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Penicillin and the Antibiotic Revolution

In October 1945, Alexander Fleming, Howard Florey, and Ernest Chain each received an almost identical telegram from Stockholm, Sweden. The Nobel Prize Committee, these messages read, was pleased to inform the three British-based scientists that they had been awarded the Nobel Prize for Medicine, for the 'discovery of penicillin and its curative action in various diseases.'[1]

This was not surprising news. In fact, a year earlier, two major newspapers had informed their readers that Fleming would receive the prestigious award in 1944.[2] Although the reporters' stories were a year ahead of their time, they were right that the global scientific community had generally agreed that the world's first antibiotic was a landmark in medical history worthy of Nobel Prize recognition. It was simply a question of when, not if, the prize would be awarded.

While the Committee's decision to award the Nobel Prize to the scientists who had developed penicillin was not controversial, the precise choice of *whom* to award the prize to was more fraught. The uncertainty arose because of the long and complicated process of the drug's development. The story began in 1928 when Alexander Fleming, a Scottish bacteriologist working at St Mary's Hospital Medical School in London, noticed that a specific strain of mould, *Penicillium notatum*, inhibited the growth of bacteria. Setting out to understand more about the mould's unusual properties, Fleming conducted additional experiments. However, he did not foresee the potential medical implications of his discovery. Fleming quickly concluded that it would be impossible to transform the antibiotic solution that he had made from the mould into a useable drug. Convinced that further research on the substance would not be fruitful, Fleming turned to other matters.

For a decade, Fleming's discovery attracted little attention. Then, in 1938, two scientists working at the University of Oxford's Sir William Dunn School of Pathology – Howard Florey, an Australian pathologist, and Ernest Chain, a German biochemist – began researching a selection of anti-bacterial compounds. Over the next two years, Chain and Florey, and their Oxford colleagues experimented on *Penicillium notatum*. During that time, the scientists made a number of important discoveries and overcame the early problems that had thwarted Fleming. By the spring of 1940, Florey and Chain had developed a drug, which they named penicillin, and had shown that the medicine was a highly effective treatment against infection in mice. The following year, they carried out the first preliminary clinical trials in Oxford.

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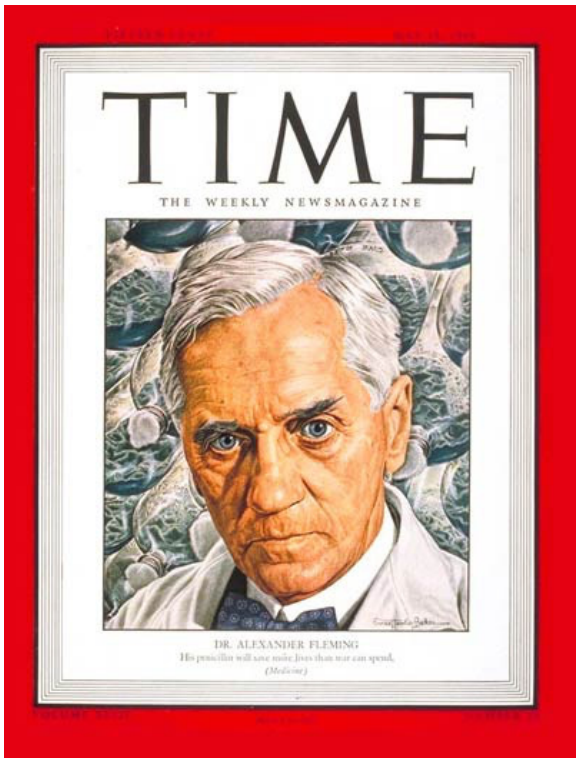
Several other scientists could also claim that they had made crucial contributions that led to the world's first general antibiotic. Initially, Florey and Chain were unable to extract the active substance from the mould in a pure, stable form. Norman Heatley, a 28-year-old biochemist who also worked in the Dunn School, solved those problems. He formulated a method to extract the active substance from *Penicillium notatum*, stabilised the active compound, and invented a semi- automated system to stabilise the drug. Soon afterwards, Andrew J Moyer, a microbiologist who headed the United States Department of Agriculture laboratory in Illinois, devised a more efficient technique to produce penicillin. Moyer's new manufacturing method meant that by the second half of the 1940s, penicillin was widely available at low cost. In short, there was no single person who the Nobel Committee could easily credit with the 'invention' of penicillin.

In 1944 and 1945, journalists wrote articles celebrating the new wonder drug and highlighting Alexander Fleming's '*Eureka!*' contribution. But the journalists' focus on Fleming sparked anger. Writing to a close friend, Florey complained that in portraying Fleming 'as the "discoverer of penicillin" (which is true)', many newspapers also implied that it was Fleming who had done 'all the work leading to the discovery of its chemotherapeutic properties (which is not true).'[3] Other scientists were also concerned about this emerging narrative. Responding to reports that the Nobel Committee would soon award the Prize for Medicine solely to Fleming, an American colleague and friend of Florey dispatched a telegram to the Nobel Committee informing them that 'credit for all clinical development [of penicillin] belongs to Florey and associates.'[4] The race was on to establish the lasting historical account of penicillin's research and development.

The effort to ensure that the Oxford team was not erased from the story of penicillin's development was partially successful. Fleming, Florey, and Chain were jointly awarded the Nobel Prize and both Fleming and Florey received knighthoods. Moreover, based on the Oxford team's work on penicillin, Lord Nuffield, the founder of Morris Motors and, later, Nuffield College, donated money to the Dunn School so that the university's department could endow three research fellowships at Lincoln College and permanently expand Oxford's research capacity.[5] The discovery was not just important, but lucrative.



In other respects, though, Florey and his friends were right that the crucial work of the Oxford scientists would inevitably be forgotten in popular accounts. Over time, the seductively simple story of an absent-minded scientist making a momentous discovery by accident proved much more appealing than the complicated tale of painstaking technical development that involved a wide cast of characters and took place around the world. By the mid-1940s, it was Fleming who had received the lion's share of accolades and whose picture was printed in hundreds of newspapers and magazines (including the cover of *Time* magazine in May 1944). As the decades passed, Fleming's role in the discovery of penicillin became common knowledge, while the contribution of Florey, Chain, Heatley, and Moyer faded away.

