CHAPTER

26

The First Synthetic Drugs and their Analogues

August Wilhelm von Hofmann distilled aniline from coal tar in 1843 while working in Giessen as a research student with Justus Liebig. Two years later, he moved to the Royal College of Chemistry in London, where he demonstrated that benzene was present in coal tar. One of his students, Charles Mansfield, subsequently isolated it by fractional distillation of the tar. Nitration of benzene with nitric acid then provided the basis of a route to the industrial manufacture of aniline dyes and other important organic chemicals.

In 1856, another of Hofmann's students, William Perkin, oxidised the aniline derivative allytoluidine in an overly ambitious attempt to synthesise quinine. Instead he obtained a dark substance that turned fabrics purple. This was the first synthetic dyestuff, which Perkin initially called aniline purple but later changed to mauveine.[1] Realising the commercial value of the dye, Perkin established his own factory the following year. This marked the start of the synthetic dyestuffs industry that was to fuel a demand for organic chemists who could discover new products through the application of research. The high price of natural dyes was a matter of concern for the rapidly expanding textile industry, which was trying to match the demand from a growing population for cheap clothing. Perkin's mauvine remained expensive to produce, but within a decade several manufacturers were developing a range of affordable new dyes from aniline, toluidine and quinoline. Although the industry began in England, it was in Germany that it thrived. Two factors largely accounted for this. Once the German economy had recovered from the collapse of its stock market in 1873, industrialisation entered its second phase in which the chemical and electrical industries rapidly expanded to compete in importance with the existing coal, iron and steel industries. The heavy investment in the manufacture of synthetic dyes soon put Germany well ahead of all its competitors in this field. The second factor that made this possible was the willingness of German universities in the 1870s and onwards to meet the need of the moment. German chemists rapidly became the leaders in the emerging field of organic chemistry and remained so until the outbreak of the Second World War. They wrestled with the nature of the structures of the novel molecules they had synthesised, skilfully breaking them apart to identify known fragments, and then deducing how the atoms were assembled in the intact molecules. New synthetic reactions were also introduced, providing routes to a vast range of novel dyes and other commercially important organic compounds, including synthetic drugs. Success bred success.[2] In marked contrast to the situation in Germany, the failure of the United Kingdom to maintain the lead that Perkin had given it with mauvine was in no small measure due to the disdain with which its universities at the time viewed industrial contacts.

The German pharmaceutical industry developed directly out of the dyestuffs industry when leading manufacturers like F. Bayer & Company and Farbenfabriken Hoechst realised that their chemists could produce medicines as well as dyes. Initially, a few dyes served as drug prototypes, but during the twentieth century the industry became completely independent of its origins and instead concentrated on chemically modifying the structures of natural

Drug Discovery. A History. W. Sneader.

products from plant or biochemical sources. In Britain, France, the United States, Canada and to a much lesser extent Switzerland, the industry continued to focus on the extraction of alkaloids and glycosides from plants, with only a minimal effort being expended on the development of synthetic drugs. Such an approach was still capable of bringing immense benefits to the sick, as illustrated by the isolation of insulin in Canada and penicillin in the United Kingdom. However, a gradual change of direction in favour of synthetic drugs came about because of shortages during the two World Wars of essential medicines normally supplied by Germany.

The majority of natural products, be they from the plant or animal kingdoms, have been isolated in academic laboratories. However, the opposite is true of synthetic drugs. With the exception of a handful of hypnotics, the first synthetic drugs were all developed in industrial laboratories or research institutes where the *raison d'être* was the development of new medicines, such as the Institute for Experimental Therapy established by Paul Ehrlich in Frankfurt.

PHENOL

When the inventor William Murdock first used coal gas in 1794 to illuminate his home in Redruth, Cornwall, he could not have envisaged the full consequences of his actions. Within seven years, buildings in Birmingham were being lit by gas and before long the streets of other major British cities were no longer dark at night thanks to locally produced gas. In the United States, gas lighting had been installed in Baltimore by 1817. There was, however, one unwelcome by-product that arose from this exciting development, namely vast amounts of apparently worthless coal tar. One of the first to examine it was Friedlieb Runge, the chief chemist of a gas works at Oranienburg near Berlin, who steam-distilled a light oil from it.[3] A portion of this oil was acidic and so dissolved in milk of lime. Runge gave the name carbolic acid to the material he then recovered by acidifying the lime solution. Charles Gerhardt named it phenol in 1842.

