it cost - belongs to a later chapter. The man himself is best caught in his own sentence: he did not neglect the observation.

Chapter 7 - The plate

The most famous petri dish in history earned its fame in the summer of 1928, and the honest account of what happened is both less tidy and more interesting than the legend.

Fleming was working that year on a problem with no obvious connection to therapeutics: the colony variants of staphylococci, and what the shape of a colony said about the virulence of the microbe. The work involved setting aside large numbers of culture plates on the laboratory bench and examining them over days. Before leaving for a holiday he inoculated a fresh stack with staphylococci and left them on the bench; on his return he began discarding the old plates into a basin of Lysol disinfectant, and it was while showing his bench to a visiting former colleague - talking through his experiments with the discarded plates fished back out of the Lysol - that he noticed one plate the disinfectant had not reached [C2, C6]. A mould was growing on it, as moulds did on plates left open in a busy laboratory. That was routine. What was not routine was the ring around the mould: for a visible distance in every direction, the staphylococcal colonies had gone translucent and were coming apart. Fleming knew that appearance. He had seen it with lysozyme, and he knew it meant something in the mould was dissolving bacteria at a distance [C2].

What he did next is the part the legend usually skips, and it is what separates noticing from discovery. He isolated the mould in pure culture - it was a Penicillium - and set out to characterise the phenomenon properly. He grew the mould on a plate for four or five days and then streaked different bacteria radially toward it: some species grew right up to the mould, others were stopped centimetres away, which showed at a stroke that the mould was releasing a diffusible substance with a specific spectrum [C2]. He grew the mould in broth and showed the broth itself carried the activity. He titrated it: the culture fluid could be diluted a thousandfold and still inhibit staphylococci, three times the staying power of phenol in the same test [C2]. He showed the activity was freely diffusible through agar, a property the older antiseptics lacked, and one he considered essential for anything meant to work inside the body [C2]. He ran his slide-cell test and found the broth killed staphylococci in blood without harming the leucocytes; he injected it into animals and found no toxicity [C2]. He checked other moulds and found they did not make the substance - his isolate was an exceptional one [C2]. And he put the broth to immediate practical use in his own laboratory: since penicillin stopped the common cocci but left the whooping-cough and influenza bacilli untouched, adding it to culture medium made those fastidious organisms far easier to isolate from the bacterial crowd of the respiratory tract [C2, C5]. That laboratory trick, not a cure, was the application his 1929 paper advertised in its own title - “with special reference to their use in the isolation of B. influenzae.”

He published in June 1929, in the British Journal of Experimental Pathology, naming the active substance penicillin after the mould that made it [C2, C5]. The paper was clear about the medical possibility - he said in his Nobel lecture that the paper proposed use against infections with sensitive microbes - and equally clear about the obstacle: the substance was unstable, and attempts to concentrate it kept destroying it [C2].

Two pieces of the received story need deflating, because later research has picked at both. The first is the tidy identification of the mould. Fleming called it Penicillium rubrum; the great American mycologist Charles Thom later corrected him to P. notatum; and modern phylogenetics has re-identified Fleming's strain - which survives in culture collections as IMI 15378 - as yet another species, P. rubens, a mould so like P. chrysogenum that the two were confused for a century [C7]. The industrial strains that descended from the famous wartime cantaloupe turn out to be P. rubens as well, so the name P. chrysogenum that fills the older literature is, for most of the penicillin story, a historical fossil [C7]. The second is the romance of the accident itself - the open window, the spore drifting in from the street, the precise sequence of weather that made the mould grow before the staphylococci. The mycologists who re-examined the record pour cold water on the open window in particular: Fleming, by the account preserved in the literature, habitually kept his windows shut, and they offer a more prosaic route for the spore. In the same building worked the Irish mycologist Charles La Touche, who was isolating hundreds of Penicillium strains from indoor air and cobwebs; one of his cultures may simply have drifted into Fleming's room [C7]. The documented connection is hiding in plain sight: the 1929 paper itself closes by thanking "our mycologist, Mr. la Touche, for his suggestions as to the identity of the penicillium" - the man who may have supplied the contaminant was the man who named it [C5]. What is documented is quite marvellous enough: a contaminated plate, an observant bacteriologist, and nine months of systematic bench work that turned an anomaly into a named substance with measured properties.

And then - almost nothing happened. Fleming's paper joined the long shelf of reports on microbial antagonism, a phenomenon bacteriologists had been describing since the nineteenth century. That, as Fleming himself saw it, was part of the problem: bacterial antagonisms were so familiar to working bacteriologists that one more of them excited nobody [C2]. He referred to penicillin in one or two further publications up to 1936, used his broth for his differential-culture trick, and gave the mould away freely. George Dreyer at Oxford asked for a sample to test whether a bacteriophage was behind the effect - it was not - and the culture went into Oxford's collection, where it waited [C1]. Fleming's colleagues Craddock and Ridley did try to wrestle the substance into a stable, concentrated form, and made real progress before the instability beat them [C6]; a distinguished team of natural-products chemists under Harold Raistrick tried again in 1932, extracted the activity into ether, found that everything they did to concentrate it destroyed it, and gave up, describing penicillin in print as an

extremely labile substance [S-H1]. The plate had spoken. For ten years, chemistry could not hear it.

Chapter 8 - The quiet decade

Between June 1929 and the summer of 1939, penicillin existed as a laboratory curiosity with a name, a filing cabinet of properties, and no future anyone could see. The usual telling treats this as a decade of neglect - the world failing to notice a miracle under its nose. The record supports something more instructive: penicillin stalled because three separate gaps had to close before it could move, and for ten years only one of them was closing.

The first gap was chemical, and it was real. Fleming's crude broth was active but hopelessly unstable, and every group that tried to go further hit the same wall. His own assistants, Stuart Craddock and Frederick Ridley, worked through the problem in the months after the 1929 paper and mapped it precisely: the activity survived evaporation only if the pH stayed on the acid side of neutral, and it could be pulled out of the broth into ether, acetone or alcohol - but nothing they tried would hold it once the solvent came off [C6]. In 1932 Harold Raistrick's group at the London School of Hygiene and Tropical Medicine, among the best natural-products chemists in Britain, took up Fleming's mould, confirmed the ether extraction, and abandoned the problem after watching the activity die under every concentrating hand [S-H1]. The molecule, as we now understand it, was simply beyond the routine biochemistry of the day: a strained ring that acid, alkali, heat, alcohol and half the metals in a laboratory could open. Florey, looking back, drew the general lesson: for decades the literature had been full of microbial antagonisms, but the chemical work on them was conspicuously poor, and without good biochemistry the biology could not advance [C3].

The second gap was conceptual. Microbial antagonism was commonplace to the bacteriologists of 1929 - "seldom," said Fleming, "can an observant clinical bacteriologist pass a week without seeing very definite instances of bacterial antagonism" [C2]. A new entry in a crowded catalogue did not announce itself as the start of a new medicine. Fleming later thought this familiarity actively hindered the field [C2]. And the therapeutic imagination of the era ran along other rails: Wright's school at St Mary's believed in vaccines and serums, in educating the patient's own defences, not in chemical bullets. Penicillin's first and for years only practical role was as a selective agent in culture medium - a way to suppress the common cocci so the whooping-cough and influenza bacilli could be isolated [C2, C5].

The third gap was motivational, and it closed last. For twenty years after Ehrlich's Salvarsan, the chemical treatment of bacterial infection had been a graveyard: one success against syphilis, then nothing [C1]. Why would a laboratory invest years in an unstable broth when chemistry's record was so bleak? The answer arrived from Germany in the mid-1930s, and it was not penicillin. Gerhard Domagk's Prontosil - a red dye that cured streptococcal infections in mice and then in patients - proved that a chemical could cure a bacterial disease inside the body,

and the French dissection of Prontosil into its active core, sulfanilamide, put a cheap, simple, unpatentable molecule into every pharmacy [C1, C10]. The sulfa drugs did more than cure; they rewrote what doctors believed was possible. Fleming put it exactly: it was “after the introduction of sulphonamide had completely changed the medical mind in regard to chemotherapy of bacterial infections” that his mould became interesting again [C2]. Then in 1939 René Dubos at the Rockefeller Institute delivered the demonstration that changed the climate of the whole field. Dubos was a soil microbiologist, and he approached the problem the way a soil microbiologist would: if antagonism between microbes was common in the petri dish, it should be commoner still in the soil, where microbes had been competing for a billion years. He screened soil bacilli, found one that killed Gram-positive bacteria, and from its cultures isolated and purified the active mixture, which he called tyrothricin [C2, C3]. The stuff was too destructive to red blood cells for use inside the body - that was why its clinical career stayed on the skin - but as a demonstration it was unanswerable: a microbial product, chemically handled and properly characterised, could be a drug [C2, C3]. Florey treated Dubos’s work as the crucial methodological proof, and Fleming judged that its favourable reception “to some extent reawakened interest in penicillin” [C2, C3]. The intellectual door Fleming had left ajar was now wide open.

Meanwhile the mould itself had been quietly travelling. Fleming’s habit of posting his strain to anyone who asked seeded it across Europe’s culture collections. It went to Oxford, where Dreyer wanted it for a phage experiment and where it survived in the collection [C1]. It went to Johanna Westerdijk’s great fungal bureau near Utrecht, which listed it in 1937 [C1]. It went to the Institut Pasteur [C1]. And it went, at least once, to Germany - to a Dr Schmidt, who could not get it to grow; Fleming recalled that none of his cultures had knowingly gone there [C1]. These journeys mattered. When war came and Britain tried to pretend penicillin’s means of production were a secret it held alone, the mould was already on the far side of every border it was supposed to be kept behind, and several occupied countries would spend the war trying to make it work, as a later chapter describes [C1].

So the quiet decade is best read not as a wasted one but as the laying of conditions. The molecule was characterised, its properties published, its mould preserved and dispersed. The chemistry that could tame it matured elsewhere - partition methods, solvent extraction, the new delicacy of the 1930s biochemistry that Florey liked to quote Szent-Györgyi on: by 1929 the methods existed to extract any natural substance, provided you had a quick test for it [C3]. Penicillin had a quick test - Fleming’s plate assays were fast and sensitive. What the molecule still needed was a team that wanted it badly enough, and in 1939 a grant application at Oxford assembled that team. The Rockefeller Foundation gave Howard Florey twenty-five thousand dollars over five years to study antibacterial substances from microbes [C6]. Ernst Chain, reading the literature for candidates,

found Fleming’s ten-year-old paper, and went to the Dunn School’s culture collection to see whether the mould was still alive. It was [C1, C6].

PART IV - OXFORD

Chapter 9 - The Dunn School

The Sir William Dunn School of Pathology at Oxford, where penicillin became a drug, was not built for the purpose. It was a small institute for experimental pathology whose professor of pathology from 1935, Howard Walter Florey - an Australian from Adelaide who had come to Oxford as a Rhodes Scholar and held a chair at Sheffield before returning - had built his reputation where biology meets chemistry [C28]. His collaboration with Ernst Chain had begun in 1938 as a systematic investigation of naturally occurring antibacterial substances, and its original subject was lysozyme, the antibacterial enzyme of tears and saliva [C28]. That apprenticeship mattered. Lysozyme had taught both men that an antibacterial substance from nature only became interesting as science once a chemist had it in a bottle; until that day the biologist was describing a phenomenon, not studying a thing [C3].