After the Second World War, the battle for credit also acquired important national overtones. In telling the story of penicillin's development, journalists and politicians incorporated the drug into celebratory narratives about national inventiveness, innovation, and character. In Britain and the United States particularly, myths of corporate ingenuity, economic opportunities missed, and discoveries stolen would shape subsequent antibiotic development and the global production of pharmaceuticals. It is this history that this case explores.

Before penicillin

The period spanning the late 19th and early 20th centuries was an era of medical transformation. During the Second Industrial Revolution, the life expectancy of infants increased dramatically while the number

of deaths from infectious diseases fell sharply.[6] New vaccines and stricter public health measures saved millions of lives while new sanitation procedures ensured that far fewer people developed infections while in hospitals and on operating tables.[7] Ironically, physicians and public health experts became far better at preventing illness than they were at treating disease. This was particularly true when doctors were dealing with bacterial diseases.

For all of the medical advances of the late 19th and early 20th centuries, as late as the 1940s, minor cuts and scrapes could still prove fatal. Unfortunately, there was very little that physicians could do if a bacterial infection spread into a patient's bloodstream. They could use antiseptics to clean dressings, sterilise surgical equipment, and disinfect the surface of wounds but they were only preventative treatments.[8] For the soldiers who suffered from cholera or gas gangrene during the First World War, doctors had no effective treatment once their infections began to spread.

In 1924, for example, Calvin Coolidge Junior, the teenage son of the then President of the United States, developed a blister while playing tennis in the grounds of the White House. Within days, the blister had become infected, the young man had developed a high fever, and he was moved to a nearby hospital so that seven of the country's leading physicians could treat him.[9] In the end, though, even the nation's best doctors could do nothing to prevent the infection from spreading. A week after his tennis game, Calvin Coolidge Jr died with the President and First Lady by his side. Describing the impact of his favourite son's death, President Coolidge later wrote that 'when he went, the power and glory of the presidency went with him.'[10]

Twelve years later, in 1936, an infection nearly killed the son of President Franklin Delano Roosevelt ('FDR'). Just weeks after his father's re-election as president, 22-year-old Franklin Roosevelt Junior developed a sore throat. Soon afterwards, doctors admitted Roosevelt to a Boston hospital with a severe sinus infection. Over the next two weeks, the young man's temperature rose to a dangerous level, he started to cough up blood, and he began to experience difficulty in breathing. His doctors advised his mother, Eleanor Roosevelt, to prepare for the worst and the First Lady rushed to Boston to be at her son's bedside.[11] On this occasion, however, the story had a happy ending. After they treated him with a new drug, Franklin Roosevelt Jr's fever began to subside and the swelling in his throat eased. One month later, the hospital discharged the President's son.[12] He was cured.

The drug that his doctors used was best known by the trade name Prontosil. Released in 1935 by the German pharmaceutical giant Bayer, the synthetic drug (originally developed as a deep red- coloured synthetic dye) stopped the growth of a range of common bacteria. Because of supply problems and the suspicions of English-speaking medical professionals towards Germany in the 1930s, however, American doctors rarely prescribed Bayer's antimicrobial. This quickly changed when the clinicians published the results of British clinical trials of the drug and after American newspapers broke the story of Franklin Roosevelt Jr's miraculous, death-bed recovery. By 1937, physicians used Prontosil as a standard treatment for pneumonia, meningitis, scarlet fever, and several other common bacterial infections.

While the media hyped Prontosil, the drug had several significant flaws. Unfortunately for Bayer, rival pharmaceutical executives soon figured out that the active ingredient in Prontosil was sulfanilamide, an organic sulphur compound, the patent of which had already expired and so competitors quickly flooded the market with generic equivalents. Worse, these antimicrobials were not effective against the bacteria responsible for anthrax, cholera, tuberculosis, or typhoid, and the drug was ineffective in the presence of pus. Sulfanilamide compounds were also mildly toxic, with common side effects that included fever, rashes, nausea, vomiting, and disorientation.[13]

Severe allergic reactions could lead to organ damage, difficulty breathing and swallowing, and a blueish discolouration of the skin. Moreover, because high doses could be fatal, the sulphur compound could not be used to treat acute infections. Prontosil was effective against bacteria but given the severe side effects, only in very specific circumstances, when the situation was clearly life threatening.

For all of Prontosil's liabilities, its existence raised hope that scientists could develop new drugs to treat bacterial infections. Inspired by the commercial and medical success of these new treatments for bacterial

infection, in the late 1930s and early 1940s, the major pharmaceutical companies and research laboratories devoted a great deal of effort to searching for novel compounds that could destroy bacteria. Within a very short space of time, scientists pinpointed several promising synthetic chemicals and natural substances but the substance that proved to be the most medically significant had in fact first been identified in 1928, seven years before the release of Prontosil.

Mould on a plate

The precise details of the discovery that would eventually lead to the successful development of the world's first antibiotic remain murky. The story often repeated in school science books and popular articles is that in 1928, Alexander Fleming, a professor at St Mary's Hospital Medical School in London, returned from a month's holiday and discovered that a discarded dish of bacterial cultures placed near a window in his laboratory had become contaminated with mould. Just as he was about to send the glass plates to be disinfected, Fleming noticed something remarkable: there were no bacteria growing close to the mould. Something in the fungus had caused the surrounding microbes to die.

Although the broad outlines of this tale are probably correct, the specifics are questionable. There is no reason to doubt that Fleming observed the mould's effect on bacteria in the way he later described. Other elements of the tale, however, are almost certainly embellishments that emerged over time. In particular, it is unlikely that the rare mould entered Fleming's laboratory through an open window, or that the *Eureka!* moment, when the scientist noticed the mould's unusual properties, coincided with his summer holiday. Instead, it is more probable that the fungus was accidentally 'carried' into Fleming's laboratory by one of his colleagues, who had their labs on the floor below, and that the mould grew only after Fleming had returned from his holiday.[14] Whatever the precise circumstances, there is no question that Fleming's accidental discovery was a moment of profound, historical significance.