Friedlieb Runge had been impressed by the ability of carbolic acid to prevent the decay of animal tissue and wood, but felt that it would be too expensive to market it as a preservative. In 1844, however, the French physician Henri-Louis Bayard incorporated coal tar in a clay-based powder for disinfecting manure to be used as a fertiliser. This won him a prize from the Société d'Encouragement for its contribution to hygiene.[4]

The first person to exploit the disinfectant properties of phenol was the industrial chemist Frederick Calvert, who had studied and worked in France from 1835 to 1846.[5] Returning to Manchester, he became a consultant chemist and introduced phenol for embalming. He became closely involved with the inventors of McDougall's Powder, a crude mixture of calcium salts and phenol patented in 1854 for purifying water and deodorising sewage. Calvert manufactured the powder and saw it become very popular as a disinfectant for stables, farmyards and any place where putrefying material was to be found. It was also applied to sores.[5]

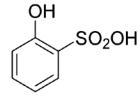
Calvert became convinced that the disinfectant in coal tar was phenol and accordingly informed the Académie des Sciences in 1859.[6] This encouraged the Dresden physician Friedrich Küchenmeister to employ pure phenol as a wound dressing.[7] Meantime, a pharmacist from Bayonne, LeBeuf, asked Jules Lemaire to evaluate his emulsified coal tar.[8] It proved very successful in treating septic wounds and in April 1862 was authorised for wound disinfection in the civil hospitals of Paris. The following year, Lemaire's book entitled *De l'Acid Phénique* was published, followed by an enlarged 2nd edition in 1865. This established Lemaire as the leading advocate of the use of phenol in surgery at that time, although his work aroused little enthusiasm in Britain.

Gilbert Declat's lengthy volume entitled *Nouvelles Applications de l'Acide Phénique en Médecin et en Chirurgie* was also published in 1865. Declat referred to phenol as a 'parasiticide'. In contrast to Lemaire, he was fully cognisant with Pasteur's ideas. He expressed the hope that phenol would be used to prevent infection and even recommended washing of the walls and surroundings of the sick room with it.

British surgeons continued to ignore the developments in France. Fortunately, Calvert had convinced public authorities in Britain of the benefits of phenol for treating sewage and a newspaper report about its use in Carlisle was read by Joseph Lister, the Professor of Surgery at the University of Glasgow.[9] Though deeply concerned about the high incidence of lethal infections following surgery, reaching 40% after amputations, he had been unaware of the studies being carried out in France with phenol. After reading the newspaper article, he applied German creosote when operating on a patient with a compound fracture of the leg. The prognosis was poor since puncturing of the skin by the broken bone had resulted in infection and Lister was unable to save the patient. He went on to modify his technique by covering wounds with dressings soaked in solutions of pure phenol obtained from Calvert. On 12 August 1865, a boy run over by a cart was admitted to the Royal Infirmary with a compound fracture of the leg. This time, the dressing successfully prevented infection. Eleven more patients were treated, with only one death. The first of several papers by Lister on antiseptic surgery then appeared in the *Lancet* in 1867.[10] By basing his use of phenol on a clear understanding of Pasteur's researches, Lister was highly successful in preventing wound sepsis and he transformed surgical practice and rendered it safe. Antiseptic surgery was soon replaced by aseptic surgery, itself a logical development of Lister's approach. With the demise of antiseptic surgery, phenol became much less important. The main objection to its use was its corrosive nature, which permitted only low concentrations to be applied to the skin. Today phenol is found only in antiseptic creams and liquids such as mouth washes.

ANALOGUES OF PHENOL

Alternatives to phenol were sought as early as 1867 when Arthur Sansom at London's Royal Hospital for Diseases of the Chest administered sulfocarbolate of potash by mouth in the mistaken belief that it would slowly decompose in the body to release small amounts of phenol and thereby act as an internal antiseptic. The product he used was a mixture of the salts of *ortho*- and *para*-phenolsulfonic acids, apparently consisting largely of the former.[11,12] This was subsequently named solozic acid, and became available commercially as a one-in-three solution in water. It was widely used for treatment of diphtheria, scarlet fever and puerperal fever until Heinrich Bechhold and Paul Ehrlich revealed its inferiority to other phenolic compounds.[13]

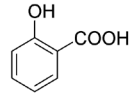


solozic acid

Salicylic Acid

Carl Thiersch, the Professor of Surgery at Lepizig, adopted a similar approach to Sansom in seeking a compound with less deleterious effects than phenol on tissues. As the first German surgeon to adopt Lister's methods, he had become well aware of its damaging effects. When he discussed the matter with Hermann Kolbe, the Professor of Chemistry and by now the leading

chemist in Germany, the latter recalled how in 1860 he and Lautemann had treated phenol with carbon dioxide in the presence of sodium under pressure to form salicylic acid.[14] Kolbe knew that, on heating salicylic acid, carbon dioxide was liberated and the acid decomposed into phenol, so he now carried out some simple tests on salicylic acid and confirmed that it had antiseptic properties. His idea that it might release phenol was never realised, but salicylic acid did find a role as an antiseptic that was somewhat less corrosive than phenol. That it was still damaging to tissues is evident from its continued use to burn out warts. Convinced of the value of salicylic acid as a substitute for phenol, Kolbe modified his original synthesis so that the acid could be produced on an industrial scale. One of his former students then opened the Salicylsäurefabrik Dr F. von Heyden in Dresden, as a consequence of which salicylic acid became cheaply available in 1874.

