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A broad spectrum of opportunities – the history of the Bayer company and the evolution of antibiotics 1945–1990

Project thesis Medicine 5095

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Introduction

The word “wonder drug” stems from the Swizz doctor Paracelsus (1493−1541) who had a dream of finding a cure for all ill, and at his time was called a wonder doctor for discovering the first treatment for Syphilis. Used today, the word “wonder drug” is associated with the discovery of penicillin, and the fierce battle to eradicate infectious disease in the 20th century. The history of penicillin began in 1928, with the discovery by Alexander Fleming (1881−1955), that a strain from a Penicillium fungus could restrain the growth of a Staphylococcus bacteria (Bud 2007, ParacelsusWikipedia 2023).

From the late 1800 and early 1900, preventive measures for infectious disease had become well known in the western world, and good health was associated with morality and good hygienic standards. The number of deaths from infectious disease had therefore been decreasing for some time before the penicillin discovery of 1928. Around the same time, the first vaccinations had also been developed, showing promising results in preventing diphtheria, tuberculosis, and tetanus in the long term. Despite the decreasing deathrate, there were still large infectious outbreaks on a regular basis, the most serious and important diseases at the time being pneumonia, meningitis, gonorrhoea, and syphilis.

The first “wonder drug” however, was not penicillin, and nor did it come from the UK or the US; it came from Germany, and the company of Friedrich Bayer (1825−1880) and Johann Fredrich Weskott (1821−1976). In 1927 the company hired Gerhard Domagk (1895−1964), who was interested in researching ways of boosting the human immune system and discovering ways of inhibiting or killing infectious pathogens from bacteria. Through his clinical experiment on mice with induced septicaemia from β-haemolytic streptococcus, he, with the help of Josef Klarer (1898−1953) and Fritz Mietzsch (1896−1958) discovered 4-Sulfonamido-2,3-diaminazobenzene. Later known as Prontosil, it grew to become the first and most efficient “wonder drug” before the launch of penicillin, making Bayer AG one of the most important pharmaceutical companies in the world at that the time.

With the emergence of the two world wars from 1914−1945, the pharmaceutical industry of the world changes drastically, with the centre of innovation moving from the chemically derived drugs in Germany, to the biologically derived penicillin in Britain and the US. With the wish of limiting Germany's impact on the world economy and growth after World War II, the German pharmaceutical industry with the Bayer company, find themselves losing the global market. For the next 20 years after the war, continuously clinging to their tradition of chemical research, the Bayer company find themselves struggling to predict what will be the next breakthrough of pharmaceutical production. Then, from the 1960s to the turn of the century, the Bayer company once again is to be spotted on the global market, now associated with the new age of penicillin-production (Bud 2007, Dalhoff 2008).

How did this transition happen? With this paper, we will try to explore the following:

- How did the transition after World War II differ from the transition after World War I?
- What impact did the post-war occupation of Germany have on the development of the Bayer company?
- How did the Bayer company get into penicillin research and production?
- How did the development of ampicillin affect the field of infectious disease, and the future of the Bayer company?

Background

Europe at peace 1870−1914

From the 1870s to World War I (1914−1918), Europe had its longest period of peace in modern time, resulting in the spread of industrialisation, from the roots in the UK to the rest of western Europe and the US. The result of the industrialisation was an enormous migration of people, from the countryside to the cities, as well as migration between countries and overseas. Britain was the superpower of the world, owning ¼ of the world's territory, containing ¼ of the world's population. They had the largest production of coal, steel and iron. At the end of the 1800s, both Germany and the US had surpassed Britain's production because of the industrial revolution. Despite peaceful times over Europe, the frictions between the countries were still alive, with diplomacy being the aid instead of weapons. Germany at this time was undergoing a huge change, with the previous principalities being gathered as the first German Reich with Bismarck as their Kanzler. German troops were not dominant at this time, but after winning the latest three wars they had initiated, against Denmark, Austria and France, Germany got the reputation of being an undefeatable country with great military power (Erling Bjøl 1986).

The Friedr. Bayer et Comp. was founded in 1863 by Friedrich Bayer and Johann Friedrich Weskott, with the purpose of manufacturing synthetic aniline dyes for the textile industry. Already from the beginning, the Bayer company revolutionised the world, by making the first synthetic dye ever. Until then, dyes had to be produced from natural origin, often from raw material collected in the colonies (Erling Bjøl 1986, Dalhoff 2008). After 20 years in business, the Bayer company had become one of the most important dyes and chemicals companies in Germany, with export worldwide, and in 1888 the company opened its own pharmacology department (Dalhoff 2008).

In the early 1900s, the understanding of how infectious disease was caused by pathogens from viruses, bacteria and other microbes, led to the understanding that pharmaceuticals could be developed to target specific pathogens and infections with the help of chemistry. The term and concept of chemotherapy was based on the work of the German Nobel Prize in Physiology or Medicine − winner Paul Ehrlich (1854−1915), who invented the concept of staining human cells

and bacteria, and in 1909 discovered the first treatment for syphilis, Salvarsan (Erik Verg 1988, Corley 2003).