The story of what happened next is less ambiguous. During the autumn of 1928, Fleming sought to learn more about the fungus. Having established that other moulds did not have the same effect, he tested solutions of *Penicillium notatum* on several different bacteria. From there, Fleming and his assistants attempted to learn more about the chemical and clinical properties of his find. It was here that they hit a roadblock. Although the mould solution appeared to be non- toxic, it was extremely unstable and impure. Not only did its antibacterial strength diminish too quickly to kill anything other than very small quantities of bacteria, because of the solution's impurities, it was also likely to be extremely toxic if administered to humans.[15] Convinced that it would be impossible to turn his mould solution into a useable drug, Fleming began working on other projects.

Before he abandoned his research on *Penicillium notatum*, though, Fleming made two decisions that would later prove crucial. First, he wrote up his findings and sent them off to be published in two scientific journals. He also sent samples of the mould to various scientific laboratories across Europe and America. At the time, his decisions had little impact. While a few scientists carried out experiments with the mould, they too would soon set it aside to focus on their own research. Fleming's journal articles, which he wrote in a characteristically precise but rather dull manner, went largely unnoticed within the broader scientific community.[16] For most of the 1930s, therefore, nobody viewed his discovery as anything remarkable.

Developing a drug at the Dunn School

In 1927, the year before Fleming began working on *Penicillium notatum*, Oxford opened an impressive new building on the edge of the University Parks. With its grandly curved oak staircase and spacious laboratories, the Sir William Dunn School of Pathology represented the epitome of scientific modernity but its early years were marked by struggles. A bequest from the estate of a wealthy London banker paid for the building's construction and the gift endowed a Chair of Pathology but the eponymous William Dunn's donation did not cover the school's operating costs. This meant that the 'Dunn School' was perennially strapped for cash. Worse, the very best researchers generally chose to study elsewhere, while the School's lectures were so dull that Oxford's undergraduates tended to avoid them.[17] When, following the sudden death of the inaugural postholder, Oxford University appointed 36-year-old Howard Florey as Professor of Pathology in 1935, the academic department that Florey inherited was not a flourishing institution.

Undaunted, Florey quickly set about overhauling the department. To improve the financial situation, he began a cost-cutting programme and devoted a great deal of his time to courting external funders. To inject new life into the department, Florey brought in young postgraduates who had secured external grants, hired former colleagues from the University of Sheffield, and reassigned many of the existing academics to new research projects.[18] His efforts paid immediate dividends: the Dunn School was inundated with scholars and grants and its reputation soared. Just one year after Florey's appointment, the University of Oxford's School of Pathology was beginning to show signs that it might become a scientific research institute worthy of its world-class facilities.

One of the most important decisions that Florey made during that first year was to hire a 28-year-old German émigré, Ernest Chain, from Cambridge. In Oxford, Chain studied an enzyme commonly found within tears, saliva, and mucus which has weak antibacterial properties. While reading scientific papers on antibacterial agents, Chain stumbled across Alexander Fleming's articles on *Penicillium notatum* and quickly discovered that Fleming had sent a sample of the fungus to the Dunn School in 1929. Curious about the mould's chemical properties, Chain performed several preliminary experiments and he was soon convinced that further study would be worthwhile. To devote sustained attention to this research project, however, Chain needed the support of his Oxford boss, Howard Florey.

One evening, as Florey and Chain walked through the University Parks, towards their homes, the young biochemist mentioned that he was interested in conducting a broad study of antibacterial substances. Florey was very supportive. In fact, he suggested that they should both investigate three different substances which attacked bacteria.[19] The first substance that the two decided to study was *Penicillium notatum*.

In spite of Florey's essential support, however, the pair were unable to start work immediately. In the 1930s (as is the case today), most scientific research was financed by short- and medium- term grants obtained from external funding agencies. Unfortunately, just as Florey and Chain were about to begin their investigation, the Dunn School's existing external grants were about to expire. A new source of funds would have to be found, which meant convincing others to believe in the new research project before their project could be launched.

This was not an easy task. Florey first sought financial support from the UK's Medical Research Council (MRC). But the research council was short of funds and indeed so strapped that while the MRC saw potential in the project, it was infamously only able to provide the Dunn School with £25, much less than the research team needed. Fortunately for them, the Rockefeller Foundation in New York had far greater resources available. In early 1940, after reviewing Florey's application, the Rockefeller Foundation granted the Dunn School a 12-month research grant of £1,500 and provided assurances that further funds would be made available the following year, so long as the Second World war did not disrupt the project.[20] With their short-term funding now secure, a team of Dunn School scientists began to study *Penicillium notatum.* One of the most influential of the researchers within this small group was Norman Heatley. Florey had hired Heatley shortly after Chain but unlike the latter's academic post, Heatley's position was not permanent. In fact, just as the Dunn School began investigating antibacterial substances, Heatley's contract in Oxford was due to end and he was about to move to Stockholm to start a new job. Ironically, the war proved to be the saving of Oxford's research team since the hostilities prevented Heatley from moving abroad and he stayed at the Dunn School not only for the duration of the conflict, but for the rest of his academic career. Stockholm's loss was Oxford's gain.

Assigned by Florey to the antibacterial substances project in 1939, Heatley made several significant breakthroughs that supported the successful development of penicillin. In addition to designing the technical apparatus in which the team could grow the mould quickly and in greater quantity, Heatley also devised a novel method to extract the active substance from the mould in a stable form.[21] The initial problems that had plagued Fleming had now been resolved by Heatley and the antibacterial substance

within the mould could be isolated and stored for long periods. Just as importantly, the Oxford team learned that when purified via a process designed by Chain, the brown powder that they extracted from the mould inhibited bacterial growth even after it was heavily diluted. Instead of being an academic curiosity, *Penicillium notatum* now had enormous clinical potential.

Throughout the spring of 1940, Florey and his team tested the drug (which they had now named 'penicillin') on small animals and their investigations confirmed Fleming's earlier findings. The scientists established that the drug was non-toxic and that the substance was effective against a wide range of bacteria, even in the presence of pus. Their excitement grew. As Ernest Chain later wrote, 'we knew now that we had stumbled across one of those very rare drugs which would not only kill bacteria in a test tube, but also in the living animal without harming it. We realised at once that penicillin could play a vital role in war medicine'[22] Yet again, however, the Oxford scientists found that their progress to the next stage would not be easy.