Florey assembled around the problem a group that fit it unusually well. He was the pathologist-organiser. Ernst Boris Chain was the biochemist: Berlin-born, trained in chemistry at the Friedrich-Wilhelm University, he had left Germany in 1933 after the Nazis came to power, spent two years under Gowland Hopkins at Cambridge, and arrived at the Dunn School in 1935, where his work ran through snake venoms, tumour metabolism, the mechanism of lysozyme and methods of biochemical microanalysis [C27]. Norman Heatley, described by a later historian as the team’s fungal expert, took on the problem of growing the mould in quantity [C1]. Money was the immediate problem, and it was solved substantially from America: in 1939 the Rockefeller Foundation granted Florey twenty-five thousand dollars over five years to investigate antibacterial substances produced by moulds and other microbes - serious money for a British laboratory on the eve of war - with the Medical Research Council and the Nuffield Trust also supporting the work, and Heatley holding a Rockefeller fellowship [C6, C28, S-H2].

The program was a survey, not a bet on one mould: the team set out to investigate antibacterial substances from microbes generally, with lysozyme as the starting interest, and penicillin - whose reported potency made it stand out in the literature - became one candidate among several, with Chain driving the chemistry of getting such substances pure [C6, C28]. The Oxford mould, luckily, was alive in the Dunn School’s own collection - the sample George Dreyer had obtained from Fleming in the early 1930s and kept [C1]. Heatley worked out how to grow the mould reliably and, just as important, how to measure what they were doing: plate assays, rings of inhibition against a standard test organism, which let the chemists track their product through every step. The yardstick became known as the Oxford unit, defined in the team’s 1941 paper with disarming honesty as the amount of penicillin in one cubic centimetre of water that matched the inhibition given by

their own reference solution - a purely arbitrary standard, they wrote, to be used “until penicillin is obtained chemically pure” [S-H3].

The extraction was the mountain, and the route over it came from knowing where the failures had been. Everyone before had pulled the activity out of the culture fluid and lost it in the attempt to concentrate. The hinge of the whole process was the molecule’s double nature, which Chain’s group mapped and exploited: penicillin is an organic acid, readily soluble in organic solvents such as ether, but stable in water only as its salt, within a narrow band around neutrality - outside pH 5 to 8 the activity dies, and acid, alkali, heavy metals, alcohols and a long list of common reagents kill it too [C4]. So the chemists drove the substance back and forth across the boundary: acidify the broth and the penicillin walks into the solvent; shake the solvent with neutral buffer and it walks back into water, leaving most of the brown broth impurities behind [C4, C6]. Purification, as Chain put it in his own account, was limited almost exclusively to this distribution between solvents and to the new partition chromatography invented in England by Martin and Synge [C4]. What emerged was a brown powder, freely soluble in water, stable for a considerable time, still impure - but strong enough to cure, and concentrated enough to test [S-H2]. Chain left a stark measure of how little they had: in all the Oxford chemical work that followed, the group never disposed of more than about two grams of penicillin in total, of which perhaps half a gram approached ninety per cent purity [C4].

It is worth pausing on what kind of team this was, because the received story of penicillin needs a hero and the reality needs a division of labour. Fleming had been a superb observer working essentially alone, and the work had stopped exactly where one man’s skills stopped. The Dunn School’s answer to the same problem was deliberately collective: Florey supplied the biological judgment and the organisation; Chain supplied the chemistry and the stubbornness to do it; Heatley supplied the growing, the assays, and the apparatus that turned bench tricks into process [C1, C27, C28]. Around them stood a wider bench - Arthur Duncan Gardner, Margaret Jennings, Jean Orr-Ewing, Gordon Sanders - whose names appear on the 1940 Lancet paper and whose hands did the bacteriology, the animal work and the pathology, with Edward Abraham joining for the chemical and clinical work that followed [C1, S-H2, S-H3]. Neither the discovery of 1928 nor the development of 1940 was the product of a solitary genius, and the later Nobel quarrel over credit, which a later chapter takes up, makes sense only against this background: the work was genuinely distributed, and the story had been sold to the public with a single name on it.

The context in which this happened should be stated plainly, because it shaped everything. The work was done as Europe slid into war and then as Britain fought; the Dunn School ran on wartime improvisation, and at least one member of the team was carrying, alongside the science, a refugee’s knowledge of exactly what the war was about [C27]. The laboratory had to double as a factory: the

Oxford group produced with its own hands most of the penicillin it tested [C1]. After many types of container had been tried, a satisfactory ceramic vessel was designed for growing the mould as a surface mat, glazed only on the inside to cut cost and stacked for sterilising; the medium beneath the mat could be drawn off and replaced, and one batch was harvested fourteen times [S-H3]. The arithmetic was pitiless: a hundred litres of culture fluid, carrying perhaps 150,000 units, yielded about one gram of therapeutic material - a third of what the broth had held [S-H3].

By the spring of 1940 the group had enough of their brown powder to ask the only question that mattered: would the substance protect an infected animal? On Saturday, 25 May 1940, they found out [C1, C14].

Chapter 10 - The first cure

The experiment that changed medicine's mind took one night. On 25 May 1940 - a Saturday, in the weeks when France was falling - the Oxford team infected eight mice with a virulent streptococcus, dosed four of them with their brown penicillin preparation, and left four as untreated controls [C1, C14]. By the small hours of Sunday morning every control mouse was dead and every treated mouse was alive. Chain, who had stayed up to watch, called the result "a miracle" [C1].

Florey's group spent the following weeks mapping what the substance could do in animals, and the full series was overwhelming: in the final experiments, every single untreated mouse died - twenty-five of twenty-five against streptococci, twenty-four of twenty-four against staphylococci, twenty-five of twenty-five against the gas-gangrene bacillus Clostridium septique - while nearly every treated mouse lived [S-H2]. Toxicity, tested hard in mice, rats and cats, barely registered, and the team noted that between forty and fifty per cent of a dose came out in the urine still active - a fact they would soon be exploiting [S-H2]. They published in The Lancet in August 1940 under the plain title "Penicillin as a Chemotherapeutic Agent": "The results are clear cut" [S-H2]. The paper was read, but its authors knew it proved only that penicillin cured mice. A human case would need not milligrams but grams, and the Dunn School's entire output was being measured in drops.

What followed was one of the strangest manufacturing episodes in medical history: a university pathology department turned itself into a pharmaceutical works. Heatley's ceramic vessels, the "bedpans," multiplied along the laboratory benches, each growing a mat of mould on its broth; the culture fluid was harvested, assayed in Oxford units, run through the acid-to-solvent, back-to-water extraction, and freeze-dried [C3, C8]. The yields were pitiful. The team needed a patient sick enough to justify the gamble and a supply large enough to finish the course, and through the winter of 1940-41 they never had both at once.

On 12 February 1941 they began anyway. The patient was Albert Alexander, a forty-three-year-old Oxford policeman dying of septicemia - the case record traces it to a sore at the corner of his mouth, though the story is usually told with a scratch from a rose thorn [C11, S-H3]. Staphylococci and streptococci were overwhelming him: his face, scalp and eye sockets were a mass of abscesses, one eye had been removed, the infection had eaten into the bone of his upper arm, and the best drug of the pre-penicillin era, sulphapyridine, had been tried and had failed [S-H3]. He was given penicillin intravenously at the Radcliffe Infirmary, and within a day the change was startling - temperature falling, abscesses settling, a dying man asking for food [C1, C11]. The team, desperately short of drug, set up a second factory in miniature: they knew from the animal work that a large share of each dose left the body in the urine still active, so Alexander's urine was collected and carried back to the Dunn School to have the drug extracted from it

again - and the clinical paper records that the first doses given to a later patient, a desperately ill small boy, had been recovered from Case 1’s urine [C11, S-H2, S-H3]. Even so, five days in, the supply ran out. The infection, only suppressed, returned. Alexander relapsed and died on 15 March 1941 [C11].

It is easy to read that ending as failure. The Oxford group read it correctly as proof. A man beyond every other treatment had responded to penicillin as long as penicillin lasted; the drug had not failed, the supply had. They chose their next patients with the arithmetic in mind - smaller bodies, more curable infections - and the results came right: children and others treated with courses the factory could actually complete, recoveries the doctors could hardly credit [C1, C11]. In August 1941 the team published its clinical series in The Lancet, and the case for the drug was made [C1, S-H3].

But the case for the drug was not the drug. Britain in 1941 could not build the industry penicillin required: its chemical and pharmaceutical plants were fully committed to the war, its capital and steel were spoken for, and no British firm could take on a speculative fermentation process of unprecedented scale [C1, C3]. Florey had tried the British establishment and found sympathy but no capacity. So in June 1941 he and Heatley did the thing that would define the next chapter of the story: they crossed the Atlantic for the United States - on Heatley’s suggestion, by the often-retold account, carrying the mould smeared into their coats against loss or confiscation - to ask a country not yet in the war to build penicillin for the world [C1, C6]. What they carried was a strain of a common mould, a set of notebook processes, and a conviction. What they started was an industry.

PART V - THE WARTIME PROJECT

Chapter 11 - Peoria

The road to mass production ran through a town that had never heard of penicillin: Peoria, Illinois, home of the US Department of Agriculture's Northern Regional Research Laboratory, one of the regional laboratories built to find new industrial uses for American farm surpluses [C15, C16]. Florey and Heatley arrived in June 1941 and were passed, by a chain of scientific goodwill, to the people who mattered: Charles Thom, the USDA's principal mycologist - the same man who had corrected Fleming's identification of the mould a decade earlier - and, through him, to the laboratory's director Orville May, its fermentation chief Robert Coghill, and a quiet fermentation mycologist named Andrew Jackson Moyer [C1, C15]. The choice was inspired, and not only because Peoria knew moulds. The NRRL's whole purpose was turning agricultural abundance into industrial products, and its staff had been working on submerged mould fermentation since the mid-1930s [C15].

Two Peoria innovations broke the production problem open, and both came from thinking like agricultural chemists rather than pharmacists. The first was the medium. The Oxford team grew its mould on a broth containing brewer's yeast extract; in the quantities an industry would need, that was unobtainable in America. Moyer, who had been studying mould nutrition for years and had found corn steep liquor effective as a mould feed back in 1937, proposed it as the substitute: the water left over from steeping maize in the starch mills, a glutinous waste product the Midwest produced in lakes [C1, C15]. The mould loved it. Combined with adjustments to the metals and carbohydrates - swapping glucose for lactose among them - the new medium multiplied the yield of penicillin many times over; the figure given in the laboratory histories is about thirty-fold [C15]. An industrial waste had become the food of the miracle drug.

The second innovation was the strain itself. Fleming's mould was a freak: Thom had once gone through his collection of roughly a thousand Penicillium strains and found only one other that made penicillin [C1]. If penicillin was to be an industry, it needed the best producing strain the world could offer, so the NRRL organised a global search - soil samples solicited from wherever Army transport planes set down, moulds sent in by laboratories and travellers [C15, C18]. The winner was found almost insultingly close to home: a mouldy cantaloupe in a Peoria market. The strain it carried, catalogued as NRRL 1951 and long known as Penicillium chrysogenum - modern phylogenetics places it, like Fleming's mould, in P. rubens - produced about six times more penicillin than Fleming's isolate [C1, C7]. The taxonomy confirms what the production records imply: NRRL 1951 is the parent of most high-yielding penicillin strains in use since [C7].