In the 1800s and early 1900s, the second wave of imperialism and colonisation went through Europe. Britain at the time being the great Empire of the world, with its colonies in America, Oceania and Asia, other countries had also started to compete in the rase for colonies, with Africa being the next goal to conquer. Until the 1800s Africa was characterized of only being a part of the previous triangle-trade, with some trading places remaining. The goal for Europe was now to ensure power over these areas, as well as influencing the local culture and religion. Under the leadership of Bismarck at the Berlin conference in 1884, Africa was divided between the different colony powers of Europe, among them Britain, France, Italy, Belgium, Spain, Portugal, and Germany (Rudi 2022). The most important threat to the colonisation was tropical disease, and pharmaceutical companies in the colonisation powers in Europe therefore invested a lot of research into finding treatments for these diseases. The pharmaceutical department of the Bayer company was focused on finding antiparasitic activity in dyes (Dalhoff 2008).

In 1910, the Bayer company hired Wilhelm Roehl (1881−1929), a doctor who had worked with Ehrlich, and who had a specific interest in tropical medicine. One of the most feared diseases in the colonies at this time was African sleeping sickness (trypanosomes), caused by the parasite Trypanosoma. The illness caused fever, flu symptoms and tremors, with coma and death as the result. With the help from Oscar Dressel (1865−1941) and Richard Kothe (1863−1925), Roehl found an effective medicine against trypanosomes in 1916. The urea-derivate got the name Bayer 205, but because of the war, it was not a registered medicine until 1923. Germanin, which the Bayer 205 was named, is until this day the most effective medicine ever invented against trypanosomes (Erik Verg 1988).

How did the transition after World War II differ from the transition after World War I?

World War I 1914–1918:

Unlike Germany, Britain did not have a well-established pharmaceutical industry before World War I. While the German pharmaceutical industry from the beginning was based on chemicals, the British industry was based on raw drugs and preparations extracted from biological agents brought to the motherland from the colonies. Even though most firms traded internationally, with almost 40% of the yearly output being sold abroad, the imported medications were often more advanced drugs from Germany, making Britain somewhat reliant of German imports (Erling Bjøl 1986, Corley 2003). Because of the high demand for German pharmaceuticals, the outbreak of World War I in 1914 was of both military and medical threat to the British population, as imports from Germany stopped. The result of the war was the identification of the necessary drugs, and the initiation of manufacturing these from home. The most important at the time being Salvarsan, for Syphilis, and Novocain, a local anastatic. Already by 1915, the homeland production of more advanced, synthetic pharmaceuticals had become a success in Britain (Corley 2003).

This was also the case in the rest of Europe. In France for instance, World War I became a turning point. With the shortage of important drugs from Germany, and with a shortage in chemists, France realised its weakness when it came to their poorly developed pharmaceutical industry. Like Britain and many other countries, they realised the need of self-sufficiency, investing in the development of several pharmaceutical companies after the war (Bud 2007, Bonnemain 2015).

As a result of the growing pharmaceutical industry in other European countries, the major German pharmaceutical companies created a cartel in 1916, which later in 1925 was established as the IG Farbenindustrie Aktiengesellschaft, including firms such as Bayer, Hoechst, BASF and Agfa (Dalhoff 2008).

Post-war years 1918−1930s:

After losing the war, the Treaty of Versailles was made by the winning nations, the UK, France, Belgium and the US. This forced Germany into long-lasting debt to these countries, destroying the German economy and industry by accelerating inflation, and occupying central industrial areas in times of unmet payment. The loss of the war also resulted in Germany losing foreign markets, patents and trademarks. For companies like Bayer, which was the most active German company abroad before the war, this was of severe damaging effect. In the US, it counteracted the return of German firms for many years, with American Bayer patents and laboratories being sold cheap to American companies. From 1918 till 1923, the German chemical industry had to surrender ½ of all existing dyestuffs and chemicals, as well as selling ¼ of the regular production at discount prices (Erik Verg 1988).

Germany was struggling to pay off their debt to the allied countries. In 1923, inflation had resulted in 1 US dollar having the worth of 49 000 marks. As a result of missing payments, the Ruhr area, where the Bayer company was located, was occupied by Belgian and French troops in 1923. The demand for German products abroad was still huge, and with the low prices, the demand grew even more, with the production soon reaching its full capacity (Erik Verg 1988). As the war had ended in 1918, both Britain, the US, France and others had successfully managed to overcome the challenge of synthetic drug production. Despite the ongoing tension of a new war breaking out in Europe, the remaining pharmaceutical companies were reluctant to continue in the synthetic field of pharmaceuticals as German low-cost drugs became available once again (Bud 2007).

The German pharmaceutical industry had changed during the war, with the cartel of BASF, Bayer, Hoechst, Agfa, Griesheim-Elektron and Weiler Ter Meer being established in 1916 (FarbenWikipedia 2023). During wartime, the cooperation between the companies in the cartel worked out quite smoothly, but the post-war times made it more difficult. Because of the control exerted by the Allied over German economy and industry, it was difficult for the companies to regain the competitive position they once dominated. The financial circumstances also forced the cartel to adapt a new structure, as bureaucracy, duplication of products, and individual research was

too expensive. The result was the merge of the eight companies in the cartel in 1925, and the development of the IG. Farbenindustrie Aktiengesellschaft. The I.G. Farben was organized with a central board, and with smaller divisions spread along the Rhine, central Germany and the Berlin area. The Bayer company, having its headquarters in Leverkusen, became part of the Lower Rhine part of the I.G. Farben, with working facilities in Leverkusen, Elberfeld and Dormagen. After some time, the different divisions of the I.G. Farben ultimately controlled themselves and remained largely independent from the influence of the central board. From 1934 I.G. Farben used the Bayer cross as their trademark (Dalhoff 2008, FarbenWikipedia 2023).