Their successful tests on animals were not sufficient proof to authorise the use of penicillin on humans. To fully establish its effectiveness and safety, the scientists needed to conduct extensive clinical trials. The scientists, though, needed a good supply of the mould if they were to use it on humans. This presented the team with a significant problem since they had already struggled to grow enough mould to trial it on small animals. Heatley had been forced to use every available surface and shallow vessel at his disposal and even pie dishes, biscuit tins, and hospital bedpans had been pressed into service. The obvious solution to their problem was for other laboratories to produce penicillin for the Dunn School and to encourage them, the Oxford team published its preliminary findings in the leading medical journal, *The Lancet*. Yet, with the country on a wartime footing, Britain's major industrial laboratories were already working flat out to fulfil their government contracts and so they could not commit to a different project with unproven clinical value. As German bombers blitzed central London, the research scientists in the Dunn School had to go it alone.

Between 1940 and 1941, Norman Heatley transformed the Dunn School from a research laboratory into a makeshift penicillin production line. The scientists' demand for increasing amounts of penicillin forced Heatley to deploy lateral thinking as he improvised the production of penicillin using recycled equipment. Unable to source additional hospital bedpans – the best vessel he had found for growing the mould in – Heatley sketched a novel design and asked a Staffordshire pottery to produce 500 ceramic pots. Meanwhile, to increase the speed with which the Oxford scientists could extract penicillin from the mould, Heatley devised and personally constructed an automated apparatus using discarded bookcases from the Bodleian Library, an old doorbell, some glass tubing, and copper coils.[23]

While Heatley devised innovative ways to boost the School's production capacity, the early, labour-intensive stages of manufacturing fell to Ruth Callow, Betty Cooke, Peggy Gardner, Claire Inayat, Patricia McKegney, and Megan Lancaster, whom the Dunn School's male scientists derisively nicknamed the 'Penicillin Girls'. Working at least six days a week and in tough and hazardous conditions, the women grew and harvested the mould that was absolutely vital to the creation of penicillin. Because historical accounts of penicillin's development only mention these women fleetingly, we know comparatively little about how their labour influenced penicillin's development. Nonetheless, while the Nobel Prize Committee did not cite these women, their work was crucial to scaling up the production of penicillin in Oxford.[24]

Seven months after Chain's first trials on mice, thanks to Heatley's innovations and to the work of the 'Penicillin Girls', the Dunn School was able to perform a human trial of penicillin at Oxford's Radcliffe Infirmary on the Woodstock Road. Florey and his colleagues first demonstrated the safety of the drug on a terminally-ill patient. They then administered a small dose of the new drug to a police officer who was dying from a severe infection caused by a scratch from a rose thorn. Unfortunately, their test produced mixed results. Although the officer's condition initially improved, the supply of penicillin ran out before he could make a full recovery and his condition quickly worsened. One month later, he died. While penicillin

had failed to save the police officer, the scientists' test demonstrated that the drug was effective against infections, and non-toxic even when injected over several days, which they subsequently confirmed when they tested five patients with less advanced infections.

The success of these early clinical trials enabled Florey to renew his appeals to British pharmaceutical companies and research laboratories, to manufacture sufficient penicillin for full clinical trials. During the early months of 1941, scientists from a host of different organisations came to Oxford and inspected the School's mould production and extraction process. At the same time, Florey wrote a second article for *The Lancet*, describing the results of his team's preliminary clinical trials. Despite these efforts, no one in Britain was impressed enough to start manufacturing the antibiotic drug. Frustrated by their recalcitrance, Florey once again turned to his patrons in the United States. Not surprisingly, the Rockefeller Foundation was far more intrigued by the scientists' findings and approved a US$6,000 grant so that Florey and Heatley could travel to the United States, to meet and try to convince 'American mould or yeast raisers' to help them.[25] In the summer of 1941, the two Oxford scientists flew to New York City.

Bringing penicillin to the United States

In the United States, Florey and Heatley met with both government and industry officials and described, in detail, the technical problems the Dunn School faced in producing penicillin. They needed significant supplies of the drug to conduct full clinical trials, the Oxford scientists explained, and they argued that penicillin had the potential to make a significant contribution to the Allied war effort. The American scientific community quickly agreed with the two of them. One expert on fungus, who was employed by the US Department of Agriculture, was particularly enthusiastic and asked his colleagues in Peoria, Illinois, if they could help.[26] Andrew Moyer, the director of this new laboratory, was unfamiliar with the Oxford team's research but was happy to learn more and to help. As a first step, Moyer suggested that the Dunn School scientists visit him in Illinois.

Heatley and Florey's trip to the American Midwest proved extremely useful and, after a very brief discussion with the Oxford scientists, the director of the laboratory agreed to harvest the penicillin mould. Moyer also suggested that Heatley should remain in Peoria so that he could be on hand to provide his expertise.

Over the next five months, Heatley and the scientists in the Department of Agriculture successively refined the penicillin production process. By applying techniques which the agricultural researchers had developed to process agricultural waste, they learned that penicillin fungus would grow faster and produce more of the active substance in the mould if they used nitrogen-rich mediums as the growth culture. At the same time, the Peoria team also began to experiment with submerged fermentation techniques to produce the drug. Manufacturing penicillin in large volumes could, it seemed, become easier and less expensive in the near future.

While Heatley was working with the agricultural scientists in Illinois, Florey visited several leading American pharmaceutical companies. At the start, Florey found his trips disheartening since corporate executives worried about the financial risk involved in the large-scale manufacture of a drug before the full clinical trials were complete. Even those executives who were keen to produce penicillin warned the British scientist that American anti-monopoly regulation would block efficient production. Here, however, Florey's contacts within the American government proved beneficial yet again. After speaking with the Oxford scientist, the chair of a powerful federal government agency assured the corporate executives within the American pharmaceutical industry that he regarded the manufacture of penicillin to be in the national interest and promised the corporate executives that antitrust rules would be waived so that companies could exchange information without fear of prosecution. Buoyed by this, leading executives in four American pharmaceutical companies reversed their stance and agreed with Florey to manufacture penicillin in advance of the completion of the full clinical trials.