A word here about "Moldy Mary." Popular retellings give the cantaloupe a human discoverer - a laboratory assistant, variously named, sent out to scour Peoria's shops for mouldy produce. Even the USDA's own retellings treat her identity as

unresolved, and the laboratory's surviving scientists remembered the episode differently [C17]. The cantaloupe is real, and documented. Moldy Mary is a legend grown on top of it, and this book leaves her there.

The third Peoria contribution was genetic, and it ran on wartime secrecy. NRRL 1951 was still a surface-growing mould, happiest as a mat on shallow broth; the deep tanks that industry was contemplating needed a strain that would produce while submerged and stirred. So the strain was bred like a crop: selections for submerged growth, then deliberate mutation. At the Carnegie Institution's Cold Spring Harbor laboratory the strain was X-rayed, lifting output into the hundreds of units per millilitre; at the University of Wisconsin, ultraviolet treatment nearly doubled it again, yielding the famous line known as Q-176, from which most production strains descend [C18]. Strain improvement has never stopped: by the early 2000s, harvest titres in modern factories ran to 40 or 50 grams per litre - a march of orders of magnitude from the broth Fleming titrated on his bench [C19].

Peoria also set the legal shape of the industry, and it was an unusual one. The processes worked out at the NRRL - Moyer's fermentation methods above all - were patented, but the patents were taken out in public hands: the patent records show Moyer assigning his fermentation patents to the Secretary of Agriculture, and the US government licensed them royalty-free [C26]. The British, for their part, had deliberately sought neither product nor process patents on the Oxford work, a stance rooted both in the medical ethics of the era and in the practical judgment that a natural product of a common mould was poor patent material [C29]. Between these two decisions, the foundational knowledge of penicillin manufacture entered the war as a shared, unpriced asset - a choice with consequences, for competition and for later regret on both sides of the Atlantic, that the business chapters of this book will follow [C1, C18].

Chapter 12 - The arsenal

In 1941 the United States did not possess enough penicillin to treat a single patient. By the end of 1942 there was enough for fewer than a hundred. By September 1943 there was enough to satisfy the demands of the Allied armed forces [C1]. That curve - from nothing to an arsenal in under three years - is the industrial heart of the penicillin story, and it was achieved by an arrangement neither Britain nor America had ever run before: a government-directed, industry-built, science-fed project in which the usual rules of commercial secrecy were suspended for the duration [C1, C29].

The American government's entry transformed the scale of everything. The War Production Board sifted a field of 175 would-be producers down to some twenty companies, chosen for their experience with penicillin, their knowledge of fermentation, their staff and their plant [C29]. The names at the front of the list were the ones that would dominate antibiotics for half a century - Merck, Squibb, Pfizer among them [C6]. The government did not merely buy the product; it built the capability. The Army Service Forces helped supply equipment; the Office of Production Research and Development existed to break production bottlenecks; and the NRRL's strain and medium improvements were passed to every partner as they emerged [C29].

The decisive process change was deep-tank fermentation. The Oxford method - mould grown as a mat on shallow broth - could never fill a country's needs; it was a surface craft, one vessel, one skin of mould. The industrial answer was to grow the mould submerged: vast aerated tanks, air bubbled through stirred broth, the mould producing throughout the volume instead of only at its surface [C1]. This was not a penicillin invention - the Peoria laboratory had worked on submerged mould fermentation since the mid-1930s, and American fermentation industry knew the craft of feeding and aerating a vat of mould: Pfizer had been making citric acid in deep tanks since the 1920s, two decades of practice that turned out to be the single most valuable industrial heritage in the project [C15, C33]. But marrying the tanks to a fragile, fussy drug, with the new Peoria strains bred to produce while submerged, was the engineering achievement on which the whole wartime supply rested [C1, C15]. The purity problem gives the scale of it: in the early broths there were about four parts of drug in ten thousand parts of liquid [C33].

The emblematic plant was Pfizer's. In September 1943 the company bought the Rubel Ice Plant on Marcy Avenue in Brooklyn, and on 1 March 1944 opened what was then the world's first large-scale penicillin factory: fourteen 7,500-gallon tanks [C33]. By the autumn of 1944, the company's own summaries recorded, one day's production from the plant often exceeded the entire production of 1943 - and most of the penicillin that landed in Europe on and after D-Day came from that converted ice plant [C33].

What made the project extraordinary was not only engineering but the suspension of rivalry. The WPB did not just hand government research to its partners; it required the partners to share their own discoveries with each other. Albert Elder, the project's director - the "penicillin czar" - put it bluntly: maximum production depended on harnessing recently developed know-how, and a single producer's drastic improvement could meet total needs only if it was applied across all the plants [C29]. The big firms were reportedly reluctant to share everything, but the stakes being what they were, the techniques and the productive strains were in fact made available across the industry - an industry-wide adoption of the best wartime developments, as one historian of the collaboration puts it [C29]. It is hard to think of another moment when competing drug companies ran, in effect, a common research programme, and the contrast with what came before and after is the point: the know-how commons was a wartime institution, and it did not survive the peace [C29].

The price collapse, when peace freed the numbers, was total. The wartime purchase price had already fallen from $200 to $6 per million units by the program's end [C15]; the Federal Trade Commission's postwar price history picks the story up at exactly that point - bulk penicillin entered the commercial market in 1945 at $6,000 per billion units, which is the same six dollars a million - and follows it down to $34.50 per billion by December 1955, about half of one per cent of the introductory price [C39]. The commission's own reading of its tables deserves quoting in spirit: falling production costs, competitive pressure between the salts and the companies, and, after 1949, the inroads of the new broad-spectrum antibiotics did the work [C39].

In parallel ran the great synthetic race, and its failure is one of the most consequential non-events in the history of chemistry. Industry and government alike had assumed that a molecule so useful would soon be synthesised outright, freeing supply from the mould entirely. The American chemical effort alone engaged some two hundred academic and industrial chemists; from 1943 a government ban kept all penicillin chemistry unpublished, and from early 1944 the British and American groups exchanged their confidential reports monthly - some seven hundred reports in all [C4]. Chain's own account carries the scale of the imbalance: at Oxford the structure work was done on about two grams of penicillin, of which half a gram approached ninety per cent purity, while the Merck laboratories alone consumed hundreds of grams of crystalline material [C4]. The money followed the same pattern - the industry's wartime plant investment ran to more than twenty-two million dollars for fermentation against about three million for the synthetic route [C15]. The synthetic pathway was cracked only in 1957, by John Sheehan's laboratory at MIT, and even then as a scientific landmark, not a factory process; fermentation had won, and every penicillin ever swallowed has been grown, not built [C25, C29].

None of this meant chaos at the factory gate. From 16 July 1943 a WPB allocation order put the entire penicillin supply under government distribution - to the research committees, the armed forces and the Public Health Service - so that a scarce drug went where the war needed it [C15]. The Office of Scientific Research and Development had been funding penicillin research since before the ramp-up: fifty-seven contracts covering preliminary studies, clinical trials and the synthesis chase [C18].

The output curve answers for the strategy. Production was 425 million units in June 1943; it was roughly 100 billion units a month by D-Day in June 1944, and some 650 billion a month by June 1945 - a WPB official counted the May-June 1944 output as an increase of more than 250-fold in monthly production within a single year [C15, C18, C29]. The two price series tell the same story from two angles, and they are worth keeping distinct: the government’s bulk contract price fell from two hundred dollars per million units in 1943 to six dollars by 1945, while the price a patient faced went from about twenty dollars a dose in July 1943 to fifty-five cents a dose by 1946 [C15, C16]. Penicillin went from a substance weighed in drops against a dying policeman’s remaining hours to a commodity stacked in military supply depots, and by 1946 it was on the open market [C6, C11].

The money, like everything else, was shared in an unusual way. The government’s own postwar accounting shows roughly three-quarters of the thirty million dollars spent on penicillin plants came from the companies themselves, with the state easing the risk rather than bearing it: the Defense Plant Corporation helped support construction, and Washington authorised rapid tax amortization of the investments [C37]. The contracts were built to match. The government organised the late-1941 meetings that corralled Merck, Squibb, Pfizer and Lederle into the program - the firms were mostly reluctant, worried among other things about penicillin contaminating their other products - and then wrote agreements whose main currency was information rather than cash: token, unfunded contracts to keep the data flowing, with patent terms requiring that anything patented under the program be licensed non-exclusively to the other contractors and the government at reasonable royalties [C37]. The economists who have studied the program call this licensing policy a deliberate substitute for government ownership [C37].

It is worth recording that the strategy had its internal critics, because the dispute clarifies what actually mattered. Albert Elder, the WPB’s penicillin director, later blamed the research establishment’s long infatuation with synthesis - and specifically A. N. Richards, the OSRD’s medical research chief - as the most important deterrent to mass production, and at least one historian has backed him [C15]. Others called the charge a gross overstatement, pointing out that no fermentation plant was ever closed or delayed for the sake of synthesis, and that fermentation construction outspent the synthetic programme about seven to one

[C15]. The fairest reading is that the synthesis chase cost attention and a modest slice of money, and bought an insurance policy that was never collected - while the unglamorous work of strains, tanks and sharing did the delivering [C15, C29].

One more decision from these years deserves its own paragraph, because the rest of this book lives in its shadow. Nobody fenced the commons. Oxford had deliberately chosen not to patent penicillin as product or process - a decision made against the fresh British memory of the Steenbock vitamin D patents, which had put an American tollbooth on British nutritional science and left, as one civil servant complained, the country paying tribute to a foreigner for an essential food factor [C29]. The American process patents that did exist - Moyer's fermentation methods - belonged to the government and were licensed royalty-free to all comers [C26, C29]. The two governments even negotiated a tiered licensing agreement to pre-empt any future synthetic-penicillin monopoly, with the fullest rights reserved for the governments and for Merck as the leading contributor; the failure of synthesis meant it was never used [C29]. For exactly as long as the war lasted, the world's most valuable drug was nobody's property. The peacetime industry noticed, drew its conclusions, and spent the following decades making sure the next miracle would be owned. That turn - from commons to property - is where the business of antibiotics begins, and it is the subject of the next part of this book [C29].

PART VI - THE FACTORY

Chapter 13 - From broth to bottle

Growing penicillin turned out, in the end, to be the easy half of the problem. The mould makes the drug and then throws it away, secreting it into the surrounding broth until the broth is a vast, warm soup of everything the mould ate and everything it excreted - and the penicillin in it is present at about four parts in ten thousand [C33]. Worse, the prize is one of nature’s fragile molecules. Penicillin is destroyed by acid if you are careless with it, by heat, by enzymes that many common bacteria carry, and by time in solution [C1, C6]. The whole art of the antibiotic factory, from 1941 to today, is the art of pulling that one delicate molecule out of the soup, quickly and cold, before it falls apart.

