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Penicillin and the Antibiotics Revolution Global History

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Abstract: Alexander Fleming was one of the 100 most important people of the 20th century for his discovery of Penicillin " It was the discovery that would change the course of history. The active ingredient in the mold, which Fleming named penicillin, turned out to be an infection-fighting agent of enormous potency" A revolutionary development in science is a change in the way scientists perceive a certain idea or belief. The finding of Penicillin by Alexander Fleming in 1928 was a revolutionary development in the field of science. The discovery revolutionized the way infections were treated as well as impacted the scientific field, the medical field, the pharmaceuticals industry, and all humanity. Alexander Fleming's discovery of Penicillin sparked the development of antibiotics, which has continued to save People's lives since the revolution, making him a revolutionary figure. Despite the fact that Fleming was not only solely responsible for the revolutionary development, it was also his discovery of Penicillin that led to the development of antibiotics.

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 disease1

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 reporters' stories were a year a hand of their time, they were right that the global scientific community had generally agreed that the world's first antibiotics were a landmark in medical history worthy of Nobel prize recognition. 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 drug 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 mold, Penicillium notatum, inhibited the growth of bacteria setting out to understand more about the mold s unusual properties, Fleming conducted additional experiments concluded that the antibiotics solution that he had made from the mold 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 Flory, an Australian Pathologist, and Ernest Chain, a German biochemist began researching a selection of antibacterial compounds. Over the next two years, chain

and Florey, and their oxford colleagues experimented on Penicillium notatum. During that time, the scientists made several important discoveries and thwarted Fleming. By the spring of 1940, Florey and chain had developed a drug, which they mice. The following year, they carried out the first preliminary clinical trials on oxford

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 antibiotics development and the global production of Pharmaceuticals.

Keywords: Antibiotic discovery. Antibiotic resistance, novel antimicrobials Revolution Discovery

Introduction

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 disease fell sharply 3 " New vaccines and stricter public health measures saved millions of lives while new sanitation procedures ensured that fewer people developed infections while in hospitals and on operating tables 4. Ironically physicians and public health experts became far better at preventing illness than they were at treating disease.

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 bacterial infections spread into a patient's bloodstream. They could use antiseptic to clean dressing, sterilize surgical equipment and disinfect the surface of wounds but they were only preventative treatments 5

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 Calvin Coolidge Junior, the teenage son of the president of the United States, developed a blister while playing tennis on 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 6. In the end, though, even the nation's best doctors could do nothing to prevent the infections 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 favorite son’s death, President Collidge later wrote that when he went, the power and glory of the presidency went with him 7

Twelve years later, In 1936, an infection nearly killed the son of President Franklin Delano Roosevelt (FDR) just a week after his father's re-election as President, 22 years old Frank Roosevelt Jr developed a sore throat soon afterward 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 doctor advised his mother, Elenore Roosevelt, to prepare for the worst and the First lady rushed to Boston to be her son's beside 8. On this occasion, however, the story had a happy ending. After they treated him with a new drug. Franklin Roosevelt Jr fever began to subside and the swelling in his throat eased. one month later, the hospital discharged the President's son 9 he was cured. The drug that his doctors used was best known by the trade name Prontosil Released in 1935 by the German Pharmaceuticals giant Bayer, the synthetic drug (originally developed as a deep red-colored synthetic dye) stopped the growth of a range of common bacteria. Because of supply problems and the suspicion of English-speaking medical professionals towards Germany in the 1930s however, American doctors rarely prescribed Bayer's antimicrobials. This quickly changed when the clinicians published 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 Pharmaceuticals Executive soon figured that the active ingredient in Prontosil was sulfanilamide, an organic sulphur compound, the patient of which had already expired and so competitor's 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 9

Severe allergic reactions could lead to organ damage, difficulty breathing and swallowing, and a blueish discoloration of the skin. Moreover, because high doses could be fatal, the sulphur compound could not be used to treat the acute infection. Prontosil was effective against bacteria but given the severe side effects, only in very specific circumstances, when the situation was life-threatening. For all of Prontosil's liabilities, its existence roused hope that scientists could develop new drugs to treat bacterial infections. Inspired by the commercial and medical success of these new treatments for bacterial infections. In the late 1930s and early 1940s, the major pharmaceutical companies and research laboratories devoted plenty of effort to search 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 first been identified in 1928, seven years before the release of Prontosil.