Welcome news though this was, the developments back in Oxford meant that in the end, the co- operation

of American pharmaceutical companies was not necessary. While Florey and Healey were absent, the scientists in the Dunn School had converted a cavernous animal house that stood behind their main building into a dedicated penicillin extraction plant.[27] Fortunately, at almost precisely the same time that the American firms agreed to manufacture penicillin, two English pharmaceutical companies – including Imperial Chemical Industries (ICI), Britain's largest chemical company – also agreed to produce the antibiotic. Immediately, things changed for the better. With domestically-produced penicillin available in greater quantities, Oxford could begin full clinical trials without having to wait for shipments of penicillin from the United States. Under the close supervision of Florey's wife, Ethel (a physician), researchers administered penicillin to 15 seriously ill patients as well as to 172 patients with localised infections.[28] These trials produced, as Howard Florey told a friend, 'astonishing results – almost miraculous, some of them.'[29] There was no longer any doubt that penicillin was a wonder drug. The challenge now was to get it as quickly as possible to those who would benefit from it the most.

Commercialising penicillin production

It was not inevitable that medical doctors would immediately adopt penicillin once clinical trials proved that it worked. After all, doctors had not widely prescribed Prontosil outside Germany until two years after Bayer released the drug. That said, the British scientists faced very different challenges in commercialising penicillin. Whereas the scientists in Bayer had been secretive about their research and had only published select details about Prontosil once the company had patented the drug, the researchers at the University of Oxford had always been very open about their research and Florey had not tried to patent penicillin. The scientific community was, as a consequence, well aware of the remarkable new drug's potential. And yet, as the Dunn School's efforts had already shown, it was not easy to scale up production. In 1943, as the Floreys wrote in their paper about the clinical trials, the drug was 'available only in very small quantities.'[30] If the antibiotic was to have an immediate impact on public health, particularly during a world war, this situation would have to change. In response, between 1942 and 1945, the British government and the country's largest pharmaceutical companies spent a great deal of money building new penicillin production facilities across Britain.

Early in 1943, the executives of ICI committed £300,000 to the building of a large production facility and during the same period, several other major pharmaceutical companies also began to manufacture penicillin. Encouraged to produce the drug by the government's General Committee on Penicillin, Boots, Britain's foremost chain of pharmacies, built a large manufacturing facility in Nottingham, and a further four plants were built by Glaxo Laboratories.[31] Alongside these corporate efforts, the Royal Navy also began making penicillin at its medical school in Somerset and the British government spent £1.3 million building the world's largest facility dedicated to production of the drug.[32] By the end of 1945, eight British companies were producing penicillin in 12 different factories around the UK.[33]

Despite their best intentions, however, these British commercial facilities were far from cutting edge. Desperate to start producing penicillin as quickly as possible, both the public and private sectors had simply replicated the Dunn School's manufacturing methods and so made use of repurposed rather than specially-built equipment. For the Royal Navy, this meant storing the mould broth in empty gin bottles (of which the Navy had a large and ever-growing supply) while at Glaxo, their employees grew the mould in milk churns.[34] Although successful in ensuring a quick increase in production capacity, this creative act of repurposing items already intrinsic to the makers' daily business, instead of relying on new materials that were increasingly prioritised for use by the armaments industry, was a short-term approach if compared to the modern facilities that American companies built specifically to manufacture penicillin. This adaptive approach meant that many of the British factories had a short commercial lifespan.

Matters proceeded differently on the other side of the Atlantic. After Heatley returned to Oxford, the American government, supported by the country's university laboratories and pharmaceutical companies, continued to search for more efficient ways to produce penicillin and between them, made several significant breakthroughs. One such was the result of an effort to find more efficient strains of mould, other than the one accidentally discovered by Fleming in London. The agricultural scientists in Illinois began to test soil samples sent to them from around the world by the US Army but ironically, the most productive

strain they discovered came from a mould growing on an ageing cantaloupe melon that they bought at a fruit market in Peoria itself. The mould not only provided higher yields of the active substance, but it grew significantly more easily than the original *Pencillium notatum* when placed in deep vats that the scientists had designed for large scale production. Both of the discoveries were to have a major impact on the construction of new and much more efficient deep-fermentation factories by America's commercial producers.

Pfizer, in particular, pioneered a novel production technique. During the First World War, the Brooklyn- based chemical company had developed new submerged fermentation techniques to produce citric acid (Pfizer's primary line of business) so they need not rely on European fruit that could no longer be imported. After the war, Pfizer adapted these same techniques to manufacture a range of other chemicals via fermentation.[35] Although the scientists in the US Department of Agriculture had already shown that penicillin could be grown in deep vats, Pfizer's executives were intially reluctant to produce the drug because it would eat into their production of other highly-profitable chemicals. Eventually, however, its corporate board agreed to take the risk and in the autumn of 1943, the firm purchased a redundant ice factory in order to construct the world's first deep-culture penicillin plant. The following year, this state-of-the-art factory became operational and Pfizer quickly became the world's largest producer of penicillin.[36] Within a few years, thanks in large part to penicillin, a minor New York chemical company had become a leading player in the global pharmaceutical industry.

By 1944, a further 20 American companies produced penicillin. Having been provided with a government exemption from anti-trust legislation, the usually competitive corporate executives freely exchanged information about the market for the drug and the production technologies that they used, collaborations that had a significant impact on the drug's manufacture. At first, for example, most of the American companies had built shallow-pan production facilities but when rival executives learned of Pfizer's success with deep-tank fermentation, the largest companies all began to grow the mould in vats.

Thanks to the early adoption of novel production methods such as deep-tank fermentation, and the investment of nearly US$30 million in the construction of 14 different factories, by 1944, the United States produced forty times more penicillin than the United Kingdom.[37] Unfortunately for Pfizer, the scale of American production meant that after the war, penicillin quickly became a commodity; for public health officials, however, the consequent rapid drop in the cost of the manufacturing process meant that penicillin could be distributed ever more widely.