The Oxford group worked out the basic trick on a laboratory bench, and their 1941 paper describes it with the plainness of a recipe, because it was one. Acidify the broth, and penicillin - an acid - becomes the kind of molecule that prefers to dissolve in an organic solvent: shake the broth with amyl acetate or ether and the drug crosses into the solvent layer, leaving most of the soup behind. Then reverse the trick: shake the solvent with a little alkaline water, and the penicillin, now a salt, crosses back into the water, concentrated perhaps fifty-fold in the two moves [S-H3]. On the bench they refined it further: droplets of extract falling through a counter-current column of amyl acetate; a shake with animal charcoal to strip out coloured impurities - a step that cost penicillin in proportion to the charcoal used, a tax on cleanliness; then a column of alumina, on which the remaining impurities and the drug travelled at different speeds, so that the strongest fraction could be caught as it washed through [S-H3]. Finally, freeze-drying turned the solution into a dry powder that could wait in a vial. Every stage leaked. The Oxford team’s own accounting for their first clinical batches is the starkest number in the wartime story: from a hundred litres of mould broth they might recover a single gram of material fit to inject - roughly a third of what the broth actually contained [S-H3].

That fragility had clinical consequences, not just economic ones. The early Oxford fractions were not pure penicillin; they were penicillin plus whatever else had survived the columns, and some of those fellow-travellers were pyrogens - fever-provoking contaminants that made patients shiver and shake after their doses. The 1941 case records say it in passing: the first samples given to one child patient produced “some shivers,” and only the later, cleaner “second fraction” - what the authors by then called “our present ‘therapeutic penicillin’” - was free of the effect [S-H3]. Purification was never a matter of elegance. It was the difference between a drug and a hazard.

Industry took the Oxford recipe and made it continuous. What a bench does with a separating funnel, a plant does with counter-current extractor towers and centrifugal contactors, running day and night, broth flowing one way and solvent the other, the acid-chill-extract-neutralise cycle timed in minutes rather than hours because every extra minute in solution was yield dying on the floor. The

companies that joined the wartime program each built their own version, and the process know-how was pooled among them under the government scheme - extraction tricks, drying methods, assay standards passed from firm to firm as fast as they were proven [C18]. The assays mattered as much as the chemistry: a drug that cannot be measured cannot be dosed. The Oxford unit - defined in the 1941 paper as the amount that just inhibited the test staphylococcus under standard conditions - gave the project a common currency long before anyone had a pure gram to weigh, so that a vial made in Brooklyn and a vial made in Oxford could be compared, prescribed and trusted [S-H3].

The product itself told the story of purity in its appearance. The early product was a crude, coloured powder - the Oxford bench decolourised its extracts with charcoal for a reason [S-H3] - and then, in 1946, Pfizer’s chemists crystallised the drug: white crystals, stable at room temperature, the first penicillin that looked like a modern medicine and kept like one [C33]. Crystallisation was more than cosmetics. A crystal is a molecule agreeing to line up with itself; a crystalline salt can be weighed, standardised, shipped and stored in a way that a sticky brown extract never could, and the crystalline form is what finally turned penicillin from a wartime emergency product into ordinary pharmacy stock. The pipeline that begins with a spore and a corn-steep tank ends, to this day, in a crystalliser - the chemistry recognisably the one the Oxford bench invented, running now at a scale its inventors never had to imagine.

Chapter 14 - The industry of improvement

The strain hunt of the Peoria chapter found the champion; this chapter is about what the champion’s descendants became, because the penicillin titre ladder did not stop climbing in 1945 - it became a permanent industry of its own. The wartime rungs are the famous ones. NRRL 1951, the cantaloupe strain, was X-rayed at the Carnegie Institution’s Cold Spring Harbor laboratory into a line producing hundreds of units per millilitre, and ultraviolet-mutated at the University of Wisconsin into Q-176, the ancestor of most production strains [C18]. The postwar rungs are less famous and more dramatic. Wisconsin’s own programme continued - strain 54-1255 among its products - and the work spread to the companies and specialist houses, where mutation-plus-screening became routine craft: irradiate or chemically mutate, plate out thousands of survivors, test each colony’s yield, keep the winner, repeat [C18, C30]. Every generation of the cycle ratcheted output upward.

The genomics era finally showed what all that selection had been doing to the mould. Comparative sequencing of Fleming’s original isolate against the industrial lines found the signature plainly: the penicillin gene cluster - the three genes that encode the biosynthetic machinery - had been duplicated in tandem through the improvement programmes, so that a modern industrial strain carries multiple copies of the whole production cassette, while the effector-gene sequences diverged from Fleming’s wild isolate and the regulatory genes stayed conserved [C30]. The breeders of the 1950s could not have seen it, but they were, in effect, photocopying the mould’s factory floor. The same study confirmed what taxonomy had already decided: the industrial lineage, like Fleming’s own mould, is Penicillium rubens - the “chrysogenum” of the old literature was a misnaming that stuck [C30, C7].

The cumulative result belongs with the price collapse of the earlier chapters as the quiet arithmetic of the antibiotic age. Where Fleming’s broth yielded single-digit units per millilitre and the wartime project celebrated thousands, production strains of the early 2000s ran harvest titres of forty to fifty grams per litre - roughly a million-fold improvement in the productivity of the organism itself, achieved almost entirely by mutation, selection and fermentation science rather than by genetic engineering [C19]. That number is the true answer to the question of why penicillin is cheap. Not the molecule - the mould, improved without pause for eighty years, in the one branch of the antibiotics industry where improvement has never stopped.

PART VII - THE FAMILY

Chapter 15 - The penicillins as medicines

A drug is not a molecule; it is a molecule in a form a patient can take. Penicillin the molecule is acid-fragile and fleeting - destroyed by the stomach, cleared by the kidneys within hours - and the history of the penicillins as actual medicines is the history of chemistry’s answers to those two facts [C1, C6]. The wartime drug was the sodium salt, an amorphous powder for injection, replaced in early 1947 by the crystalline form; the potassium salt and the first deliberately engineered formulation, procaine penicillin, arrived in 1948 [C39].

Procaine penicillin attacked the fleetingness. Suspended with the local anaesthetic procaine as an insoluble salt, injected into muscle, it dissolved slowly - a depot under the skin leaking penicillin into the blood for a day instead of an afternoon. It was discovered in the mid-1940s, marketed in 1948, patented in 1950, and licensed so widely - after interference settlements, lawsuits, and a deliberate licensing policy by its owner, Lilly - that it became a standard item of every producer’s catalogue [C39]. The same logic, stretched further, gave benzathine penicillin: an even less soluble salt, a depot lasting days to weeks, the form still used where a single long-acting injection matters more than blood levels - the Wyeth product patent on it was licensed to three companies under an interference settlement [C39]. Both survive on the World Health Organization’s Model List of Essential Medicines to this day - the current (2025) list carries benzylpenicillin, benzathine benzylpenicillin, procaine benzylpenicillin and phenoxymethylpenicillin alike - the depot penicillins of rheumatic fever prophylaxis and syphilis [C44].

The stomach problem took longer and mattered more for ordinary practice, because an injectable drug belongs to clinics and an oral one belongs to everyone. The answer was phenoxymethyl penicillin - penicillin V - a side-chain variant stable enough in acid to survive swallowing; patented by Lilly in the new wave of penicillin product patents of the early 1950s and licensed to Wyeth, it turned penicillin into a tablet and a sweetened suspension, the medicine of the home and the GP’s bag [C39]. With ampicillin and then amoxicillin - the oral broad-spectrums of 1961 and 1972 - the family completed its move from the syringe to the medicine cabinet [C31, C32].

Two threads of this book meet in these formulations. One is industrial: procaine, benzathine and penicillin V were the first penicillins on which anyone held product patents at all - the basic molecule having never been patented - and the Federal Trade Commission’s patient tabulation of who licensed what to whom is the beginning of the antibiotics patent thicket that a later chapter follows into the broad-spectrum era [C39]. The other is clinical, and it points the other way: the long-acting depot that makes a single injection protect a child for weeks is also a long, low tail of sub-inhibitory concentration - exactly the exposure pattern Fleming warned about in 1945, when he told the world to use enough [C2]. The

medicine and the resistance problem were, from the beginning, the same chemistry.

Chapter 16 - The decorated nucleus

For its first fifteen years as a medicine, penicillin was what the mould said it was. Fermentation gave essentially one product, the molecule the world calls penicillin G, and it had the limitations the mould had never needed to care about: it was wrecked by stomach acid, so it went into a syringe rather than a pill; it was powerless against the Gram-negative bacteria hiding behind their outer membrane; and it was cut apart by penicillinase, the enzyme that more and more staphylococci were learning to make [C2, C6]. Chemists looked at the molecule and saw what the mould could not: a load-bearing frame - the fused beta-lactam and thiazolidine rings - carrying a single side chain that nature attached and chemistry might replace. If that side chain could be swapped for others, one could in principle design penicillins the way one designs tools: acid-proof ones to swallow, broad-spectrum ones to reach the Gram-negatives, armoured ones to survive the enzyme [C6].

Everything depended on getting the bare frame, the nucleus without its side chain: 6-aminopenicillanic acid, 6-APA. Sheehan’s total synthesis at MIT had pointed the way in 1957, but the practical route came from an unexpected direction. At the Beecham Research Laboratories in England, a team that included Peter Doyle, John Nayler, George Rolinson and Fred Batchelor found that the mould’s own fermentation broths contained the naked nucleus itself - and that the nucleus could be harvested, purified and re-decorated by ordinary chemistry. Their paper, “Synthesis of penicillin: 6-aminopenicillanic acid in penicillin fermentations,” appeared in Nature on 24 January 1959 [C23]. It is one of the great quiet papers of pharmaceutical history. The mould would grow the frame; chemists would bolt on the working parts. The age of the semisynthetic penicillins had begun, and with it the modern antibiotic industry: from here on, innovation meant side chains [C6, C23].

The first targets were the known weaknesses. Against the enzyme war came methicillin, a penicillin whose bulky side chain physically shielded the beta-lactam ring from penicillinase; introduced in Britain in 1959 and approved for American clinical use in 1960, it restored the upper hand over the resistant staphylococci that had been accumulating in hospitals through the 1950s [C6]. Against the Gram-negative wall came ampicillin. Beecham launched it as Penbritin in 1961, and the British Medical Journal of 22 July that year carried the paired announcement papers - Rolinson and Stevens on its microbiology, Brown and Acred on its chemistry - showing a penicillin that reached across the Gram divide into E. coli, the typhoid bacillus and their kin [C31]. Ampicillin was the first penicillin that a GP could plausibly call broad-spectrum, and it became one of the most prescribed drugs on earth.

One weakness remained in ampicillin itself: swallowed, it was absorbed unevenly. Beecham’s answer, a decade on, was amoxycillin - the spelling later simplified to

amoxicillin - announced by Sutherland and his colleagues in the BMJ of 1 July 1972: the same spectrum as ampicillin, the same vulnerability to penicillinase, but absorbed so much better by mouth that a given oral dose produced about twice the concentration in the blood [C32]. That single pharmacokinetic advantage made it the penicillin of the medicine cabinet, the default for ear infections and strep throats two generations later. The procession continued down the wish-list: carbenicillin, introduced in 1967, reached even Pseudomonas, the hospital pathogen that shrugged off everything else in the family [C6].