In the rest of Europe, similar collaborations between the pharmaceutical companies were created. Despite their substantially bigger size compared with the I.G. Farben, the pharmaceutical industry in the rest of Europe and America did not manage to compete with the knowledge in organic synthesis of the Germans. This was of great importance to the I.G. Farben, which needed international recognition to win back their position in world trade after the war (Dalhoff 2008).

In 1927 the Bayer part of the I.G. Farben hired Gerhard Domagk, who was interested in researching ways of boosting the human immune system and discovering ways of inhibiting or killing infectious pathogens from bacteria. Through his clinical experiment on mice with induced septicaemia from β-haemolytic streptococcus, he discovered that a sulphonamide-containing azo dye, manufactured at Bayer's for decades, spared the mice from septicaemia. In 1932, after reviewing all available sulphonamide-containing azo dyes at Bayer, the Bayer chemists Josef Klarer and Fritz Mietzsch found the compound with the best antibacterial activity known as 4-Sulfonamido-2,3-diaminazobenzene. After undergoing more clinical studies, also in human patients with septicaemia, Bayer and Domagk could launch the sulphonamide-drug under the name Prontosil and Prontosil rubrum in 1935. Prontosil grew to become the first and most important "wonder drug" before the launch of penicillin, making the Bayer company and the I.G. Farben one of the most important pharmaceutical companies in the world at the time, holding 17 % of the shares in the world market by 1938 (Bud 2007, Dalhoff 2008, Gradmann 2016).

The discovery of penicillin and World War II 1928−1945:

The antibacterial properties of penicillin were discovered by Alexander Fleming in 1928. He discovered a fungus growing on one of his petri dishes cultured with Staphylococcus bacteria, discovering the growth of the bacteria being limited by the growth of the fungus. The original penicillium strain in Fleming's petri dish was Penicillium notatum, and it was the base for the penicillin-research at Oxford, England. In Oxford and England, they saw penicillin as the opportunity to get Britain into the world market of advanced pharmaceuticals, and penicillin research became a central topic of Britain's pharmaceutical industry in the interwar period (Corley 2003, Bud 2007).

By the 1940s, Penicillin research had also started in America, they as well believing penicillin would have greater potential as "the wonder drug" than the sulphonamides. In the US, they developed the method of deep fermentation for penicillin manufacturing, which increased the production speed and rate, and soon became the preferred method of manufacture. In Europe, the resources needed for making larger, deep fermentation plants were lacking due to the war, and the US therefore got a head-start in the penicillin manufacturing (Bud 2007). The Penicillium notatum strain was later swapped for the more productive strain Penicillin chrysogenum, resulting in Penicillin G (Bud 2007).

Despite several reports from England and the US suggesting that the antibacterial properties of penicillin were superior to those of sulphonamides, the major pharmaceutical companies in Germany remained optimistic about the potential of sulphonamides. Germany was denied samples from the penicillin-producing fungus of Fleming during the war, and with little to no experience in biological research or manufacturing, there was little hope of future penicillin production in Germany before 1945 (Bud 2007, Dalhoff 2008).

Post-war years 1945−1950, IG Farben and the Nuremberg trial

The US, benefited by the positive impact the war had on the country's economy and production, soon gave themselves the role as a reliable and trustworthy supplier of economic support. America had a strong belief in liberalism and capitalism; economic growth being the strongest indicator of success (Grimnes 1986).

The years following 1945, were characterized by poor harvest seasons, and long, cold winters. Most of Europe were starving, and because of the destroyed infrastructure after the war, with bad overall health of the populations, epidemics of infectious diseases became more common once again (Grimnes 1986, Bud 2007).

The initial attempt of the Bayer company to get back their share in the world market, was to fight the major penicillin-manufacturing companies head-on. They wanted to regain their central role as a world-wide supplier alone, instead of going into collaboration with the American companies with the risk of being seized. American firms, like the rest of the world, were also reluctant to get into partnership and collaboration with German companies, because of the events during the war (Dalhoff 2008, Gradmann 2016).

After the end of World War II, German officials where to be judged and prosecuted in the courts established by the Allied forces in the different zones. The I.G. Farben trial was the 6th trial in the American court, known as the 6th Nuremberg trial. I.G. Farben was considered to have been friendly to the Nazi regime, having been part of the enslavement of war prisoners in the concentration camps in Poland. I.G. Farben had had close connections with the regime since 1933. It is not clear whether this connection was based on the company being a supporter of the Nazi party and Hitler, or if they by their extensive connection to the rest of the world, was trying to influence the regime in a more peaceful direction. Despite these hypothetical attempts to change politics in Germany at the time, the I.G. Farben profited by the Nazi regime, by getting monopoly in the pharmaceutical industry in Germany, support and protection from the government, and access to free labour from prisoners of the concentration camps (United States Holocaust Memorial Museum , Weinstein 2002). The IG Farben trail ended in 1948, with 13 of the 23 accused members from the company being charged

with the sentence of “crimes against humanity”. The 3 members Helmuth Vetter (1910−1949), Friedrich Entress (1914−1947) and Eduard Wirths (1909−1945) were charged with participation in the SS, and the contribution in drug testing and medical research on war-prisoners in Auschwitz (United States Holocaust Memorial Museum , AuschwitzBirkenauMemorial 2022).