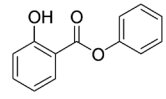


salicylic acid

Although it never replaced phenol in surgical practice, salicylic acid became popular as an internal antiseptic at a time when it was widely believed that many diseases arose from the presence of pathogenic bacteria in the gut. This led Carl Buss at St Gallen in Switzerland to administer salicylic acid by mouth to typhoid patients. When the course of their disease was routinely checked by thermometry, it became obvious that salicylic acid was an effective antipyretic. However, it did not lower body temperature by curing the typhoid infection. Widespread interest was aroused in 1875 when Buss published his observation that repeated doses of salicylic acid could control fevers without causing the side effects of quinine, at that time the standard antipyretic.[15] Salomon Stricker at the University of Vienna Medical School then tested salicylic acid for its ability to reduce the temperature of patients with rheumatic fever. To his surprise, it also proved to be of definite value as an antirheumatic drug.[16] A similar observation was made by the Scottish physician Thomas MacLagan,[17] while the French physician Germain Sée confirmed the specific value of salicylic acid in rheumatoid arthritis and gout.[18] Surprisingly, many physicians were unaware of these reports until the 1950s when, at last, there was universal recognition of the importance of salicylate therapy in rheumatoid arthritis.[19]

Phenyl Salicylate

Salicylic acid was normally prescribed as its sodium salt. Many patients complained about its unpalatibility and irritating effects on the stomach. An attempt to improve upon both it and phenol as internal antiseptics was made by the Polish chemist and physician Marceli Nencki in 1883, when he reacted the two drugs together to form phenyl salicylate.[20] After being swallowed, this passed unchanged through the stomach because it was highly insoluble. It was more soluble in the small intestine, where the portion that dissolved then decomposed to liberate small amounts of the parent drugs. After Hermann Sahli had tested phenyl salicylate in Berne, it was generally believed that some benefit was to be derived from these small amounts.[21]

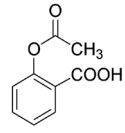


phenyl salicylate

Phenyl salicylate was marketed under the name 'Salol' and it was many years before there was general recognition that any advantage it had over salicylic acid was offset by the prolonged onset of activity and variability of therapeutic response. Until then, it was a popular substitute for salicylic acid as an antipyretic and antirheumatic. It was an early example of the gullibility of many when presented with a drug exhibiting chemical novelty unsupported by reliable clinical proof of efficacy.

Aspirin

After being appointed in 1896 by F. Bayer & Company of Elberfeld to stimulate research so as to free the company from its dependence upon universities for the supply of new compounds, Arthur Eichengrün began to prepare esters of phenolic compounds that irritated the stomach. He expected that the masking of the phenol would protect the stomach, while the esters would decompose once they reached the more alkaline conditions of the gut and release the active drug for it to be absorbed into the circulation. Felix Hoffmann was given the task of preparing acetylsalicylic acid, a crude version of which may have been synthesised in 1853 by Charles von Gerhardt.[22] After acetylsalicylic acid had been prepared, it was tested in the spring of 1897 by the company pharmacologist Heinrich Dreser. He rejected it – despite the tests appearing to Eichengrün to show that it was superior to any other salicylate. Acting on his own initiative, Eichengrün tested the compound on himself, then arranged for it to be clandestinely evaluated by physicians in Berlin. The outcome of this was not only to confirm that acetylsalicylic acid was an effective substitute for salicylic acid, but also that it had unexpectedly relieved pain when a patient with toothache happened to be given a sample to consume. Once the analgesic properties had been confirmed in other patients, the colleague who had conducted the secret trials brought this to the attention of Bayer management. They responded by arranging for Kurt Witthauer of the Deaconess Hospital in Halle and Julius Wohlgemuth in Berlin to conduct independent clinical trials of the drug.[23,24] The outcome persuaded Bayer management to market acetylsalicylic acid under the proprietary name Aspirin®, which was coined by Eichengrün from 'a' for acetyl and 'spirin' from *Spirea ulmaria*, the now obsolete name of the plant from which salicin was obtained. To ensure the success of the new drug, F. Bayer & Company circularised more than 30 000 doctors in what was probably the first mass mailing of product information. Eichengrün was rewarded for his efforts by being promoted to Director of Pharmaceutical and Photographic Research, while Hoffmann became Director of Pharmaceutical Sales.