Obviously, the enormous military demand for penicillin was a key reason for the rapid increase in global production. In the spring and summer of 1943, the reports of the effectiveness of the drug in treating wounded soldiers greatly impressed American and British leaders alike and persuaded both civilian and military officials that penicillin was vital to the war effort. Frustrated by the initial supply shortages, these powerful constituencies tried to do what they could to ensure that penicillin production rose as quickly as possible. By the autumn of 1943, military doctors could access penicillin in large quantities to treat battle injuries. Penicillin also permitted soldiers who had contracted syphilis and gonorrhoea to return to the war front more quickly. When Allied troops landed on the beaches of Normandy on D-Day, military medics and mobile army hospitals were well supplied with penicillin.

Soldiers were not the only people to benefit from the drug. Although the American government heavily restricted civilian use of penicillin at first, the astonishing increase in production by the mid 1940s meant that it soon relaxed its controls. By the summer of 1945, most Americans could buy the drug at their local pharmacy but in Britain, restrictions

remained in place throughout the war. It was not until the summer of 1946, with increases in both domestic production and American imports, that the British government lifted its restrictions and allowed doctors to prescribe penicillin freely. Five years after scientists in the Dunn School had struggled to produce enough penicillin to treat just one patient, the antibiotic was widely available on both sides of the Atlantic.

Globalising penicillin

By the end of 1945, Canada, the United Kingdom, and the United States all possessed substantial quantities of the world's first antibiotic. Yet the rest of the world still needed penicillin.

The governments in France, Germany, Japan, Holland, the USSR, and China had all tried and failed to manufacture the drug during the Second World War.[38] Using only what they could glean from Fleming's and Florey's published research, national officials could not reproduce the operational breakthroughs that had enabled large-scale commercial production in Britain, America, and Canada. By 1946, while the frantic pace of penicillin-factory construction had slowed in North America and Britain, for the rest of Europe and Asia, the race to produce the miracle drug was just beginning.

In the second half of the 1940s, the use of penicillin surged across Europe. International aid organisations established to promote post-war reconstruction and most memorably led by the Marshall Plan, particularly supported the production of penicillin. In 1946, for instance, the short-lived United Nations Relief and Rehabilitation Agency (UNRRA) unveiled an initiative to build penicillin plants in six European countries. Through its programme, the host countries financed the construction of the factories themselves while UNRRA supplied *Penicillium* cultures, technical blueprints, and the necessary production equipment, as well as provided training for workers in these plants. Although rising Cold War tensions meant that this scheme was not as successful as officials leading the relief agencies had hoped, the expertise that UNRRA provided did transfer know-how in the production of penicillin to countries as diverse as Yugoslavia, Belarus, Poland and Italy, to name just a few.[39]

Several non-Communist Asian countries also received aid to build domestic penicillin manufacturing facilities during the same period. In 1951, the Indian government, headed by Prime Minister Jawaharlal Nehru, which had long sought to produce penicillin within the country since the late 1940s, accepted assistance from the World Health Organization (the WHO was the successor to UNRRA) to build its own penicillin factories. In return for participating in an international network of penicillin production and training facilities that the WHO sought to establish, India received a grant of more than US$1 million to construct a deep-tank penicillin plant, as well as technical assistance from the WHO.[40]

In Japan's case, it was American government officials and pharmaceutical industry executives who provided assistance, not the WHO. In 1947, General Douglas MacArthur, head of the US- led occupation authority in Japan, asked the Chief Executive Officer of US pharmaceutical firm Merck if he would help Japanese companies to produce penicillin. As a result, for seven months, Merck's scientists taught the production process to the Japanese pharmaceutical manufacturers.[41] By the time the Merck scientists had departed, ten different Japanese companies were manufacturing the antibiotic and within three years, Japan was self-sufficient in penicillin production.[42] While the specifics of India and Japan's development of domestic production facilities may have been different, the outcome was much the same. By the mid-1950s, both nations were producing significant quantities of penicillin and Japan and India would go on to become significant players in the global pharmaceutical industry.

Not everyone was equally pleased by the post-war increase in penicillin production. Having established themselves as the dominant producers, many US pharmaceutical companies became increasingly reluctant to discuss their latest research and production methods, and particularly unwilling to share their technical know-how. For this reason, although the Americans provided the majority of the funding for the UNNRA, it was the Canadians who supplied the bulk of the equipment to the rest of the world. Indeed, it was at a Canadian deep-fermentation factory in Toronto that most training sessions for overseas workers took place. From the American officials' point of view, the fact that other countries did not have access to penicillin was a problem.; they reasoned that outbreaks of disease could spark disorder and political unrest. But for the executives of America's leading pharmaceutical companies, their expertise in penicillin production provided an opportunity to make money through licensing agreements and export sales. By 1946, the age of commercial openness about penicillin production was suddenly over.

While Americans were questioning the commercial implications of sharing information, in Britain, by

the mid-1940s, the public was raising a different set of concerns about the economic impact of freely exchanging information about a wonder drug. Before the end of the Second World War, British MPs and journalists had begun to ask why the United Kingdom could not match the American's rate of penicillin production. In the House of Commons, MPs had demanded to know why British domestic manufacturers appeared to have fallen short and the scientists at the Dunn School had been forced to turn to American funders for support.[43]

After 1945, Britain's frustration about its declining status in penicillin production in particular, and as an industrial power more broadly, turned into public resentment. The British public was particularly incensed that American patents now controlled the global production of penicillin. Arguing that America had taken advantage of Britain, the country's politicians and journalists singled out the high fees that British pharmaceutical companies paid to American corporations in order to manufacture penicillin.[44] The British had both discovered and developed the wonder drug and yet, politicians argued, corporations in the United States now controlled the global intellectual property rights. In their view, British manufacturers were paying their counterparts for assistance, while opportunistic American executives were making a fortune from penicillin's clinical development in the United Kingdom.