Mold on a Plate

The precise details of the discovery that would eventually lead to the successful development of the world's first antibiotics 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 mold. just as he was about to send the glass plate to be disinfected, Fleming noticed something remarkable no bacteria were growing close to the mold 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 mold'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 mold entered Fleming's laboratory through an open window, or that the Eureka! Moment, when the scientists noticed the mold's unusual properties, coincided with his summer holidays, 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 the mold grew only after Fleming had returned from his holiday 10

During the autumn of 1928, Fleming sought to learn more about the fungus. Having established that other mold did not have the same effect, he tested the solution 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 mold 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, but because of the solution's impurities, it was also likely to be extremely toxic if administered to humans 11. Convinced that it would be impossible to turn his mold solution into a useable drug, Fleming began working on other projects.

Before the 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 mold to various scientific laboratories across Europe and America. At the time, his decision had little impact while a few scientists experimented with the mold; they too would soon set it aside to focus on their research. Fleming's journal articles, which he

wrote in a characteristically precise but rather dull manner, went largely unnoticed within the broader scientific community.12

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 researcher generally chose to study elsewhere, while the lectures were so dull that Oxford's undergraduates tended to avoid those 13. when following the sudden death of the inaugural post holder, 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, so Florey quickly set about overhauling the department to improve the financial situation, he began a cost-cutting program and devoted a great deal of his time to courting external. 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 projects 14. 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 a sign that it might become a scientific research institute worth its world-class facilities. One of the most important decisions that Florey made during that first year was to hire a 28 years old German emigre, Ernest Chain from Cambridge. in oxford chain studied an enzyme commonly found with tears, saliva, and mucus. Which has weak antibacterial properties while reading scientific papers on the antibacterial agent, chain stumbled across Alexander Fleming's articles on Penicillium notatum and quickly discovered that fungus at the Dunn School in 1929. Curious about the mold's chemical properties, chain performed several preliminary experiments and he was soon convinced that further study would be worthwhile. To devote sustained attention to his research project. however, the 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 15 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 1939s 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 when meant convincing others to believe in the new research project before their projects could be launched.

In early 1940, after reviewing Florey's application, the Dunn school a 12-month research grant of 1,500 pounds and assured that further funds would be made available the following year, so long as the second world war did not disrupt project 16 with their short-term funding. now secure, a team of Dunn school scientists began to study Penicillium notatum.

Assigned by Florey to the antibacterial substances project in 1939, Heatly 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 mold quickly and in greater quantity, Heatly also devised a novel method to extract the active substance from the mold in a stable form 17. The initial problems that had plagued Fleming had now been resolved by Heatley and the antibacterial substances within the mold could be isolated and stored for long periods. 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 finding. The scientists established that the drug

was nontoxic 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 know 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 a living animal without harming it. we realized at once that penicillin could play a vital role in war medicine18. Their successful test on animals was not sufficient proof to authorize 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 mold if they were to use it on humans. This presented the team with a significant problem since they had already struggled to grow enough mold 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, biscuits 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 journals. The lancet, yet with the country on a wartime footing, Britain's major industrial laboratories were already working flat out to fulfill their government contracts and so they could not commit to a different project with unproven clinical value.