The Bayer company was part of the Lower Rhein fraction of the I.G. Farben during the war, and the company was led by Ulrich Haberland from 1943. Haberland had been connected to the work of I.G. Farben since 1928, and had leading local roles since 1931. Although these significant appointments by the I.G. Farben, his employment status was never found to be written down, and so as the Nuremberg trials proceeded, he was never accused of participation in the actions of the Nazi regime or the I.G. Farben during the war. As the I.G. Farben was closed by the Allies, the Lower Rhein fraction changed its name back to the Bayer company and received Haberland as the new CEO (Erik Verg 1988, FarbenWikipedia 2023, HaberlandWikipedia 2023).

Germany and Berlin were occupied by the American, British, French and Soviet forces after the war, dividing the country into zones led by the military from the different nations. There was no agreement in which direction Germany was to develop, except that the country was to demilitarise, and that industry should be held to a minimum, and to be controlled by the occupying nation (Grimnes 1986, Bud 2007). America soon initiated the gathering of the three western German zones, and by then divided Germany between the world’s two superpowers.

During the occupation of Germany, the difficulties in the country soon became visible. All major cities in Germany had taken great damage by the war. The population was starving, and many people had lost their homes and family during the war. Rape against German women had become common during the war, and as the war came to an end, the fear of rape was universal. As the foreign troops conquered Germany, the women were left on their own, dominating the civilian population at the time. Relations between the occupying nations’ troops and the German women became almost a standard practice in post-war Germany, with 50−90 % of all American soldiers having affairs with German girls (Heineman 2001).

After the coup in 1948 by the communist party in Czechoslovakia, helped by the Soviet regime, the US with Western Europe strengthened their focus to stabilise and develop Germany (Bud 2007). Still, there was great ambivalence to what extent Germany was to industrialize (Bud 2007). In an attempt to understand the development of the Nazi party in Germany from the 1920s, the answer was often assumed to have a connection with German history and culture. It was therefore emphasised that an evolution of Germany into a modern, liberal and peaceful nation, could only be achieved with the influence of other nations, especially from the US (Grimnes 1986, Heineman 2001). In order to regain their role in international pharmaceutical sales, the Bayer company, associated with both the I.G. Farben and the Nuremberg trials, did therefore not just have an enormous obstacle to tackle when it came to getting experience in penicillin research, but also in order to change their reputation.

What impact did the post-war occupation of Germany have on the development of the Bayer company?

The Allied forces soon took control over all facilities previously owned by the I.G. Farben. There was no initial agreement in the goal of this occupation, other than the restriction and control over German industry. The Bayer companies' laboratories and plants were occupied and partly controlled by the British Military Forces. Due to the immediate need for sterile products and pharmaceuticals, the company was allowed to continue their production already by the end of 1945 (Erik Verg 1988). Western Europe received economic support from the US through the Marshall plan from 1948−1952. The US wanted Europe and the world to be an open market, and initiated the removal of restrictions in trade during the same period. With their capitalistic ideology, the US motivated Europe to move towards more competition in marketing and production. In 1950, this resulted in the fractioning of the previous I.G. Farben, restricting the size of the different daughter companies to prevent the establishment of monopolies (Grimnes 1986, Erik Verg 1988, Bartmann 2001). The Bayer company was re-established in 1951, with their headquarters in Leverkusen, and additional facilities in Dormagen, Elberfeld and Uerdingen (Erik Verg 1988, Bartmann 2001).

Even though the fractioning of the I.G. Farben initiated the return of German pharmaceutical industry, the future for them to return to the world market was unlikely. The German pharmaceutical industry had once again acquired a bad reputation, with the loss of foreign connections. Bayer's world market share had vanished during the war, with American and British firms taking over the world market. Bayer's production had sustained and was already at the level of production before the war in 1951, but in the same 6 years period from 1945, the world market had grown eightfold, without the participation of Bayer (Gradmann 2016). From 1952 the Bayer company returned to the stock market, changing its name to Bayer Aktiengesellschaft, Bayer AG (Erik Verg 1988).

Europe had been the centre of the world for many decades, but as World War II ended and power was shifted from Europe to the two superpowers, the US and the Soviet Union, so did the pharmaceutical headquarter of the world move from central Europe with Germany and sulphonamides to the US manufacturing penicillin (Grimnes 1986, Bud 2007). Pfizer became one of the leading producers of Penicillin in the US, producing ½ of all penicillin in the country by 1944 (Bud 2007). In order to compete with the Americans, the Bayer company needed to re-establish foreign subsidiaries.

The international expansion of the Bayer AG started when they bought back the Alianga Commercial in Brazil in 1952, making it their first foreign subsidiary after the war. The Bayer company had been part of the Brazilian pharmaceutical market since 1911. The country, with its need of both dyestuffs for fabric industry, crop protecting chemicals for agriculture, and modern pharmaceuticals for disease, made it a lucrative market for sales.

How did the Bayer company get into penicillin research and production?