Two consequences of the decorated nucleus deserve emphasis here, because the rest of the book returns to both. The first is industrial: 6-APA became a commodity in its own right, the shared starting material of a whole drug class, and its manufacture eventually concentrated in a handful of plants, most of them in China [C8]. The second is biological, and darker. The enzyme that methicillin was built to evade did not stand still. Within about a year of methicillin’s introduction, resistant staphylococci were being observed in British hospitals - the first sighting of what the world now calls MRSA [C24]. The side-chain war turned out to be an arms race, not a victory. But that is the resistance story, and it has earned its own part of this book.

Chapter 17 - The family beyond penicillin

Penicillin’s children did not stop at decorated penicillins. The mould had shown that microbes make weapons against other microbes, the Oxford work had shown that such a weapon could be turned into a medicine, and the wartime factories had shown that it could be made by the tonne. Once all three lessons were learned, the hunt was on - and the first great find beyond penicillin came from the same small Oxford circle. Edward Abraham and Guy Newton, working with a fungus then called Cephalosporium acremonium, isolated a new antibiotic, cephalosporin C, and showed that it carried a different nucleus from penicillin’s: 7-aminocephalosporanic acid, 7-ACA, in place of 6-APA [C6]. What Beecham had done with the penicillin nucleus could now be done with the cephalosporin one, and was: side chains came off and on, and generation after generation of cephalosporins followed, each reaching further across the bacterial world [C6].

Nor were moulds the only arsenal. Once microbiologists understood that antibiosis was a general phenomenon rather than a Penicillium quirk, they began screening the soil microbes wholesale, and the bacteria - above all the Streptomyces, the filamentous soil organisms that had sat in culture collections for decades - turned out to be the richest weapons-makers of all [C6]. The beta-lactam family itself kept growing from these new sources: the carbapenems, found in Streptomyces, carried yet another variant nucleus and an unusually broad reach; the monobactams, from a different set of bacteria, showed that a single beta-lactam ring could stand alone [C6]. Each new nucleus became, in turn, a frame for chemists to decorate, exactly as 6-APA had been. The industrial echo is striking: today essentially all of the world’s 7-ACA - the cephalosporin starting material - is made in China, just as most of the world’s 6-APA is, two commodity streams flowing from a technology that began on a bench in Oxford [C8].

The deepest legacy, though, was not any single drug but the platform. Quinn’s history of the wartime project closes with the point, and it deserves to stand: the mass fermentation methods built for penicillin were a radical departure from all previous pharmaceutical manufacturing, and they did not stay penicillin’s. The same tanks, the same aeration, the same recovery chemistry produced the postwar parade of new antibiotics - streptomycin, tetracycline, erythromycin, vancomycin - and then escaped the antibiotic category entirely, making possible the bulk production of steroid hormones like cortisone and complex vitamins like B12 [C18]. Decades later the same basic technology, with genetically engineered microbes in place of the mould, would produce human insulin and growth hormone. Biology, not chemistry, had become a platform for drug manufacture, and the biotechnology industry is one of penicillin’s direct descendants [C18]. The mould on Fleming’s plate did not merely give the world a drug. It taught the world a way of making drugs, and that way of making things is still, quite literally, alive in the tanks.

PART VIII - THE BUSINESS

Chapter 18 - The antibiotic dollar

The postwar antibiotics business was born in a strange legal posture: the molecule that founded it belonged to no one. Penicillin's process improvements were patented by the US Department of Agriculture and licensed royalty-free to all applicants, and the Federal Trade Commission, tallying the result in 1958, drew the line directly: "As a consequence, many companies entered into the penicillin business during the late 1940s, the years when penicillin production boomed" [C39]. The boom was real and it was enormous - prices falling ninety-nine and a half per cent in a decade while volume climbed past counting - but the lesson the industry drew from it was not that knowledge should be free. It was that the next molecule must be owned [C39, C29].

The ownership era arrived with the broad-spectrum antibiotics, and the Federal Trade Commission's deadpan litigation record is the best surviving portrait of it. When tetracycline appeared, three companies raced to claim it; the Patent Office threw out the product claims in November 1954 as unpatentable over the prior art; and then, on 11 January 1955, US Patent 2,699,054 for tetracycline issued anyway, to Pfizer's Lloyd Conover - and Pfizer filed infringement suits against Bristol, Upjohn and Olin Mathieson the same day [C39]. The countersuits, transfers, settlements and cross-licences that followed - Bristol paying Cyanamid royalties on a product everyone had been told could not be patented, Squibb buying bulk from Bristol to resell under its own label - are the antibiotics industry of the 1950s in miniature: immense therapeutic value wrapped in a legal thicket so dense that the FTC needed a chapter of timelines to describe it [C39]. The commission's count fixes the scale of the shift: of 671 antibiotics patents issued between 1942 and September 1956, nearly 86 per cent went to corporations as assignees of employee inventors, and only about 5 per cent to the United States government that had owned the founding technology outright [C39].

Oxford's side of the ledger aged badly. The university that had deliberately declined to patent penicillin - against the background of British resentment at American patenting of a vitamin D discovery, and out of a conviction that a life-saving drug should not be fenced - watched the postwar firms amass exactly the commercial patent estates Oxford had forsworn [C29]. In 2020 Oxford's own Vice-Chancellor, looking back, called the 1940s handoff a mistake [C29]. The word deserves scrutiny rather than repetition. The wartime arrangement did what it was designed to do: it made penicillin abundant and cheap faster than any licensing negotiation could have [C18, C37]. What it failed to do was endow the institutions that made the discovery with any claim on the industry the discovery created - and the modern antibiotic market, where the money follows the patent rather than the public good, is the long playing-out of that settlement [C29, C8].

By the end of the 1950s the shape of the business was set: a handful of integrated houses - Merck, Pfizer, Squibb, Lilly, the newer broad-spectrum powers - selling

branded antibiotics at prices protected by product patents, promoted to doctors with a marketing intensity no earlier drug had ever received, and priced, per dose, at levels the wartime bulk buyers would not have believed [C39, C6]. The antibiotic dollar was born. The next chapter of this book tells how thoroughly it died: the same products, off patent, became the commodity streams running through seven 6-APA sites, five of them in China [C8]. Between those two states - monopoly glamour and commodity margin - lies the whole economic biography of the molecule.

Chapter 19 - The manufacturing map

The wartime project made penicillin an American industry, and for a generation it stayed one: the tanks were in Brooklyn and Terre Haute, the strains descended from a Peoria cantaloupe, and the companies were the household names of the American century. Walk the supply chain in the 2020s and the geography is unrecognisable. The drug is the same, the fermentation is the same in kind, but the tanks have moved - decisively, and almost entirely, to Asia [C8].

The anatomy of the move, as the Wellcome-BCG analysis mapped it in 2022, is clearest if you follow a single pill of amoxicillin backwards. The finished medicine is made everywhere. The amoxicillin active ingredient is made at seventeen sites worldwide - six in Europe, three in India, eight in China - which looks, at first glance, like a broadly dispersed capability [C8]. But every one of those sites is a decorating shop: each begins from 6-APA, the bare penicillin nucleus, and the world’s entire supply of that intermediate comes from an estimated seven manufacturing sites, five of them in China [C8]. The pattern for the cephalosporin nucleus is starker still: every site in the world making 7-ACA, the starting material for ceftriaxone and cefuroxime, is in China [C8]. Across a representative shortlist of forty antibiotic active ingredients, close to seventy per cent of manufacturing sites are in China and India [C8]. The decorating of molecules remains global; the growing of them - the capital-heavy, low-margin, fermentation end of the business - has concentrated to a degree the wartime planners, who treated penicillin as a munition and put its production into some twenty companies under government coordination, would find astonishing [C8, C18, C29].

India’s place on this map has its own long history. India built its first penicillin plant in 1955 with support from the World Health Organization and UNICEF - a public-sector beginning for what became one of the world’s great generic pharmaceutical industries, and a reminder that the migration east was not only a story of cost but of deliberate capability-building in countries that had waited, in the penicillin era’s first decade, at the end of the allocation queue [C29]. The historian’s account of that first plant also records the era’s asymmetry: a British discovery, industrialised in America, licensed and re-licensed as it travelled, arriving in the decolonising world as technology to be bargained for [C29].

Why the concentration happened is a matter of arithmetic, and the arithmetic previews the broken-market problem of a later chapter. Antibiotics off patent earn commodity margins; commodity margins push production to the lowest-cost capable sites; the lowest-cost capable sites, for a fermentation-and-chemistry business with significant waste streams, have for decades been in China and India. The Wellcome-BCG analysis that maps this concentration also names its risks: low margins and a small number of API sites leave the supply chains of even first-line antibiotics exposed - to factory shutdowns, to quality failures, to new

environmental regulation, to the ordinary accidents of concentrating a world's supply of a drug class in a handful of postcodes [C8]. The wartime project built redundancy into penicillin because lives depended on it by the million. The modern market built the opposite, because the accounts demanded it. Both logics are visible in the drug's story; only one of them was thinking about the patient.

Chapter 20 - The drug goes global

Penicillin was born British, industrialised American, and for its first years rationed like the strategic material it was: the wartime allocation lists decided which soldiers, which allies and which civilians got it, and much of the world waited at the end of that queue [C29]. How the drug escaped the queue - how it became something countries made rather than something they were allotted - is a story repeated nation by nation, and two of those national stories show the pattern best.

Japan’s began on the first anniversary of the surrender. On 15 August 1946, in a Tokyo where almost no factories were running except small workshops feeding the black market, the presidents of thirty-nine companies gathered with welfare-ministry officials at Ueno’s Seiyoken Hall to found the Japan Penicillin Manufacturing Association [C38]. The occupiers had their own reasons to push: the Allied occupation government had decided that penicillin manufactured in Japan from local raw materials would cost the occupation less than penicillin shipped in, and the ministry had proposed two associations on the occupation’s behalf - one corporate, to link the manufacturers, and one academic, the Japan Penicillin Research Association, to direct the research [C38]. The companies were not eager. Iwadare Toru, then president of Banyu Seiyaku, remembered it later with a dry honesty: “it seems strange to think of it now, but at the time both the government and firms were not very enthusiastic about developing penicillin” [C38]. What Japan built anyway, over the occupation years, was more than a copy of the American plant. The historian Victoria Lee calls the process domestication rather than transfer: submerged-fermentation technology arrived, but it was grafted onto a deep prewar Japanese tradition of agricultural chemistry - a national microbiology of koji and brewing that had spent a century learning to see microbes as transformers of scarcity into abundance - and the graft shaped Japanese antibiotic research for decades [C38].

India’s story, which this book tells alongside the modern manufacturing map, runs on the same motive: a first plant built in 1955 with World Health Organization and UNICEF support, a public-sector beginning for what became one of the world’s largest antibiotic industries [C29]. The terms were the era’s terms: the technology moved on licences that had to be bargained for, so that a British discovery, industrialised in America, reached the decolonising world as property to be negotiated [C29]. The allocation queue is long gone. What replaced it - a concentrated, cost-driven, commodity industry - is the map the previous chapter drew, and its risks are now everyone’s.