Between 1940 and 1941 Norman Heatley transformed the Dunn school from a research laboratory into a make-shift penicillin production line. Heatley asked sketched a noval design and asked a Stafford shire pottery to produce 500 ceramic pots. Heatley devised and personally constructed an automated apparatus using discarded bookcases. From the Bodleian Library and old doorbell, some glass lubing and copper coils 19. while Heatley devised innovative ways to boost the school's production capacity the early labor, and 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 mold that was absolutely vital to the creation of 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 20 chain first trial on mice, the Dunn school was able to perform a human trial of Penicillin at Oxford's Redcliff Florey and his colleagues first demonstrated the safety of the drug on a terminally - ill patient. They administer a small dose of the new drug to a. A police officer was dying from several infections 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.

In 1943, as Florey wrote in their paper about the clinical trials, the drug was available only in very small quantities 21 If antibiotics were 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 pharmaceuticals companies spent a great deal of money building new penicillin production facilities across Britain. Early in 1943, the executive of ICI committed 300'000 pounds 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 governments

General Committee on the penicillin, boots, Britain's foremost chain of pharmacies, built a large manufacturing facility in Nottingham, and further four plants were built by Glaxo laboratories.22. Alongside these corporate efforts, the Royal Navy also began making penicillin at its medical school in Somerset and British government spent 1.3 million pounds building the world's largest facility dedicated to the production of the drug 23. By the end of 1945, eight British companies were producing penicillin in 12 different factories around the UK.24.

Despite their best intentions, however, these British commercial facilities were far from cutting edge. Despite starting to produce penicillin as quickly as possible both the public and private sectors had

simply replicated the Dunn schools manufacturing methods and so made use of repurposed rather than specially-built equipment. For Royal Navy, this meant steering the mold broth into an empty gin bottle. while at Glaxo, their employees grew the mold in milk churns 25 Although successful in ensuring a quick increase in production capacity, this act of repurposing items already intrinsic to the makers' daily business, instead of relying on new materials that were increasingly prioritized 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.

Pfizer, In Particular, pioneered a novel production technique. During the first world war, the Brooklyn -based chemical company developed a new submerged fermentation technique to produce citric acid. so, they did not rely on European fruit that could no longer be imported. After the war, Pfizer adopted these same techniques to manufacture a range of other chemicals via fermentation 26. Pfizer executives were initially 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 first largest producer of Penicillin.27 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 antitrust legislation. the usually competitive corporate executives freely exchanged information about the market for the drug and the production technologies that they used, a collaboration that had a significant impact on the drug's manufacture. At first, most American companies had built shallow-pan production facilities but when rival e executives learned of Pfizer's success with 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.28 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.

In 1946, with an increase in both domestic production and American imports, 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 antibiotics were widely available on both sides of the Atlantic.

Conclusion:

In 1945, Canada, the United Kingdom, and the United states' all possessed substantial quantities of the world's first antibiotics and the rest of the world needed penicillin. The governments of France, Germany, Japan, Holland, the USSR, and China had all tried and failed to manufacture the drug during Second World War 29. Using only what they could glean from Fleming 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 Asia, the race to produce the miracle drug was beginning

In the second half of the 1940s, the use of Penicillin surged across Europe International Aid organizations were established to promote post War reconstruction and most memorably led to 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 Plant in six European Countries through the program, the host countries financed the construction of the factories themselves while UNRRA supplied penicillin cultures, technical blueprints, and the necessary production equipment, as well as provided training for workers in these plants. Although rising cold war tension 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 30.

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$ I million to construct a deep tank Penicillin Plant, as well as technical assistance from the WHO 31. In 1947, General Douglas MacArthur, head of the US-led occupation authority in Japan, asked the chief executive officer of US Pharmaceuticals firm Merck if he would help Japanese companies to produce penicillin. As a result, for seven months, Merck scientists taught the production process to the Japanese pharmaceuticals manufacturer 32. By the time the Merck scientists had departed, ten different Japanese companies were manufacturing the Antibiotics and within three years, Japan was self-sufficient in penicillin production 33.