Of course, the reality was more complex than the British simplistic 'theft' stories suggested. Because English laws at the time did not permit UK inventors to patent natural substances, Alexander Fleming could not have controlled the intellectual property of penicillin in 1928. Moreover, while Howard Florey could have patented the production processes to manufacture penicillin that they devised at the Dunn School, it was Florey's decision not to do so that meant that Britain subsequently had to pay the Americans for access to Oxford's discoveries. It was true that Andrew Moyer in Peoria, and the American pharmaceutical companies, held various patents relating to penicillin. However, none of these patents was for research done in the Dunn School; the American patents were for production processes that employed the new culture mediums, the new production technology, and the new strain of penicillin that the scientists in Peoria had developed and which were subsequently refined by American pharmaceutical companies.[45] Even if Howard Florey had patented the Dunn School's early work on penicillin, by 1946, Oxford's patents would have had little value because of the subsequent development of deep fermentation technology within the United States.

While this post-war interpretation that the Americans stole penicillin was not accurate, the narrative exerted a powerful influence on the British imagination and inspired a powerful policy response. Determined to ensure that such an outcome would never happen again, the British government changed English law so that in future, British scientists could patent a drug and not just the production processes to manufacture that drug. At the same time, the British government also founded a new public agency, the National Research Development Corporation (NRDC), to commercialise national innovations. In addition to providing financial assistance to promote products and processes invented in British universities and government laboratories, the government mandated that the new agency should create a portfolio to hold any patents from publicly-funded research.[46] For many prominent politicians and journalists, it was this second function that they considered to be the most important development. Indeed, when London's *Daily Herald* (a Labour Party-supporting newspaper) announced the creation of the NRDC, its headline read: '5 million to stop foreigners filching our ideas'.[47] Led by the explicit moral arising from the fable of penicillin, the University of Oxford has pre-emptively claimed the intellectual property rights of its scientists' discoveries ever since.

After penicillin

As with the development of Prontosil a decade earlier, the medical and commercial success of penicillin led to a surge in antibiotic research. Throughout the 1940s and 1950s, a generation of biochemists devoted their careers to finding a synthetic version of the world's first antibiotic – a feat that was not commercially viable until 1960.[48] At the same time, other researchers devoted their attention to developing new antibiotics. Ironically, this proved to be easier than synthesising penicillin but, that said, the shifting national and international environment changed how scientists went about developing the next generation of antibiotic drugs.

Almost immediately after the development of penicillin, scientists working at Rutgers University in New Jersey developed the world's second major antibiotic, streptomycin. Far from an accidental discovery, microbiologist Selman Waksman directed a team of researchers at Rutgers to systematically identify the new drug. With financial support from the pharmaceutical giant Merck, the Rutgers scientists searched

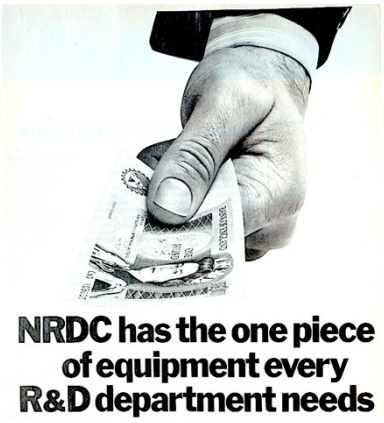
among thousands of soil samples to identify organisms that might be able treat tuberculosis – a disease that penicillin could not treat.[49] In 1943, they found a mould that fitted their criteria.

Within a year of their initial discovery, the Rutgers team had created a drug from the mould and had trialled it on animals. In sharp contrast to Oxford's experience, Waksman's research group had no problem in persuading the American pharmaceutical companies to produce the compound before they had concluded the clinical trials. The executives at Merck were particularly eager to gain access to what appeared to be a very valuable drug and provided financial support along with a steady supply of streptomycin with which to conduct the clinical trials. In 1944, Merck began to send the scientists significant quantities of the drug and the team began clinical trials at a tuberculosis sanitorium in New York State.[50]

Because of penicillin's success and the changing attitude in English-speaking countries towards patenting scientific discovery, the academics were more savvy about the intellectual property rights for streptomycin. At the start, Merck had negotiated with Waksman that the pharmaceutical company would hold both the patents and the exclusive commercial rights. In 1945, however, as the scientific community came to understand the medical and commercial significance of streptomycin, Waksman appealed to the executives at Merck to waive their patent rights so that a consortium of pharmaceutical companies could manufacture the antibiotic more cheaply.[51] Remarkably, the executives agreed and transferred the intellectual property rights to Rutgers at no cost and signed a non-exclusive license agreement to produce the drug.[52] As a result, soon after penicillin became widely available, a second major antibiotic also entered the market. In 1952, seven years after Fleming, Florey, and Chain received their Nobel Prizes, the Nobel Prize Committee awarded Selman Waksman a Nobel Prize for his discovery and in time, Waksman used the lucrative patents that he held for antibiotic to establish the Waksman Institute of Microbiology at Rutgers.

Meanwhile, the Dunn School had also begun testing a new substance that would eventually lead to yet another antibiotic: cephalosporin. Much like penicillin, cephalosporin's development did not begin in Oxford. Instead, the long process started on the coast of Sardinia, when Giuseppe Brotzu, an Italian bacteriologist, began researching the bacteria responsible for typhoid fever. During the 1940s, Brotzu had noticed that there were high concentrations of the typhoid- causing bacteria in the island's sewers and that those sewers discharged directly into the sea. Surprisingly, though, there were no outbreaks of typhoid among local beachgoers. Speculating that micro-organisms in the sea or in the sewage water were acting like *Penicillium notatum*, Brotzu took samples. The solution that he subsequently made from these samples was both non-toxic and also worked as an effective antiseptic against a range of bacteria.[53]

Brotzu recognized that his discovery of a new anti-bacterial organism in the Sardinian sewage was significant. However, while executives in the American pharmaceutical industry were quick to support research into new antibiotics, the Italian pharmaceutical firms were far more risk averse. Even worse, the leading scientific journals rejected Brotzu's research papers. Determined to find someone who could transform the new substance into a drug, Giuseppe Brotzu founded his own academic journal and then sent a copy of his own article, as well as a sample of his suspected antibiotic, to the head of the laboratory first responsible for isolating and purifying penicillin.[54] Brotzu's academic entrepreneurship paid off when Oxford took up his cause.