aspirin

Dreser was asked by the Bayer management to publish the results of his further examination of aspirin after its testing in Berlin, in order to lend scientific credibility to the new product.[25] His paper omitted any reference to either Eichengrün or Hoffmann and gave no indication of how aspirin came to be developed. The first account of this did not appear until a year after the Nazi party came to power in Germany in 1933. It was published in a history of chemical engineering as a short footnote that claimed to be based on a communication from Felix Hoffmann to the author.[26] This alleged that when Hoffmann had been asked by his rheumatic father to find an alternative to the foul-tasting sodium salicylate, he searched the literature and came across acetylsalicylic acid, then preparing it in pure form. On the fiftieth anniversary of

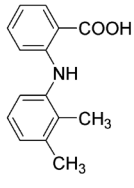
the introduction of aspirin, Arthur Eichengrün published the only detailed account ever written by any of those directly involved in the development of aspirin.[27] In this, he implied that history had been rewritten by the Nazis to hide the fact that it was a Jew who was primarily responsible for the development of the most famous drug in history. This appears to have been as unpalatable to some as sodium salicylate was supposed to have been for Hoffmann's father, leaving the present writer to attempt to set the record straight on the centenary of the introduction of aspirin.[28]

How aspirin worked remained a mystery until 1971 when John Vane at the Institute of Basic Medical Sciences of the University of London and the Royal College of Surgeons of England demonstrated that it blocked prostaglandin synthesis.[29] The precise manner in which this occurred was subsequently shown to be through the permanent transfer of the acetyl group from aspirin on to the hydroxyl group of a serine residue located 70 amino acids from the C-terminal end of the cyclooxygenase (COX) enzyme that promotes the formation of prostaglandins.[30]

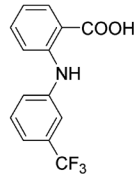
Another effect of aspirin that has been successfully exploited is its antiplatelet activity, which also arises from blocking of prostaglandin synthesis. In 1949, Gibson described his successful use of aspirin in a small group of patients with vascular problems.[31] Around the same time, Lawrence Craven in California realised that his tonsillectomy patients who had taken a chewable aspirin preparation for pain relief were more likely than others to bleed.[32] Craven went on to conduct an uncontrolled investigation on 8000 patients who regularly consumed aspirin and claimed that none suffered heart attacks.[33] None of his publications appeared in prominent journals and, when he died of a heart attack despite taking aspirin, any credibility his work might have carried was undermined. Fortunately, in New York in 1967, Harvey Weiss established that the prolongation of bleeding time caused by aspirin was due to an impairment of platelet aggregation.[34] He suggested that aspirin might be an antithrombotic drug and in 1971 was able to provide experimental evidence that this was the case. He urged that clinical trials be carried out. Three years later physicians in Wales published the results of the first randomised, controlled clinical trial of aspirin in patients who had experienced a previous heart attack.[35] Since then, it has taken many years for it to be generally accepted that low doses of aspirin reduce the risk of myocardial infarction in patients with cardiovascular disease.

Aspirin Analogues

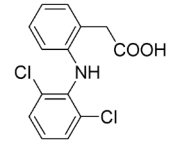
Anthranilic acid (*o*-aminobenzoic acid), an analogue of salicylic acid in which the phenolic hydroxyl is replaced by an amino group, is inactive. Parke, Davis and Company developed a non-steroidal anti-inflammatory agent called mefenamic acid, by adding a second benzene ring that drastically reduced the basicity of the aromatic amino group in order to prevent zwitter ion formation. It was patented in 1961.[36] The researchers also confirmed that flufenamic acid, which had originally been synthesised in 1948, was a useful anti-inflammatory drug.[37] Geigy researchers subsequently developed diclofenac by taking into account the structural physicochemical characteristics of existing anti-inflammatory agents.[38]



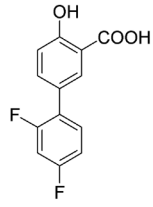
mefenamic acid



flufenamic acid



diclofenac



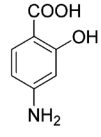
diflunisal

Diflunisal was introduced by Merck Sharp and Dohme after more than 500 compounds had been synthesised and evaluated in a 15 year long search for a longer-acting, safer analogue of aspirin.[39] It is similar in its therapeutic profile to arylpropionic acid-derived non-steroidal anti-inflammatory drugs.

p-Aminosalicylic Acid

While investigating the nutritional requirements of the causative organism of tuberculosis, *Mycobacterium tuberculosis*, in 1940 Frederick Bernheim, a biochemist at Duke University Medical School in North Carolina, discovered that benzoic and salicylic acids increased oxygen utilisation.[40] This indicated that these acids were serving as nutrients for the bacteria. Taking into consideration the recently announced antimetabolite theory, he went on to antagonise the effect of these acids with 2,3,5-triiodobenzoic acid.[41] In conjunction with Alfred Burger and others, Bernheim then examined a diverse range of halogenated aromatic acids and phenolic ethers as potential antimetabolites. Some of the latter were active, but unsuitable for clinical application because of side effects on the central nervous system.