After Penicillin

As with the development of Prontosil a decade earlier, the medical and commercial success of Penicillin led to a surge in Antibiotics research. Throughout the 1940s and 1950s, a generation of biochemists devoted their careers to findings a synthetic version of the world's first Antibiotics a feat that was not commercially viable until 1960 34

At the same time, other researchers devoted their attention to developing new Antibiotics. Ironically, this proved to be easier than synthesizing penicillin but, that said, the shifting national and international environment changed how scientists went about developing the next generation.

Almost immediately after the development of penicillin, scientists working at Rutgers University in New Jersey developed the world's second major Antibiotics, streptomycin. For from accidental discovery, microbiologist Selman Waksman directed a team of researchers at Rutgers to Synthetically Identify the new drug. With financed support from the Pharmaceuticals giant Merck. The Rutgers Scientists searched among thousands of soil samples to identify an organism that might be able to treat tuberculosis - a disease that penicillin could not treat 35

In 1943, they found a mold that fitted their criteria. within a year of their discovery, the Rutgers team had trialed it on animals. In sharp contrast to oxford's experience, Wakeman's research group had no problem persuading the American Pharmaceutical companies to produce the compound before they had concluded the clinical trials. In 1944, Merck began to send the scientist significant quantitative of the drug and the team began clinical trials at a tuberculosis sanitorium in New York state.35. Because of Penicillin's success and the changing attitude in English-speaking countries toward patenting scientists, the academics were savvier about the intellectual property rights for streptomycin. At the start, Merck had negotiated with Waksman that the pharmaceutical company would hold both by Patent and the exclusive commercial right. In 1945, however, as the scientific community came to understand the medical and commercial significance of streptomycin, Waksman appealed to the executive at Merck to waive their Patent rights so that a consortium of pharmaceutical companies could manufacture the antibiotics more cheaply 36. Remarkably, the executive agreed and transferred the intellectual property rights to Rutgers at no cost and signed a nonexclusive license agreement to produce the drug.37. As a result soon after Penicillin became widely available, a second major Antibiotics 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 antibiotics 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 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 1940, Brotzu noticed that there was a high concentration 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 microorganisms 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 effectively against a range of bacteria 38. Brotzu recognized that his discovery of a new antibacterial 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 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 39. Brotzu 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 samples. Excited by the Potential antibiotics, In 1951, the administration in the NDRC filed a range of Patents on behalf of the Dunn School oxford's researcher proceeded slowly, however At first, the researcher studied two of the three antibacterial substances which they believed had the greatest commercial potential. After a time, however, Abraham realized that the third substance was the more likely candidate, and a long and costly development process funded by the UK's MRC and NRDC soon followed 40

The NRDC would ultimately recoup the cost of the development of cephalosporin many times over. yet, it was not until 1959 that the oxford Scientists realized 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 drug. 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 pounds and the commercial proceeds began to come back to oxford. Royalties from the sale of cephalosporin went both to the NRDC and to the charitable trust established by Edward Abraham and close collaboration between them, their trust has since donated more than 30 million pounds to support scientific research in the Sir William Dunn School of Pathology, and Lincoln college and the current reserve of the trust total some 200 million pounds 41

Having given away the intellectual property of Penicillin, Britain, and oxford in particular had subsequently converted its Scientific research into sizable royalties with cephalosporin.

Success and the New Problems

Penicillin, Streptomycin, cephalosporin, and their derivative had a remarkable commercial and public health impact. During the 1950s and 1960s, those chemical companies involved in the early stage of antibiotics production given to be among the largest pharmaceutical companies in the world. simultaneously, oxford 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 disease which was significant causes of death before the 1940s became readily treatable condition 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.

During the 1950s and 1960's given the low cost of antibiotics, the farmer began to routinely administer these drugs to healthy herds of livestock in order to prevent infection and boost animal growth rates 42. The 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-resistance 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 43. The wonder drugs of the 1950s and 1960s that could be produced so cheaply were now being used too widely.

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