In 1948, with the foundation of WHO, the three largest threats for human health were limited to:

- Influenza
- Infant mortality
- Venereal disease

UNICEF being established the same year also had mothers' health as a priority (Bud 2007). Syphilis and gonorrhoea were therefore two of the most important infectious diseases to treat in post-war Europe. Syphilis and gonorrhoea would endanger a potential pregnancy, increasing the risk of pregnancy complications, birth complications and neonatal malformations. Long-time infection with syphilis also had the risk of causing organ failure and death.

German women having interactions with foreign soldiers was among other things nicknamed "Veronika Dankeschön", short VD, implying the increase in venereal disease as a result of the elaborate prostitution. Estimates done by the German social work organization showed that the cost of treating the VDs in 1947 equalled the yearly sum of pensions to almost 18 000 war widows or orphans (Heineman 2001). To battle the substantial increase in cases of syphilis and gonorrhoea in Germany after the war, all four occupation zones established closed venereal wards. The wards addressed their services mainly to prostitutes, with daily gynaecological examinations and regular testing for sexual transmitted diseases. In case of a positive test result for gonorrhoea or syphilis, the women were held in the ward for treatment until they could deliver a negative test result (Schochow, Bjoernsgard et al. 2020). From 1946, penicillin was the preferred treatment for gonorrhoea, replacing the previously used sulphonamides. Penicillin was made in either Britain or the US until 1946, when penicillin production also started in Germany (Schochow, Bjoernsgard et al. 2020). In 1948, still 1/6 of Britain's penicillin production was shipped to West-Germany (Bud 2007). From 1950, syphilis was also exclusively treated with penicillin, removing Salvarsan from the recommended treatment regime (Schochow, Bjoernsgard et al. 2020).

The Bayer company wanted to explore other elements of battling infectious disease. Gerhard Domagk was still a central figure at the research department of Bayer, and with the increasing cases of tuberculosis after the war, he initiated the research for chemical anti-mucosal agents. This work resulted in the development of Conteben, which had good effect on tuberculosis of the larynx, skin, and intestines, but various effect on pulmonary tuberculosis. In the US, they discovered Streptomycin, an antibiotic with even better effect on tuberculosis. Streptomycin had the ability to cure tubercular meningitis, and it had fewer side effects in comparison to Conteben (Erik Verg 1988).

Around the same time, bacterial resistance to sulphonamides was increasing. Sulphonamides such as Dispetales, had been used unregulated as an over-the counter drug since the 1930s, resulting in the misuse of the drugs (Dalhoff 2008).

Already from the beginning, bacteria were known for producing substances against antibiotics in order to survive. Experiments in 1945 showed that penicillin used inside a hospital with no previous usage of the drug had better effect than in hospitals with previous penicillin usage. This led to the hypothesis of bacteria becoming more viable after being introduced to antibiotics. In the case with sulphonamides, this was especially seen in cases of self-treated gonorrhoea. People could buy the drug without prescription, resulting in overuse and resistance within 10 years (Bud 2007).

As the age of both sulphonamides and anti-mucosal drugs slowly was coming to an end, the Bayer company sought to get knowledge about the production of penicillin. In 1949, they got into collaboration with the American company Schenley Laboratories. The Bayer company had previously good experience with collaborating with American firms, having sought out a deal with the US Firm Sterling after World War I (Bartmann 2001). Still, the collaboration between the Bayer company and Schenley Laboratories turned out to be a failure. Schenley Laboratories had too limited knowledge about penicillin to be of any use for the Bayer company, and the Bayer company did not manage to produce exclusive pharmaceuticals for the American market (Dalhoff 2008).

The Bayer company eventually managed to get themselves into the field of penicillin, by acquiring the license for production of Penicillin G, Penicillin V, Tetracycline and Chloramphenicol from European firms. In the years 1950−1960, the company produced 21 % of all antibiotics in Germany, and 13,1 % of all antibiotics in the world. The market for sulphonamides decreased over the same period, and constituted only 1 % of the German sales by 1960 (Bartmann 2001). By 1956 the Bayer company had grown to become the largest international pharmaceutical company in Germany, with subsidiaries in South America, Europe, and Asia (Bartmann 2001).

How did the development of ampicillin affect the field of infectious disease, and the future of the Bayer company?

In Boston in 1959, the American specialist in infectious disease Maxwell Finland (1902−1987), argued that antibiotics rather than decreasing and eliminating infections, caused the development of more dangerous and life-threatening bacteria. Previously harmless bacteria could now be lethal. In 1955−1957, 50 % of all admitted septicaemias in Seattle died, despite being treated with penicillin. New-borns where especially vulnerable, since more childbirths now happened in a clinic, with nurses being carriers of resistant bacteria that could infect the mother and infant (Bud 2007). Although it was scientifically agreed that antibiotics should be used with caution due to the potential risk of resistance, using penicillin instead of changing the habits of the population was considered more beneficial than harmful.

S. aureus and S. pneumonia were the two types of bacteria that caused the most concern when it came to developing resistance. Both being part of the normal flora of most humans, they are two of the bacteria most often in contact with antibiotics, therefore with the highest risk of developing resistance to one or more antibiotics. S. pneumonia was known for potentially causing pneumonia, with life threatening potential in elderly and immune suppressed patients. S. aureus had earlier only been of concern when it came to war wounds and other skin lesions, potentially causing septicaemia, but with an increase in conditions being treated in hospitals, and with an increase in advanced surgical procedures, infection with S. aureus was becoming more common.