Bernheim had communicated his findings to his friend Jorgen Lehmann at the Sahlgren's Hospital in Gothenburg. Reflecting on the past at the age of 83, Lehmann has written that in 1943 he was convinced that the positioning of the amino group in the sulfanilamide antagonist *p*-aminobenzoic acid was critical; hence he felt that a *p*-amino group should be introduced into salicylic acid to provide a tuberculostatic drug.[42]



p-aminosalicylic acid

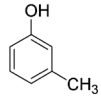
Lehmann asked the Ferrosan Company of Malmo (now incorporated into Kabi Pharmacia) to supply him with *p*-aminobenzoic acid as it had previously been prepared only in quantities insufficient for biological evaluation. As a result, he was able to test it in January 1944 and found it to be tuberculostatic in animals, with a wide margin of safety. In March of that year, a child with a severely infected wound was successfully treated by local application of the drug. By the end of the year, 20 patients had received the drug by mouth and results were most promising. Lehmann published the result of two years of clinical trials, confirming that *p*-aminosalicylic acid (PAS) could cure tuberculosis.[43]

It was later established that *p*-aminosalicylic acid was best used in combination with the much more potent drugs streptomycin and isoniazid. The combination of these drugs proved to be a major step in overcoming the problem of bacterial resistance towards streptomycin. On its own, *p*-aminosalicylic acid lacked sufficient potency for routine clinical application. There were two other shortcomings. It was rapidly excreted via the kidneys, resulting in the need for

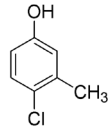
oral administration with quantities of 12 g daily in four or more divided doses. This compounded the second problem, which was that it caused distressing gastrointestinal disturbance. The problem could not be overcome either by formulating it differently or by the synthesis of analogues. Once a range of alternative drugs became available in the 1980s, *p*-aminosalicylic acid was no longer prescribed.

Cresols

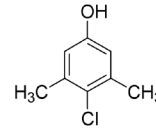
In 1886, Oswald Schmiedeberg claimed that cresol was not only more potent but also less toxic than phenol.[44] As cresol consisted mainly of *m*-cresol, together with its *ortho* and *para* isomers, any reduced toxicity was probably due to the smaller amount that could dissolve in water. Kalle and Company of Frankfurt introduced chlorocresol as a bactericide in 1897. Many alkly, halo and haloalkylphenols have been introduced since then.



cresol



chlorocresol



chloroxylenol

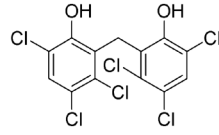
The findings of the first extensive investigation into their activity was reported in 1906 by Bechhold and Ehrlich, who found that although polyhalo compounds were more potent than monohalo compounds, they did not retain activity in the presence of serum.[13] Monohalophenols were subsequently shown by Laubenheimer to be less affected by the presence of serum.[45] This was of considerable importance for compounds that were to be used in the clinic. Klarmann discovered that in higher molecular weight phenols the spectrum of antibacterial activity did not change uniformly with alteration to the chemical structure.[46] In several instances he found that structural modification enhanced activity against most organisms, yet removed all activity against specific organisms. This phenomenon was to be encountered repeatedly in the antibiotic era.

A well-equipped unit supported by the Medical Research Council, the Rockefeller Foundation and the Bernhard Baron Trustees was opened at Queen Charlotte's Maternity Hospital in London in 1931 with the objective of finding a solution to the problem of puerperal fever. This had been the cause of death in two or more out of every thousand women within days of giving birth. Leonard Colebrook, the bacteriologist in charge of the new unit, was particularly concerned about a form of the disease caused by haemolytic streptococci, in which there had been a mortality rate of over 25%. He collaborated with his cousin, a chemist who worked for the Reckitt company in Hull, in the development of a non-irritant antiseptic that could kill streptococci on the skin of the midwives' hands. He experimented on himself by smearing his hands with virulent bacterial cultures, a procedure that led to the development of chloroxylenol solution as a non-irritant antistreptococcal hand disinfectant, which greatly reduced the incidence of puerperal fever caused by streptococcal infection.[47] It remains the most important of the cresols to have been introduced into medicine.

Hexachlorophene

William Gump began an investigation of halogenated bisphenols in the laboratories of Givaudan–Delawanna in New York in 1937, which resulted in the development of hexachlorophene as a skin disinfecting and cleansing agent after the Second World War

had ended.[48] It had the advantage of retaining activity in the presence of soap and hence was introduced in creams, soaps and cleansing lotions sold to the general public.