The pattern generalises. Wherever penicillin production took root outside the United States - in occupied Japan, in newly independent India, in the war-damaged industries of Europe - it did so as a deliberate act of state or institutional will, not as a spontaneous commercial migration [C38, C29]. The drug’s

chemistry was free; no product patent ever fenced it [C39]. What was not free was the know-how, and know-how moved only when someone - an occupation government, a UN agency, a national ministry - decided to pay the price of moving it. That is the first lesson of the drug’s globalisation, and it anticipates the last problem of this book: if access to antibiotics depends on such decisions, who makes them now, and for whom?

Chapter 21 - The broken market

Here is the central economic paradox of the antibiotic age, and penicillin's own success built it. Antibiotics are among the most valuable technologies in the history of medicine, and they are among the worst businesses in the pharmaceutical industry. The old ones - amoxicillin, the generic penicillins, the cephalosporins - sell by the tonne at commodity margins so thin that manufacturers can and do walk away, switching their plants to more profitable non-antibiotic ingredients when the arithmetic turns [C8]. And the new ones, the drugs the world urgently needs against resistant bacteria, barely get built at all: the pipeline of new and innovative antibiotics is, in the words of one recent analysis, very limited [C8].

The logic is not mysterious. A genuinely new antibiotic is a drug the world's doctors will deliberately ration. The whole point of a last-resort medicine is that it is held in reserve, used as little as possible for as long as possible, so that resistance stays rare - and a product whose customers are paid to buy as little of it as they can does not repay the billion-dollar climb through development and trials. The industry's own analyses describe the consequences at the production end too: low margins concentrate manufacturing in a few sites, a few sites make fragile supply, and the molecules with the most at-risk supply chains include exactly the last-resort generics the world can least afford to lose [C8].

The proposed repairs all attack the same junction: payment must be separated from volume. Delinked reimbursement - a fixed annual payment for a critical antibiotic, whatever its sales, or additional payments to manufacturers meeting quality and environmental standards - turns a last-resort drug from a bad product into a bought insurance policy, which is what, socially speaking, it is [C8]. Pilot versions exist; the general fix does not [C8]. Meanwhile the counterfactual bill mounts: the O'Neill Review's estimates put the cost of unchecked antimicrobial resistance to the global economy at a hundred trillion dollars by 2050 [C40].

It is worth ending this chapter where the book's middle began. The world has solved this exact problem before, under worse conditions, in less time. The wartime penicillin project took a fragile laboratory curiosity to mass production in three years because a government treated the drug as a mission: it organised the search for strains, pooled the companies' process secrets, financed the plants, coordinated the trials and set the standards - and the companies, whatever else they gained, made money [C18]. The modern antibiotic market inverts that arrangement: maximum reliance on private incentive, minimum mission, and a slow-motion shortage of both new drugs and reliable old ones as the result. The mould has not stopped making penicillin. What has stopped, on current form, is the system that once knew how to turn a molecule into a munition.

PART IX - RESISTANCE

Chapter 22 - How resistance works

The most prophetic document in the penicillin story is not a discovery paper but a warning, delivered in December 1945 by the man who started it all. In his Nobel lecture, Fleming told his audience exactly how the miracle would be misused, and he told it as a parable about a Mr. X, who has a sore throat, buys some penicillin, gives himself too little to kill his streptococci, and thereby educates them instead: the survivors are the ones that shrug the drug off, and Mr. X's wife later catches the educated strain and dies of a pneumonia that penicillin cannot touch [C2]. His closing instruction was as blunt as instructions get: "If you use penicillin, use enough" [C2]. He was not guessing. In his own laboratory it was easy to make microbes resistant by exposing them to sublethal doses; evolution needed no encouragement, only selection [C2].

Resistance to penicillin is not one trick but several, and the bacteria had begun work on all of them before the drug existed. The first trick is to break the weapon. In 1940 - before penicillin had treated a single patient - an enzyme that inactivates it was already on record, produced by bacteria that penicillin does not kill [C4, C6]. Penicillinase, and the broader family of beta-lactamase enzymes that followed, does exactly what the drug does, in reverse: where penicillin's beta-lactam ring snaps onto the cell-wall-building enzymes and jams them, the bacterial enzyme snaps the ring itself open, and the drug falls apart as waste [C6]. This is the resistance of the staphylococci that filled hospitals through the 1950s, the resistance methicillin was built to outmanoeuvre [C6].

The second trick is to move the target. Penicillin kills by binding its PBPs - the enzymes that cross-link the cell wall - but a bacterium that acquires a differently shaped PBP renders the drug's aim useless. That is the mechanism behind MRSA: the resistant staphylococci carry an imported gene, mecA, encoding a substitute wall-building enzyme, PBP2a, that penicillin and its relatives cannot grip, so wall-building proceeds while the drug looks on [C24, C6]. The genetic sleuthing of this gene carries a humbling lesson: its origins reach back to a staphylococcal ancestor from the 1940s - which is to say, the raw material of MRSA was old before methicillin was new [C24]. As the previous chapter recorded, resistant strains were observed within about a year of methicillin's introduction; the mould's counters and the chemists' counters-to-counters had met their match in a gene that had been waiting in the wings [C24].

The third trick is to keep the drug out. Gram-negative bacteria wear an outer membrane that penicillin G never learned to cross - this is the Gram divide from the first plate, a boundary of the drug's spectrum that is also, in effect, a standing form of resistance - and bacteria further vary the porin doorways in that membrane and pump unwanted molecules back out, denying the drug the concentration it needs at its target [C2, C6]. Break the weapon, move the target,

lock the door: between them, these mechanisms cover nearly every penicillin defeat of the last eighty years.

None of this required malice or even use. Selection needs only exposure, and exposure is what a successful drug does. Nor was penicillin singled out: streptomycin, the second great antibiotic, was already noted for rapidly inducing resistance by 1945, as Florey observed while accepting his own Nobel share [C3]. The pattern was general because the biology is general. What made penicillin’s case historic was scale: the first antibiotic was also the first mass selection experiment, run on every patient, every ward and eventually every farm on earth. How that experiment unfolded - the hospital staphylococci, the warnings ignored, the mobile genes that carry resistance between species - is the next chapter.

Chapter 23 - The spread

The resistance era did not creep up on anyone. It opened, on schedule, within about a year of the drug's first use: four penicillin-resistant staphylococcal strains were isolated from patients in the course of treatment for localised infections, and the reports multiplied from there [C6]. Nor was the mechanism a surprise - Abraham and Chain had found penicillinase back in 1940, in a resistant Gram-negative rod that had contaminated their Penicillium cultures and in an extract of E. coli, and they had shown that staphylococci could be made resistant in the laboratory simply by growing them, generation after generation, in the drug's presence [C6]. The bacteria had the countermeasure before the weapon was issued. All that use added was selection.

The speed of what followed still startles. By 1947 - five years after penicillin's introduction - the majority of Staphylococcus aureus isolates in hospitals were resistant to it, and the resistant strains were not staying put: an inter-hospital staphylococcus known by its phage-typing name, the 80/81 complex, became the world's first encounter with a multiple-resistant pathogen, spreading from ward to ward and country to country [C6]. It was Mary Barber in England who first called attention to what was happening in the hospitals, and the alarm quickly went global - reports of the same pattern arrived from the United States, Canada, Australia, Norway, Sweden, Denmark, France, India and Chile [C6]. The hospital, the very institution the drug was supposed to make safe, had become the reactor in which resistance was bred and the network along which it travelled.

The pattern repeated at each escalation. The semisynthetic armoured penicillins - methicillin and its kin - were engineered specifically against the penicillinase strains, and as the family chapter recorded, resistant staphylococci were observed within about a year of methicillin's introduction: MRSA, whose imported mecA gene carries genetic material dating to a staphylococcal ancestor of the 1940s [C24]. Each new side chain bought a shorter reprieve than the last, because the bacteria were never starting from zero - they were drawing on an old, shared arsenal. Beta-lactamase enzymes exist in whole families, carried not only on chromosomes but on plasmids and transposons, the mobile genetic elements that let one bacterium hand a resistance gene to another like a copied file [C6]. Resistance, in other words, is not only inherited vertically, mother cell to daughter. It is traded horizontally, across strains and even across species, and every treated patient is a market where the trade is brisk.

By the 1960s the centre of gravity had shifted again, this time from the cocci to the Gram-negative rods - E. coli, Klebsiella, Proteus and their kin, bacteria behind their outer membranes that medicine understood less well and drugs reached less easily [C6]. The Finnish bacteriologist Maxwell Finland's longitudinal surveys of infection made the uncomfortable observation plain: the introduction of new antimicrobial agents was accompanied, at the level of whole patient populations,

by a shift toward more drug-resistant organisms and more virulent ones - the therapeutic gains partially nullified by the ecological response [C6]. And medicine itself kept recruiting new victims for the resistant pathogens: as intensive care, catheters, artificial joints and cancer chemotherapy spread, so did the population of immunocompromised patients on whom environmental bacteria like Pseudomonas could prey [C6]. The antibiotic era did not merely fight an enemy. It rebuilt the battlefield, again and again, in the enemy’s favour - and each time, the counterattack had to be paid for in new chemistry, which is where the pipeline story of the next chapter begins.

Chapter 24 - The discovery void

The antibiotic age had a golden quarter-century, and it is worth pausing on how suddenly it ended. Between the early 1940s and the mid-1960s, the platform penicillin built - screen the soil microbes, ferment the winner, purify, decorate - delivered essentially every antibiotic family in the modern pharmacopoeia: the penicillins, the cephalosporins, streptomycin and the aminoglycosides, the tetracyclines, the macrolides, chloramphenicol, vancomycin [C18, C6]. Then the discoveries stopped. Not the drugs - chemists went on making fine new drugs for decades by decorating the old nuclei, the semisynthetic strategy this book followed from 6-APA onward - but the classes, the genuinely new frames with genuinely new mechanisms. The microbiologist Christopher Walsh dated the gap precisely: no major classes of antibiotics were introduced between 1962 and 2000 [C41]. Lynn Silver, reviewing the field in 2011, argued even that understates it: the three novel classes that did arrive in the 2000s - linezolid, daptomycin, retapamulin - belonged to chemical families first reported or patented in 1978, 1987 and 1952. On the timeline of discovery, as opposed to introduction, Silver’s review found no successful discoveries of new antibacterial classes since 1987 - not a gap, she concluded, but a discovery void of unknown extent, and the field’s later literature has continued to quote that verdict rather than overturn it [C41].

Why the well ran dry is partly a story of success. The Waksman platform worked so well in its first two decades because the soil actinomycetes are generous producers and the easy producers were found first; by the 1960s the same screens kept returning the same organisms and the same compounds. The low-hanging fruit was gone, and the scientific obstacles to finding more - culturing the uncultured majority of microbes, getting molecules through the Gram-negative outer membrane, distinguishing a real hit from the background of known toxins and detergents - turned out to be harder than the economics [C41, C6]. Silver’s sober conclusion was that even unlimited money would not by itself have restarted discovery, because the scientific problems were real [C41].

And the money, of course, was not unlimited - it was leaving. The void is a scientific fact, but it became a permanent condition through the broken market of the earlier chapter: as generics drove the old drugs to commodity margins and the stewardship logic promised low sales for any new one, the industry redeployed its research budgets to chronic diseases where a successful drug is taken daily for decades rather than occasionally for a week [C8]. By the time the O’Neill Review counted the cost in 2016, the pipeline of new and innovative antibiotics was, in the supply-chain analysis the Review drew on, very limited [C40, C8]. The mould that taught the world to mine microbes for weapons had one more lesson to teach, and it is the one the present chapter records: the mine is not exhausted because the microbes ran out of chemistry, but because the world stopped paying to dig.