Overuse of antibiotics for infections in humans was not the only force driving antibiotic resistance. From the 1950s, at least ¼ of all antibiotics produced had been used on animals. After the war, the consumption and production of meat increased immensely, and it was found that adding small portions of antibiotics to the animals' food, boosted their growth. The farmers could deliberately starve their animals, and still gain the same amount of meat in a shorter period of time. The quantities of antibiotics needed for this growth, were much lower than that needed to destroy infectious bacteria. By adding antibiotics to animal feed, the bacteria were therefore challenged but not killed, resulting in more resistant strains developing (Bud 2007).

Penicillin and other antibiotics derived from soil were mass produced by many pharmaceutical companies in the world by the 1950s, leading to prices plummeting. By 1953, the price of 100,000 units was less than 1 cent (Bud 2007). With the growing concern of drug resistance, and with the low profit from penicillin sales, interest in synthetic antibiotics that could potentially be patented, grew (Bud 2007). The structure of penicillin was determined by Dorothy Hodgkin at University of Oxford in 1945 and published in 1949 (Bud 2007). During the following years, scientists studying penicillin, found that there was not one structure, but that there were already different types of penicillin with different sidechains. In 1954, the Beecham company, led by H.G. Lazell, began their journey to develop the world's first semisynthetic penicillin.

The Beecham company had missed out on the penicillin revolution, but had interest in the field, and wanted to modernise manufacturing of antibiotics. Ernst Boris Chain (1906−1979) was a German, Nobel Prize winning chemist, who worked as a consultant at the Beecham Laboratories. In many of the penicillin plants at the time, it had occasionally been discovered a more chemically active form of penicillin G. When the beta-lactam ring of the broth was chemically and biologically studied, the bioactivity in these broths was much higher than what would be expected. Ernst Chain suggested that the phenomenon was linked to the side chain attached to the beta lactam ring (Dalhoff 2008). The researchers at the Beecham Laboratories studied the different penicillins G, V, O and S with iodometric analysis and bioassay (Dalhoff 2008). The penicillin was studied with both a p-aminophenylacetic acid precursor and without a precursor. In the broth with precursor, the chemical and biological assays were similar, but in the broth without precursor, the chemical assay showed

increased activity, with higher penicillin titers compared with the biological assay. After 6 months, the Beecham group, with Chain and their Italian co-workers, had obtained crystals from the core material, discovering 6-amino penicillanic acid (6-APA) (Bud 2007, Dalhoff 2008). By using 6-APA derived from deacetylation of penicillin V (Dalhoff 2008), Beecham was able to produce semisynthetic antibiotics by adding different sidechains of organic acids to the 6-APA core (Bud 2007).

The deacetylation of penicillin V was a difficult procedure, with uncertain purity of the resulting 6-APA. Because of their small size, and technological difficulties with production, Beecham got into partnership with Bristol-Myers in the US in 1959. Bristol-Myers was at this point already an established antibiotic manufacturer and was supporting work at MIT for research in synthetic antibiotics (Corley 2003, Dalhoff 2008). By the end of 1959, the first semisynthetic antibiotic, pheneticillin, was launched, and a year after, in 1960, they launched methicillin.

Methicillin was at the time the most effective antibiotic ever to be produced, with little or no resistance. Methicillin required 6-APA in pure form as the base for synthesis, making production more difficult. At the Bayer company, they found that the bacterial acylase used for deacetylation of penicillin V, could specifically cleaved the phenylacetyl unit of penicillin G, leaving the beta-lactam core intact (Dalhoff 2008). Penicillin G was already very cheap, and the process of Bayer therefore became a quick, cheap, and stable way of producing 6-APA (Bud 2007).

Methicillin was beneficial because it could sustain beta lactamase, a compound produced by bacteria to survive beta lactam penicillins. Methicillin was believed to be the revolution for antibacterial resistance, but only one year after it was launched, the superbug MRSA (methicillin resistant S. aureus) was detected (Bud 2007).

The Beecham company continuously searched for new semisynthetic antibiotics, using 6-APA as the core. The goal was to find a drug that could sustain oral intake. In the process, the Beecham company got into partnership with the Bayer company. While Bayer had managed to regain a substantial foreign market, the Beecham company had never been more than a local supplier on the British market (Bartmann 2001, Corley 2003).

The Beecham company received the method invented by the Bayer company of producing 6-APA from penicillin G, while the Bayer company was allowed to market and sell the finished product (Dalhoff 2008).

In 1961, Ampicillin was launched as an oral, broad-spectrum antibiotic. Ampicillin was marketed under three different names: Penbritin by Beecham, Ampicillin by Bayer, and Polycillin by Bristol.

The process of manufacturing 6-APA from penicillin G was later improved with a method based on fermentation invented by Gist-Brocades N.V. in 1966. The process was outlicensed to the Bayer company, and the two made an agreement 1969 of sharing potential improvements of the process with each other. With the help of Bayer, Gist-Brochades N.V. expanded around 1975, increasing fermentation of penicillin for production of 6-APA by Bayer (Dalhoff 2008). From the 1970s, Bayer focused their work on manufacturing and selling 6-APA to different pharmaceutical companies, as well as ampicillin.