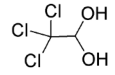


hexachlorophene

Tragically, a manufacturing blunder in France led to the sale of a baby powder containing 6% hexachlorophene, which resulted in the death of 20 children before the cause was discovered. It was subsequently confirmed that severe neurotoxicity had previously occurred in infants after absorption of hexachlorophene through the skin on repeated application.[49] This led the US Food and Drug Administration in 1972 to ban sales to the public of all formulations containing more than 0.1% hexachlorophene. Other drug authorities did likewise, with hexachlorophene being allowed to remain in use as a skin disinfectant for health care workers.

HYPNOTICS

Chloral hydrate was synthesised in 1832 by Justus Liebig, who also discovered that it decomposed into chloroform and formic acid when treated with alkali.[50] This caught the attention of two investigators, Rudolf Buchheim and Oskar Liebreich, who both then discovered the hypnotic action of chloral hydrate.[51]

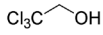


chloral hydrate

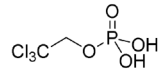
Buchheim had wondered whether excessive alkalinity of the blood, which was thought to be a complicating factor in some diseases, could be reduced by administration of chloral hydrate. The idea behind this was that as treatment of chloral hydrate with caustic alkali liberated chloroform and formic acid, then alkaline blood should do likewise. Buchheim believed that the chloroform thus released in the blood might even be converted into hydrochloric acid, thereby supplementing the alkali-neutralising action of the formic acid. However, on taking a draught of chloral hydrate to test his hypothesis he and several of his colleagues quickly fell asleep. Buchheim thought this proved that chloroform had been released, but had not then broken down into hydrochloric acid. His investigation was abandoned and not reported until 1872, three years after Liebreich had introduced chloral hydrate as a hypnotic drug.[52]

Liebreich, an assistant professor at Berlin University's Pathological Institute, also tried to use chloral hydrate to liberate chloroform in the blood. Unlike Buchheim, he actually hoped the chloroform would induce unconsciousness. He was therefore delighted when experiments on rabbits confirmed his expectations. The animals awakened unharmed several hours later. When 1.35 g of chloral hydrate was administered to a disturbed individual by subcutaneous injection, he slept for 5 hours. A subsequent dose of 3.5 g in water kept him asleep for 16 hours. Liebreich published his findings in August 1869.[53,54] Within a few months, chloral hydrate was in use all over the world as the first safe hypnotic, despite its unpleasant taste and the frequency with which it caused gastric irritation. An early shortage of supplies of chloral hydrate raised the price of a draught to three shillings and sixpence in the United Kingdom, or

just under US $1, leading to the expression, 'A sleep costs a dollar!' The shortage ended after Schering built a factory in Berlin to produce it. Daily consumption in both Britain and the United States passed the 1 ton mark within a decade, which no other contemporary drug even remotely rivalled. Chloral hydrate remains in use around the world.



trichloroethanol

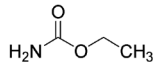


triclofos

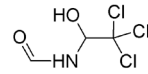
It soon became evident that if any chloroform at all was released in the blood after administration of chloral hydrate, it could only be trace amounts. It is nowadays realised that the alkalinity of blood is so slight as to be unable to induce decomposition of chloral at all, but in the 1860s there was no awareness of the subtleties of Sørenson's pH scale, which was not introduced until 1909. Joseph von Mering, a protégé of Schmiedeberg, correctly suggested that chloral hydrate was converted in the body into the active hypnotic trichloroethanol,[55] but it was not until 1948 that there was experimental proof of this.[56]

Trichloroethanol could not be administered as a drug because of its unpleasant taste, as well as a tendency to cause nausea. Its phosphate ester, triclofos sodium, was introduced by Glaxo in 1962.[57] This is rapidly hydrolysed in the gut to liberate trichloroethanol. There was no problem with palatability when triclofos was formulated in an elixir as its water-soluble sodium salt.

The discovery of the hypnotic properties of chloral hydrate brought home to many people the potential of synthetic drugs as therapeutic agents. It also set the scene for what was to become for many years the sole alternative to basing the structures of synthetic drugs on those of natural products, namely the idea of designing a new drug that would decompose to release a pharmacologically active agent. An early example of this approach is seen when Schmiedeberg selected urethane as a potential anaesthetic in small animals.[44] He thought it would break down in the body to release not only alcohol, a central nervous system depressant when large doses were consumed, but also ammonia and carbon dioxide, which were both known to be respiratory stimulants. The anaesthetic action of urethane that Schmiedeberg then observed was later shown to be due solely to the intact molecule, with neither carbon dioxide nor ammonia being released in the body. His hypothesis may have been wrong, but it resulted in the introduction of an anaesthetic that is still used in small animals.



urethane



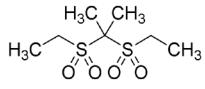
chloralformamide

The approach of designing drug molecules to liberate active substances can also be seen in analogues of chloral hydrate that were marketed in the 1880s. For example, Joseph von Mering patented chloralformamide as a hypnotic in 1889, more than 50 years after it had first been synthesised.[58] He also believed that ammonia and carbon dioxide would be liberated as respiratory stimulants, which would counteract any respiratory depression that occurred as a result of overdosing. The new drug turned out to be no safer than chloral hydrate, though it was less irritating to the stomach.