Chapter 25 - The reckoning

Every warning in the resistance chapters of this book has a price tag, and in 2014 the British government asked an economist to compute it. The Review on Antimicrobial Resistance, chaired by Jim O’Neill, delivered its final report in May 2016, and its headline numbers have framed the debate ever since: about 700,000 people a year were already dying from drug-resistant strains of common bacterial infections, HIV, TB and malaria - a figure the Review itself called likely an underestimate - and, if nothing changed, 10 million lives a year by 2050, more people than currently die from cancer, with a cumulative hundred trillion US dollars of global economic output at risk over the same period [C40].

Numbers that large deserve a sentence of care, and this book gives it one: these are modelled estimates, not counts, and the Review said so. The comprehensive global burden study that followed measured the problem on a different basis - bacterial resistance only, where the Review’s estimate had also counted resistant HIV, tuberculosis and malaria; modelled from three decades of mortality data; and published in 2024, eight years after the Review - so its figures are not directly comparable with the Review’s: it put deaths directly attributable to bacterial resistance alone at about 1.14 million in 2021, and its reference forecast for 2050 ran to about 1.9 million deaths a year attributable and 8.2 million associated [C45]. Within the trend sits the demographic inversion this book’s hospital chapters predicted: between 1990 and 2021, deaths from resistance fell by more than half among children under five and rose by more than 80 per cent among adults over seventy, concentrating the burden exactly where modern medicine leans hardest on antibiotic cover [C45]. The direction of the O’Neill numbers is not in doubt; their magnitude is now a live scientific argument, and this book reports the projections as projections. What the O’Neill figures did was translate a clinician’s anxiety into a finance ministry’s language, and the translation changed the politics: antimicrobial resistance stopped being a hospital story and became a treasury story [C40].

The deeper point of the Review’s analysis is the one this whole book has been building. Antibiotics are not one drug class among many; they are the load-bearing wall of modern medicine. Gut surgery, caesarean sections, joint replacements, chemotherapy, neonatal care - the routine miracles of the modern hospital all assume that the bacterial infections they invite can be treated, and if the antibiotics lose their effectiveness those procedures do not merely become less pleasant, they become unofferable [C40]. Penicillin’s own history shows both halves of why that wall now crumbles. The demand side is evolution, patient and unstoppable, selecting through every prescription ever written. The supply side is the broken market of the previous chapter: a discovery pipeline that no longer refills what resistance empties [C40, C8].

The Review’s recommended response covered both sides at once - reduce demand through sanitation, vaccination, diagnostics and stewardship; renew supply through new incentives for drugs, diagnostics and vaccines, including the delinked payments that would buy new antibiotics as insurance rather than as volume [C40]. A decade on, pieces of that package exist and the burden’s upward trajectory has not bent [C45]. The penicillin story ends, then, not with a triumph to celebrate but with a capability to defend: the mould’s gift, industrialised by a wartime project, globalised by deliberate policy, cheapened to a commodity, and now spent faster than it is replenished. Fleming’s closing instruction from 1945 - use enough, and no more - turns out to have been the whole strategy in one sentence. The world has still to organise itself to follow it.

PART X - THE CONSEQUENCES

Chapter 26 - Medicine remade

The easiest way to miss what antibiotics did is to look only at the diseases they cured. The deeper effect is architectural: modern medicine is built on the assumption that bacterial infection is manageable, and almost nothing in a contemporary hospital makes sense without it. The O'Neill Review put the point in a single plain list of what antibiotics underpin: gut surgery, caesarean sections, joint replacements - procedures that deliberately breach the body's barriers and would carry forbidding infection risks in a world without effective drugs [C40]. Add the treatments that suppress immunity itself - cancer chemotherapy, organ transplantation, the care of premature infants - and the dependence deepens: these are therapies that work only because the infections they invite can be treated, and their rise dates, with no ambiguity, from the antibiotic era [C40, C8].

The transformation can be watched at the scale of a single speciality. Surgery before antibiotics was bounded by sepsis: the operation could be technically brilliant and the patient could still die of the wound, as the wartime sulfa experience showed and the Oxford team's 1941 paper took as its yardstick [S-H3]. Antibiotics did not make surgery sterile - antisepsis had done the first half of that work two generations earlier - but they made deep, long, deliberate surgery routine: open abdomens, replaced hips, transplanted organs, each one an invitation to infection that the drugs quietly decline on the patient's behalf [C40]. The same pattern runs through obstetrics, where the childbed fever that had stalked maternity wards became first treatable and then rare; through oncology, where chemotherapy's collateral neutropenia is survivable because febrile patients can be covered; and through the intensive care unit, an institution whose entire existence - ventilators, central lines, weeks of invasive support - is a bet that the antibiotics will hold [C40, C10].

This is why the resistance crisis is not one drug class's problem, and why this book's resistance chapters insist on the architectural metaphor. If the wall of antibiotic cover weakens, what fails is not a formulary line but the load-bearing structure of the hospital: the O'Neill projections of ten million deaths a year by 2050 are, in large part, projections about what happens to surgery, obstetrics, oncology and intensive care when their foundation thins [C40]. Penicillin's deepest legacy is thus invisible in the best sense: a whole civilisation of medical practice erected on top of it, so completely that the practitioners of that medicine rarely think about the mould at all. The remaining chapters look at the places where the foundation shows its cracks - the farm, the allergy clinic, the stewardship office - before the conclusion asks what the mould's bargain demands of us now.

Chapter 27 - The farm

The largest users of antibiotics on earth are not hospitals. They are farms - and the collision between penicillin's world and agriculture's was visible early enough that a government formally reckoned with it in 1969. The occasion was the report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, chaired by Professor Michael Swann, and the minister's statement to the House of Commons on 20 November that year records both the finding and the remedy in unhedged terms. The committee found that administering antibiotics to farm livestock "poses certain hazards to human and animal health since it has led to the emergence of strains of bacteria which are resistant to antibiotics" [C42]. Its principal recommendation was to split the drug class in two: "feed" antibiotics, of economic value in livestock production but of little moment in human medicine, could remain available without prescription; "therapeutic" antibiotics - the ones human medicine depends on - could not. And it named the consequence: the use of penicillin and the tetracyclines in feedingstuffs should be prohibited [C42].

Pause on the date. This is November 1969: twenty-four years after Fleming's Nobel warning, nine years after the first MRSA sighting, and the regulatory apparatus of a major agricultural power is only just drawing the line between drugs for growth and drugs for cure. The biology of why the line mattered was already this book's resistance chapters: the same mobile genes, the same selection arithmetic, run in a pig shed as in a surgical ward, and the farm offered selection at a scale no hospital could match - whole herds dosed daily at sub-therapeutic levels, the exact regimen Fleming's Mr. X parable had warned against in 1945 [C6, C2].

The farm chapter of the penicillin story is, in fairness, also a chapter about abundance: antibiotic-supported husbandry helped make animal protein cheap in the postwar decades, which is precisely why the practice proved so hard to restrain and why the committee's own test for a "feed" antibiotic began by conceding its economic value in livestock production [C42]. But the long-run ledger is the One Health ledger the modern analyses now keep: human health, animal health and the environment are one system for resistance purposes, and the penicillin family - the first drugs to be fed to herds and the first to be banned from feed - is where the world learned that the bill is shared [C8]. Swann's split of the pharmacopoeia into feed and therapeutic halves was the first regulatory admission of an uncomfortable fact: an antibiotic is a commons, and what one sector spends, every sector loses.

Chapter 28 - Myth and memory

On 10 December 1945, Fleming, Florey and Chain stood together in Stockholm and received the Nobel Prize in Physiology or Medicine, and the press coverage settled the story into the shape the public has kept ever since: a lone Scot, a contaminated plate, a miracle [C2, C3, C4]. The Nobel archive tells a more interesting truth, and it is the truth this book has followed. Read the three lectures side by side and they divide the work without rancour and without ambiguity. Fleming's lecture is the discoverer's: the plate, the mould, the broth, the first assays, and - remarkable in a laureate's moment of glory - a warning about resistance that reads as prophecy [C2]. Florey's is the organiser's: the survey of what the mould's rivals had achieved, the case for systematic work, the account of what it took to turn a laboratory observation into a tested drug [C3]. Chain's is the chemist's: the purification, the instability, the structure, the synthesis chase and its failure [C4]. The prize was given to three men because the achievement had three irreducible parts, and each laureate said so from the podium.

The legend's raw material was real, which is why it lasted. Fleming did make the observation, did name the substance, did publish it in 1929 with the suggestion - italicised by history - that it "may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes" [C5]. And the discovery was genuinely accidental, which Fleming himself never disguised: "I did not invent penicillin. Nature did that. I only discovered it by accident" [C34]. But between the accident and the medicine lay thirteen years and the work of a large team - the Oxford chemists and clinicians, the Peoria agricultural scientists, the mutation geneticists, the engineers and the companies - and the legend has no room for any of them. It has no room for the plate's own prehistory either: Fleming was not the first to see a mould inhibit bacteria, only the first to study the substance and pursue it [C6]. Even the mould's journey to the window ledge has been mythologised; modern mycology's best reconstruction involves Fleming's mycologist colleague C. J. La Touche, whose spores Fleming thanked him for helping identify in the 1929 paper itself [C5, C7].

The myth did harm, and not only to the historical record. A story in which penicillin arrived by luck understates what the penicillin project proved - that organised science, funded deliberately and coordinated across governments, universities and companies, can industrialise a molecule in three years - and thereby makes the antibiotic era's later failures look like fate rather than choice [C18, C37]. The mould's bargain, the subject of this book's conclusion, was never with luck. It was with the institutions that chose to do the work. Remembering the plate is right. Remembering only the plate is how a society talks itself into believing that miracles happen to it, instead of being built by it - and that is precisely the belief the current antibiotic crisis is busy punishing.

PART XI - LIMITS AND FUTURE

Chapter 29 - The allergic minority

No account of penicillin’s limits is complete without the people the drug cannot serve. Penicillins are the most commonly implicated drugs in both immediate and delayed hypersensitivity reactions, and the reactions are real: anaphylaxis to penicillin is rare but can kill in minutes, and no responsible clinician treats an allergy label lightly [C43]. The strange modern fact is not that the allergy exists but how wide the label has spread beyond it. About ten per cent of the general population - and up to fifteen per cent of hospitalised patients - carry a penicillin allergy label in their records [C43]. Yet when allergists actually evaluate those patients, the overwhelming majority tolerate penicillins without incident, and the label can be removed [C43]. The mismatch has a simple anatomy: labels are acquired casually - a childhood rash of uncertain origin, a nausea that was really the illness, a family story - and once written into a record they are copied forward for decades, outliving the evidence that created them [C43].