After Howard Florey received Brotzu's sample, he asked one of the Dunn School's young biochemists, Edward Abraham, to investigate the new substance. Abraham quickly discovered that there were three different substances with antibiotic properties within the Italian sample. Excited by the potential antibiotics, in 1951, the administrators in the NRDC filed a range of patents on behalf of the Dunn School. Oxford's research proceeded slowly, however. At first, the researchers studied the two of the three antibacterial substances which they believed had the greatest commercial potential. After a time, however, Abraham realised that the third substance was the more likely candidate and a long and costly development process funded by the UK's MRC and the NRDC soon followed.[55]

The NRDC would ultimately recoup the costs of the development of cephalosporin many times over. Yet, it was not until 1959 that the

Oxford scientists realised that the fungus from the Sardinian sewage water represented a completely new family of antibiotic drugs. News of their discovery soon spread and pharmaceutical companies across Europe, Asia, and North America excitedly licensed the new antibiotics from the NRDC. Finally, in 1964, companies began to sell the first cephalosporin- based drugs. Because it was far less likely to produce an allergic reaction in patients and is effective against an even wider range of bacteria than penicillin, the new antibiotic was a rapid commercial success. By 1978, annual sales amounted to more than £600 million and the commercial proceeds began to come back to Oxford. Royalties from the sale of cephalosporin went both to the NRDC and to charitable trusts established by Edward Abraham and a close collaborator. Between them, these trusts have since donated more than £30 million to support scientific research in the Sir William Dunn School of Pathology, and Lincoln College (the college where Edward Abraham held a fellowship thanks to Lord Nuffield's donation), and the current reserves of the trusts total some £200 million.[56] Having given away the intellectual property of penicillin, Britain, and Oxford in particular, had subsequently converted its scientific research into sizeable royalties with cephalosporin.

Success and the new problems

Penicillin, streptomycin, cephalosporin, and their derivatives had a remarkable commercial and public health impact. During the 1950s and 1960s, those chemical companies involved in the early stage of antibiotic production grew to be among the largest pharmaceutical companies in the world. Simultaneously, Oxford's Dunn School cemented its reputation as a world-leading biomedical research institute. Perhaps most importantly, minor injuries and diseases became much less life-threatening. In almost all countries, pneumonia and syphilis – diseases which were significant causes of death before the 1940s – became readily treatable conditions. And because of the pioneering work of Howard Florey, Ernest Chain, Norman Heatley, Edward Abraham, and many others, by the 1960s, there was little reason for people to worry about dying from a blister sustained during a game of tennis.

While the widespread (and cheap) availability of antibiotics significantly improved public health, those same drugs also resulted in a new, unanticipated set of problems. Bacterial infections soon came to be regarded as a technical problem that modern science could cure rather than a public health issue that required preventative measures. Doctors prescribed antibiotics freely while sanitation and hygiene standards created to prevent the spread of bacteria in the pre-antibiotic age slipped. Confidence in the curative power of the new antibiotic drugs led to complacency.

The fact is that antibiotics reduced but never eradicated the threat to human life posed by bacterial infections. Although the new drugs were effective against a range of common illnesses, some bacterial strains, such as the 'superbug', Methicillin-resistant *Staphylococcus aureus* (MRSA), were completely resistant to antibiotics. Even worse, other bacteria that had been effectively treated by antibiotics soon developed resistance to treatment because of evolution, although this was not an entirely unexpected outcome. In his 1945 Nobel Prize lecture, Alexander Fleming spoke of the dangers of antibiotic 'underdosage' and warned that common bacteria could evolve to become resistant to the new wonder drugs.[57] Fleming's words proved prophetic. Within a decade of his pronouncement, a number of newly antibiotic-resistant bacteria strains spread around the globe and caused major epidemics.[58] Indeed, the threat posed by bacterial infections not only affected humans.

During the 1950s and 1960s, given the low cost of antibiotics, farmers began to routinely administer these drugs to healthy herds of livestock in order to prevent infection and to boost animal growth rates.[59] This routine use led to intensive livestock farming and ever cheaper supplies of meat and fish around the world but it also promoted the spread of disease-resistant bacteria in both human and animal populations. Public concern particularly grew in the mid-1960s, when scientists demonstrated that farmed animals treated with antibiotics were the source of several outbreaks of *Escherichia coli* and salmonella.[60] The wonder drugs of the 1950s and 1960s that could be produced so cheaply were now being used far too widely.

These problems have only increased in the last 50 years. Pharmaceutical companies developed more and more antibiotics during the 1960s, 1970s and 1980s but then, as the initial excitement about them subsided, corporate executives adjusted their business

strategies. Instead of purposely developing new antibiotics to be used infrequently in short courses – making them far less lucrative – pharmaceutical executives instead concentrated on the development of new drugs that must be taken regularly and for prolonged periods.[61] Moreover, as successive generations of antibiotics became commodified, the commercial development of antibiotics slowed. Although there is a growing need for novel antibiotics to treat the drug-resistant bacteria responsible for hundreds of thousands of deaths annually, the 50 or so antibiotics currently under development globally offer little improvement on existing compounds and certainly nothing as remarkable as penicillin, streptomycin, or cephalosporin.[62]

This is not to say that things will not change. Gripped by fears about the very real possibility of a 'post-antibiotic apocalypse' driven by increasing bacterial resistance, global public health agencies have launched public campaigns to encourage the responsible use of existing drugs.[63] At the same time, some countries have banned the indiscriminate use of antibiotics in animals.[64] Although these drugs are not prescribed with the same wild abandon as they once were during the middle decades of the 20th century, their use around the globe is still increasing and many scientists predict that deaths from antibiotic- resistant bacteria will soar in the 21st century. In the 1920s, doctors had few tools to treat bacterial illness; one hundred years later, medical professionals have many more tools at their disposal, yet increasingly, the wonder drugs, such as penicillin, are becoming less effective. While the 'Blue Plaques' which celebrate the remarkable development of penicillin still adorn the walls of Oxford's laboratories and hospitals, the global abundance arising from the golden age of antibiotics has created its own intractable problems.

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