Ampicillin is a broad-spectrum antibiotic, with effect on both gram-positive and gram-negative bacteria. Due to its stable beta-lactam ring, it can sustain the beta lactamase enzyme produced by bacteria to resist antibiotics such as penicillin G.

Ampicillin soon grew to become one of the most used antibiotics in the world, and the sale increased tenfold in the US from 1962 to 1964. The consumption of all penicillins grew until the turn of the century, with ampicillin being the most popular for outpatient use in the US (Bud 2007).

The closest competitor for ampicillin was tetracycline. Ampicillin was more expensive, but it had better effect on most infections (Bud 2007), and could be used in children where tetracycline was contraindicated. Tetracycline had shown unfavourable side-effects in children, causing intracranial hypertension, yellowing and malformation of the teeth, and delayed bone growth (Brosset, Nouaille et al. 1987).

The proceeding paragraphs names some of the most important infections accessible by ampicillin, illustrating its importance as an antibiotic from 1960s−1990s.

Otitis media

Otitis media is a secondary infection of the middle ear, caused by eustachian tube dysfunction after a primary upper airway infection. The bacterial otitis media is most commonly caused by H. influenza or S. pneumonia. Complications of the condition is hearing loss, tinnitus, vestibular neuritis, meningitis and encephalitis. Otitis media is common in the paediatric population, and in the 1980s, treatment with antibiotics was recommended for all cases in children, and ampicillin was commonly preferred (Lisby-Sutch, Nemec-Dwyer et al. 1990).

Sinusitis

A common infection of the upper airways is sinusitis. The infection causes obstruction of the draining system of the nose, making it favourable for bacterial growth in the sinuses. Long-term, complicated infections are associated with chronic rhinitis, nasal polyps, and asthma. Because of these potential complications, all cases of sinusitis were recommended treated with antibiotics, ampicillin being the drug of choice (Slavin 1988).

Haemophilus influenza:

Haemophilus influenza is a rod bacterium, causing infection in the soft tissue of the head and neck. Infection is especially common among children, with the highest prevalence among those under 5 years of age. Sign of infection is periorbital cellulitis, periorbital abscess, sinusitis, supraglottitis and otitis media. Severe infection can cause meningitis, epiglottitis, septicaemia and death (Simpson, McGill et al. 1981).

From 1950 to 1980, H. influenza was increased as a significant cause of paediatric morbidity and mortality. In the US, 75 % of all meningitis' in children under 5 years was caused by H. influenza,

making it the most prevalent cause of meningitis in young children (Muñoz 1980). The mortality rate of H. influenza was 5−8 %, with approximately 800 annual deaths in the US by 1980 (Muñoz 1980). Ampicillin, in combination with chloramphenicol, became the recommended treatment of H. influenza in 1975 (Williams and Moosdeen 1986).

Foodborne illness:

The meat consumption in the world sharply increased after the 1950s, causing an equal increase in the number of food-derived infections, the most common being Salmonella and E. coli. In the US, the number of infections with Salmonella tenfolded from 1950−1970 (Bud), further increasing from 1975 (Goldberg and Rubin 1988). Salmonella strains were found in mass production of food products, especially associated with the poultry industry. In most cases the bacteria cause food poisoning with diarrhea, but severe cases have been reported, with infection of the aorta, endocardium, bone, and meninges (Goldberg and Rubin 1988).

A rarer, but more lethal food-derived infection is listeriosis. Caused by the bacteria Listeria monocytogenes, it was increasingly reported around the world in the 1980s. The bacteria are associated with raw and processed food, especially dairy products, leafy vegetables and fish, and cause infection of the central nervus system and internal organs. The most common manifestations are meningitis, encephalitis, brain abscess, and septicaemia (Farber and Losos 1988, Nau, Schuchardt et al. 1990).

Ampicillin developed to become the recommended treatment for both Salmonella and Listeriosis by the 1980s (Marget and Seeliger 1988) (Espaze and Reynaud 1988).

Endocarditis:

Enterococci, the most common strains being E. faecium and E. faecalis, are common pathogens to humans. 5−15 % of all cases of endocarditis in the US in 1990 was shown to be caused by enterococci. Enterococci can also cause UTI, intraabdominal infection, pelvic infection, wound infection and bacteraemia. In 1990, it was the third most common reason for hospital-acquired infection (Murray 1990).

Osteomyelitis

Osteomyelitis is an infection of the bone, caused by a bacterial infection located adjacent to the bone, or as a complication to trauma or surgery with exposure of the bone. It usually affects children, S. aureus being the most common cause. The infection is usually complicated with additional anaerobic bacteria. Ampicillin became the recommended treatment in the 1980s, supplied with surgery if necessary (Armstrong and Rush 1983).

PID:

Pelvic inflammatory disease, PID, is the inflammation of the endometrium, fallopian tubes, adnexa, and other structures of the pelvis, most commonly caused by the migration of a sexually transmitted disease from the vagina, through the cervix, to the endometrium of the uterus. The worst complication of PID is infertility (Cunha 1990).

Gonorrhoea was the most reported sexually transmitted disease in 1883, with 2−2,5 million cases annually in the US. The incidence of PID was 600 000−1 000 000, 10−15 % resulting in infertility (Handsfield 1983). Gonorrhoea was recommended treated with ampicillin, while chlamydia was treated with tetracycline or doxycycline (Handsfield 1983).