The label is not harmless. The allergists’ own tally is blunt: a penicillin allergy label is associated with longer hospital stays, more perioperative infections and higher overall mortality, because the substitute antibiotics are typically broader-spectrum, costlier and less effective, with more collateral damage - including antibiotic resistance and C. difficile [C43]. Multiplied by millions of records, the label is itself a driver of the resistance problem this book has described, steering prescribing away from the narrow, targeted drugs toward the heavy artillery [C43, C40]. Hence the rise of “delabeling” as a deliberate clinical practice: structured history-taking, skin testing for the small minority whose history suggests a genuine IgE-mediated reaction or anaphylaxis, and direct graded challenge for the low-risk majority, who prove on testing - with reaction rates of only four to ten per cent even before any skin test - that the label never described them [C43].

There is a historical symmetry here worth noting. Penicillin began its career with an impurities problem - the fever-provoking pyrogens in the Oxford fractions that made early patients shiver - and purification solved it [S-H3]. It ends, in this corner of its story, with a different impurities problem: the impurities are in the medical record, not the vial, and the purification required is of information rather than chemistry [C43]. A drug that ten per cent of people believe they cannot take is, in effect, ten per cent withdrawn. Getting those patients back - safely, one tested record at a time - is one of the cheapest antibiotic victories currently available, and it requires no new molecule at all.

Chapter 30 - Stewardship

Stewardship is the name the antibiotic era eventually gave to Fleming's closing sentence. "If you use penicillin, use enough" [C2] contains the whole doctrine: enough to cure, which protects the patient; and no more than enough, which protects the drug - because every unnecessary dose, every too-short course, every antibiotic taken for a viral cold is selection pressure applied to no one's benefit [C6, C2]. What changed in the decades after 1945 is that the doctrine acquired an institutional form. The O'Neill Review's demand-side programme lists the components plainly: reduce the need for antibiotics through sanitation, infection prevention and vaccination; reduce their careless use through better diagnostics, so that a prescription answers a demonstrated bacterial need rather than a guess; and police the whole through surveillance and prescribing oversight [C40]. Stewardship is that programme at the level of the hospital and the clinic: the right drug, at the right dose, for the right duration, for the patients who actually need it.

The obstacles are not mainly technical. A prescription is a decision made in ninety seconds by someone with a waiting room, under uncertainty, against the patient's expectation of leaving with something; the world's antibiotics are spent one such decision at a time. The stewardship tools that work are therefore organisational as much as pharmacological - guidelines and audit, rapid diagnostics that shrink the uncertainty, delayed-prescription strategies that shrink the expectation, and the delabeling programmes of the allergy chapter, which return whole categories of patients to the narrow drugs [C40, C43]. The supply-side reforms get more press, but the arithmetic of resistance runs through the demand side: the cheapest new antibiotic is the one the world does not have to invent because the old ones still work.

There is, though, a harder question stewardship cannot dodge, and this book's global chapters force it. Rationing a resource is easiest where the resource is plentiful. Much of the world still suffers the opposite problem - too little access, not too much use - and the history this book has told, of allocation queues and licensed technology and a manufacturing map concentrated far from the patients, means that stewardship preached globally can shade into gatekeeping locally [C8, C29, C38]. The honest formulation is the one the wartime project itself modelled: penicillin was rationed when scarce and released when abundant, and the object of policy was always to move the drug from the first condition to the second [C29]. Stewardship's goal is the same now - not to keep antibiotics from people, but to keep antibiotics working for them. The difference between those two ambitions is the whole art.

Chapter 31 - What comes next

The penicillin story ends in the present tense, so this last chapter before the conclusion is an inventory of open doors. The first door is the oldest: more antibiotics. The discovery void is real but not metaphysical - the soil microbes are still there, mostly uncultured and unread, and the one proven way to refill the pipeline is to pay for the digging, which is what the delinked incentives of the broken-market chapter are for: buy new antibiotics as insurance, not as volume [C41, C40, C8]. The O'Neill Review's supply-side package - market-entry rewards and purchase guarantees alongside the research funding - remains the template, implemented so far in pieces rather than in full [C40].

The second door leads beyond antibiotics altogether. The Review catalogued the alternatives with an economist's even-handedness: bacteriophages - the viruses that prey on bacteria, natural or engineered; lysins, the enzymes phages use to burst their hosts; monoclonal antibodies; probiotics; immune stimulation; antimicrobial peptides; and vaccines, which prevent the infections that drive the prescriptions in the first place [C40]. None of these is a fantasy. Phage therapy predates penicillin itself and persists in a few medical traditions; lysins and engineered phages are now serious candidates. But none is yet a replacement, and the Review's own framing kept them in the category of things that might reach market within a decade - useful supplements to a functioning antibiotic base, not substitutes for it [C40]. The base still has to be defended.

The third door is the one this book has been arguing for throughout: institutions. Penicillin's history says that the binding constraint is rarely the science alone. The molecule was known for thirteen years before anyone organised its development; the wartime project then industrialised it in three; the postwar market dissipated the production commons in twenty; and the current crisis is, at bottom, an institutional failure to value a shared capability [C18, C37, C39]. What comes next therefore depends less on any single breakthrough than on whether the world's governments can again do what the 1940s project did - coordinate the work, pool the knowledge, pay for the capacity, and keep the drug working for the people at the end of the queue. The mould did its part in 1928. The rest has always been up to institutions, and it still is.

Chapter 32 - Conclusion: the mould’s bargain

A spore drifted onto a plate in the summer of 1928, and everything else in this book was chosen. That is the sentence the penicillin story keeps trying to teach, and the one its mythology keeps trying to erase. The discovery was luck; nothing after it was. A bacteriologist who kept the plate and published the observation [C5]. A team that chose, in a country at war, to spend its best chemists on an unstable mould extract [C3, S-H2]. A government that chose to organise an industry rather than wait for one [C18, C37]. A government laboratory in an Illinois river town that chose to feed the mould on corn-steep waste and breed it like a crop [C15]. Companies that chose to pool their secrets, under contracts written to make sharing the default [C37, C39]. An occupation administration and a young republic that chose to build the capability rather than queue for the allotment [C38, C29]. At every point, the molecule only ever offered possibilities. People and institutions did the converting.

The bargain the mould offered, it turns out, was never “make me and be cured.” It was: make me, and keep making me - because I am not a possession but a capability, and capabilities decay. The bacteria were always going to answer; Fleming saw that and said so, in the plainest words a Nobel podium has carried, in 1945 [C2]. The market was always going to under-produce a drug whose value lies in being held in reserve; the postwar patent thicket and the seven-site 6-APA map were the predictable shapes of leaving the answer to price [C39, C8]. And the bill for both truths was always going to arrive at the hospital door, which is where the O’Neill arithmetic - ten million deaths a year by 2050 if nothing changes - ultimately lands [C40].

But the same history that explains the crisis refutes despair about it, and that is why this book was written the way it was: molecule first, industry second, limits last. The world has already done the impossible version of this task once. It took a laboratory curiosity to a planetary commodity in five years, without a template, under bombardment, and it did so by exactly the means now proposed again as if they were novel: mission funding, pooled knowledge, coordinated production, prices set by policy, supply treated as strategy [C18, C37, C39]. The antibiotic crisis is not a failure of knowledge about what works. It is a failure to choose what works - to keep choosing it, decade after decade, once the crisis of the moment has passed.

So the mould’s bargain, stated plainly: a finite, magnificent, perishable capability, free to any society willing to maintain it, and lost by any society that treats it as self-maintaining. Penicillin itself is eighty years into the test and still in the formulary - still curing strep throats and preventing rheumatic fever, still made by the tonne from the descendants of a Peoria cantaloupe [C7, C15]. The question the story leaves us is not whether the mould kept its side of the bargain. It is whether we will keep ours.

REFERENCE

Glossary

6-APA (6-aminopenicillanic acid) - the penicillin nucleus: the fused beta-lactam and thiazolidine rings without a side chain, the starting material for all semisynthetic penicillins.

7-ACA (7-aminocephalosporanic acid) - the cephalosporin nucleus, the equivalent starting material for the cephalosporin family.

AMR (antimicrobial resistance) - the acquired ability of microbes to survive drugs that previously killed or inhibited them.

Antibiosis - the historical term for one microorganism's inhibition of another, the phenomenon penicillin emerged from.

API (active pharmaceutical ingredient) - the pure drug substance in a medicine, before formulation.

Beta-lactam - the four-atom ring at the heart of penicillin and its relatives; also the name of the whole antibiotic class built around it.

Beta-lactamase (penicillinase) - a bacterial enzyme that opens the beta-lactam ring and destroys the drug.

Broad-spectrum - active against a wide range of bacteria, including Gram-negatives; originally the tetracyclines, later ampicillin and others.

CMR (Committee on Medical Research) - the OSRD committee that coordinated American wartime medical research, including the penicillin programme.

Corn steep liquor - the nutrient-rich waste water from maize steeping, adopted at Peoria as penicillin fermentation feed.

Deep-tank (submerged) fermentation - growing the mould dispersed through aerated, stirred broth in large tanks, instead of as a surface mat.

Delabeling - the clinical practice of testing and removing incorrect penicillin-allergy labels from patient records.

Delinked reimbursement - paying for an antibiotic by fixed fee rather than per unit sold, so conservation does not bankrupt the maker.

Depot formulation - an insoluble penicillin salt (procaine, benzathine) injected into muscle and released over days or weeks.

Discovery void - the absence, documented from 1987 onward, of newly discovered antibacterial classes.

Gram-positive / Gram-negative - the two great bacterial architectures: thick exposed cell wall versus thinner wall hidden behind an outer membrane.

Intermediate - a commodity chemical part-way to a finished drug; 6-APA and 7-ACA are the penicillin industry's key intermediates.

mecA / PBP2a - the imported gene, and the substitute wall-building enzyme it encodes, behind MRSA.

MRSA - methicillin-resistant Staphylococcus aureus, resistant to the penicillinase-proof penicillins.

NRRL (Northern Regional Research Laboratory) - the US Department of Agriculture laboratory in Peoria where penicillin production science was built; strain NRRL 1951 is its cantaloupe isolate.

One Health - the recognition that human, animal and environmental health form one system, including for resistance.

OSRD (Office of Scientific Research and Development) - the US wartime science agency, parent of the CMR.

Oxford unit - the original penicillin measure: the amount just inhibiting the test staphylococcus under standard conditions.

PBP (penicillin-binding protein) - the bacterial cell-wall-building enzymes that penicillin attacks.

Penicillin G (benzylpenicillin) - the original fermentation penicillin; acid-fragile, injectable.

Penicillin V (phenoxymethylpenicillin) - the acid-stable oral penicillin.

Pyrogen - a fever-provoking contaminant of early penicillin preparations.

Q-176 - the Wisconsin ultraviolet-mutant strain from which most industrial penicillin strains descend.

Semisynthetic - made by chemically modifying a fermentation-produced nucleus (6-APA, 7-ACA) rather than by total synthesis.

Serum therapy - treatment with antibody-rich serum from immunised animals, the pre-sulfa specific therapy for pneumonia and other infections.

Stewardship - the organised practice of prescribing antibiotics so as to preserve their effectiveness.

Sulfa drugs (sulphonamides) - the first systemic antibacterial chemicals, introduced from 1935; penicillin's immediate predecessors.

Titre - the concentration of drug in a fermentation broth, the industry's basic productivity measure.

WPB (War Production Board) - the US agency that ran the wartime penicillin production programme.