Sulfonmethane

In the summer of 1887, Eugen Baumann at the University of Freiburg asked his colleague Alfred Kast to see whether some novel sulfur compounds that he had prepared had any

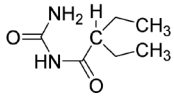
pharmacological activity. Kast began by injecting a suspension of 2 g of sulfonmethane into a dog.[59] Initially, there was no apparent reaction from the animal, but several hours later it staggered and fell unconscious. The dog did not awaken until several hours later. The experiment was repeated on other animals, confirming that sulfonmethane was a hypnotic.[60] It was marketed the following year by F. Bayer & Company.

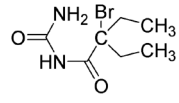

sulfonmethane

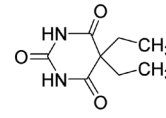
As a hypnotic that combined palatibility and absence of gastric irritancy with freedom from circulatory disturbance, sulfonmethane was to be one of Bayer's first profitable pharmaceutical products. It retained its popularity until the introduction of the more rapidly acting barbiturates rendered it obsolete.

The Barbiturates

Consideration of the chemical nature of the hypnotics discovered during the last two decades of the nineteenth century convinced von Mering that a key feature in their molecular structure was the presence of a carbon atom containing two ethyl groups. Knowing of work already carried out by others on urethane and urea derivatives, he and Emil Fischer investigated diethylacetylurea, finding it to be as potent a hypnotic as sulfonmethane.[61] Its bromo derivative, carbromal, was later marketed by Bayer as a hypnotic.[62]


diethylacetylurea

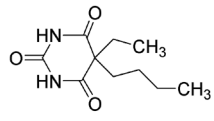

carbromal

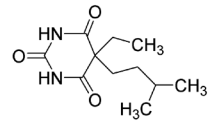

barbital

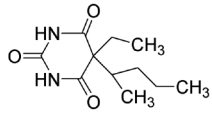
After finding diethylacetylurea to be a hypnotic, von Mering prepared 5,5-diethylbarbituric acid, unaware that it had already been made 20 years earlier.[63] The parent compound of this series, barbituric acid, had been synthesised by von Baeyer in 1864, and is variously said to have been so named after a young maiden with whom its discoverer was then in love, or, more prosaically, on account of its first preparation being on St Barbara's Day.[64] After von Mering established that 5,5-diethylbarbituric acid was a hypnotic in animals, he discussed the compound with Fischer. The latter doubted the reliability of the synthesis and instructed his nephew, Alfred Dilthey, to synthesise it and several related compounds. When tested on a dog, 5,5-diethylbarbituric acid proved to be the most potent of the 19 compounds that had been synthesised and was much more potent than von Mering's compound. This provoked Fischer to remark that he now had the true compound, which explains why it was given the proprietary name of Veronal® (Latin: *verus* = true) when it was marketed by F. Bayer & Company.[65] Fischer filed a patent on the new hypnotic at the end of January 1903 and a detailed report appeared the next year.[66] All previous hypnotics, with the possible exception of chloral hydrate, were now rendered obsolete.

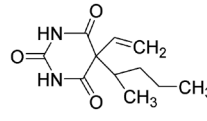
When the United States entered the First World War in 1917, Congress passed the *Trading with the Enemy Act* to allow American firms to manufacture unobtainable German drugs covered by patents, such as Veronal® and Salvarsan®. Royalties were paid to the Alien Property Custodian for distribution to the American subsidiaries of German companies when the war ended. The Act required the American products to be given a new name approved by

the American Medical Association (AMA). This practice of giving a drug an approved, or generic, name in addition to that chosen by its original manufacturer ultimately became standardised throughout the world. In the case of Veronal®, Roger Adams at the University of Illinois devised a manufacturing process for the Chicago-based Abbott Laboratories. The drug was then given the AMA approved name of barbital.