Septicaemia in neonates:

Septicaemia is a life-threatening condition of organ failure, as a complication to infection. It is caused by an overreaction of the human immune system by the foreign pathogens. Septicaemia can be caused by all bacteria and is an especially important cause of morbidity and mortality among infants and children. The most common infections causing septicaemia in neonates are group B beta haemolytic streptococci, HSB-infection, and the most common manifestation of septicaemia in neonates is meningitis (Klein 1984). The bacterium is acquired from the mother during birth and cause severe infection 0−3 weeks after birth. Studies done in 1988 showed beneficial results of using ampicillin as prophylaxis in women in labour with known or suspected streptococcal infection (Boyer and Gotoff 1988, Rudigoz, Bensoussan et al. 1988).

Meningitis:

Bacterial meningitis is the infection of the membranes, meninges, of the brain and the spinal cord. Bacterial meningitis in children was of great concern during the 1970s, showing high mortality rates, especially among children. In neonates, the cause was most common GBS-infection acquired during birth, while H. influenza was the most common cause in older children (McCracken 1984). Ampicillin showed good effect on both GBS and H. influenza (McCabe 1983, Whitby and Finch 1986, Sáez-Llorens and McCracken 1990).

Discussion

Before both World War I and World War II, Germany dominated the pharmaceutical industry of the world. While other countries in Europe, such as Britain and France, was focusing on raw drugs derived from biological material, the German pharmaceuticals were based on chemistry. Europe was in a large way reliant of German pharmaceuticals before both World War I and World War II, but the difference after World War II in comparison to World War I was the recognition of penicillin as the new wonder drug. Penicillin became the revolution of infectious disease, showing great effect on most infections in Europe and the US at this time. Germany, with little previous experience in biologically derived drugs, had therefore lost the benefit of experience they had before the 1940s.

Another big difference between the post-war years, was the occupation of Germany from 1945, and the proceedings regarding the I.G. Farben in the Nuremberg trials of 1947. After World War I, Germany was in yearlong debt to the winning nations, and because of the resulting cheap prices for advanced German pharmaceuticals, the industry was quickly back on the world market. After World War II on the other hand, the US and penicillin had taken over the throne of pharmaceutical production. The market had changed from preferring chemically derived drugs, to preferring penicillin for infectious disease. The German industry was largely controlled by the occupying nations until the mid-1950s, and the reputation of the German pharmaceutical companies was in some way compromised after the revelations of connections to the Nazi regime and the concentration camps. In many ways this reputation was saved by the fractioning of the I.G. Farben done by the Allied forces, since the new established companies were not associated with the Nuremberg trials or Nazi-Germany. The immediate need of pharmaceuticals after the war, also ensured that business in Germany had to be re-established to a certain level, in order to keep the population in Germany healthy.

The fractioning of the I.G. Farben resulted in the re-establishment of the Bayer company as a new stock company known as the Bayer AG. The company continued to have their headquarters in Leverkusen, with additional laboratories in Elberfeld, Dormagen and Uerdingen. The Bayer AG

spent the next 10 years after 1950 trying to regain their position as an international manufacturer, focusing research into both anti mucosal drugs and sulphonamides. Despite their best efforts to fight penicillin, the Bayer AG soon realised their need for foreign subsidiaries, in order to compete with American firms.

The German population was struggling to survive after World War II, with famine, prostitution and poverty causing epidemics of infectious disease. Penicillin soon got the reputation as a wonder drug against bacterial infections, becoming the recommended treatment for both syphilis, gonorrhoea, meningitis and pneumonia to name a few. With the high need of sufficient amounts of penicillin in Germany, local production was initiated by the occupying nations. The Bayer AG managed to get the licence of Penicillin G, Penicillin V, Tetracycline and Chloramphenicol from other European firms in the 1950s and became one of the largest producers of penicillin in Germany by 1960. Their penicillin production also accounted for more than 10 % of the total production in the world, and with their growing number of foreign subsidiaries, the Bayer AG was the largest pharmaceutical company in Germany by 1956.

The mass production of penicillin in the 1940s and 1950s results in incredibly low prices for the drug, and emergence of bacterial resistance. The field of pharmaceuticals moved back into the field of chemistry as a base of research and production. The Beecham company pioneered in the field of advanced pharmaceuticals by discovering the first semi-synthetic penicillin in the world. With 6-APA as the core, new types of penicillin could be manufactured in the laboratory. The Bayer AG improved the production of 6-APA and got into partnership with the the Beecham company. This collaboration resulted in the development of ampicillin and became the solution of the Bayer AG's goal of once again being part of the world's leading pharmaceutical companies. The Bayer AG marketed and sold ampicillin to most of Europe, as well as several other countries in the world where the company had subsidiaries. In addition, they made the production of 6-APA into a successful business, selling it to other companies for further semi-synthetic penicillin production. Ampicillin became the recommended treatment for a wide range of infections and was especially important in the treatment of infections in the paediatric population.

From 1960−1980, the world's production and consumption of antibiotics double folded, and from 1980−1990, it grew another 50 %. Ampicillin by Bayer AG was one of the most prescribed antibiotics in the world by 1990. The discovery of 6-APA and ampicillin was therefore of great importance in the development of the Bayer AG after World War II, transforming the company from a small local supplier in the post-war years, into once again being a central part of the world market.

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