butobarbital


amobarbital

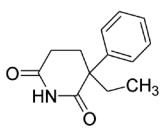

pentobarbitone


quinalbarbitone

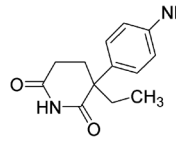
During the First World War, Chaim Weizmann (who later became the first president of Israel) discovered that a bacterium known as *Clostridium acetobutylicum* could convert cheap starchy materials to acetone and *n*-butanol. This was of immense military significance as the United Kingdom was desperately short of acetone for the production of naval explosives. Once peace was restored, the Weizmann process resulted in a sudden drop in the price of *n*-butanol, previously an expensive chemical. Carl Marvel and Roger Adams at the Urbana campus of the University of Illinois synthesised 5-butyl-5-ethylmalonic ester in 1920.[67] This was to be the key intermediate in the synthesis of the butyl analogue of barbital, butobarbital (also known as 'butethal'), by Arthur Dox and Lester Yoder of Parke, Davis and Company.[68] This new barbiturate was about three times as potent as barbital, with a shorter duration of action, which minimised any drowsiness on awakening. The increased potency and more rapid metabolic destruction of butobarbital are both due to the enhanced lipophilicity caused by introduction of the longer butyl group. This favours entry into the brain, which is the site of action, and into the liver, which is the site of metabolic deactivation. Shonle and Moment of the Eli Lilly Company in Indianapolis announced their synthesis of amylobarbital (now known as 'amobarbital') a year after the introduction of butobarbital.[69] Both drugs were of similar potency, but the branched carbon atom on amobarbital rendered it more susceptible to metabolic deactivation, shortening the duration of action still more. It and similar barbiturates such as pentobarbitone and quinalbarbitone (secobarbitone) became highly popular hypnotics until the 1960s, when mounting concern about both their habit-forming properties and use in suicide led to their decline.

Drugs Structurally Related to Barbiturates

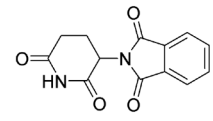
No hypnotics to challenge the barbiturates were developed until the 1950s, by which time there was concern about accidental overdosing by drowsy patients, as well as their use in suicide attempts. In 1952, Tagmann and his colleagues at Ciba in Basle announced that they had found a potent hypnotic among a series of dioxotetrahydropyridines structurally related to the barbiturates.[70] The new compound, glutethimide, was initially hailed as safer than the barbiturates – a claim that did not withstand the test of time.



glutethimide



aminoglutethimide



thalidomide

Aminoglutethimide was marketed for the treatment of epilepsy in 1960 after Ciba researchers found it was a stronger anticonvulsant but had weaker sedative–hypnotic properties than glutethimide.[71] In 1963, Ralph Cash, a paediatrician at the Sinai Hospital in Detroit, reported that it had induced the typical signs of Addison's disease (adrenal insufficiency) in a young girl who had been receiving it for five months to control her epilepsy. After similar reports from other doctors appeared, laboratory studies revealed that the drug had blocked steroid biosynthesis. It was withdrawn from the market in 1966. Cash demonstrated that aminoglutethimide inhibited the desmolase enzyme that removed the side chain from cholesterol to form pregnenolone, a prerequisite for steroid hormone synthesis.[72] Subsequently, it was administered to patients with Cushing's disease in the hope that they might benefit from its ability to inhibit overproduction of corticosteroids, but results were disappointing. In the 1970s physicians began administering aminoglutethimide to women with metastatic breast cancer, supplementing the drug with dexamethasone to compensate for diminished cortisone levels in the body.[73] The value of aminoglutethimide, especially in those women who had relapsed after initially responding to tamoxifen, is now established.

Another analogue of glutethimide was introduced by Chemie Grünenthal, a company established immediately after the Second World War by a soap and toiletries manufacturer keen to obtain a stake in the growing market for antibiotics, then in desperately short supply. Heinrich Mueckter, who qualified in medicine before the war, was appointed as research director on the basis of his wartime experience with the German army virus research group. In 1953, his assistant Wilhelm Kunz was given the task of preparing simple peptides required for antibiotic production. In the course of this he isolated a by-product that was recognised by a Chemie Grünenthal pharmacologist Herbert Keller to be a structural analogue of glutethimide. A series of related compounds were examined, from which one was examined in detail by Keller for its suitability as a hypnotic agent. Unusually, it did not abolish the righting reflex of animals – a standard laboratory test for hypnotic activity. Keller conducted a series of studies on the mobility of mice exposed to the drug, thalidomide, comparing it with several barbiturates and other central nervous system depressants.[74] After investigating its toxicity in mice, rats, guinea pigs and rabbits, he came to the conclusion that it was a remarkably safe sedative.

Chemie Grünenthal approached manufacturers throughout the world, with the outcome that several who were keen to enter the market for sedative–hypnotics marketed it with their own brand name. This was to lead to the greatest tragedy in the history of modern drugs, for the new sedative was a teratogen.

Thalidomide was introduced on the German market in 1956. In November 1961, Hamburg paediatrician Widukind Lenz reported a large increase in the number of infants with phocomelia attending ten clinics in North Germany. Instead of limbs, they had stumps. This had previously been one of the rarest malformations known, with no cases having been seen in these clinics in the decade prior to 1959. Yet there were 477 cases in 1961. Lenz attributed the increase to the taking of thalidomide by mothers during the first trimester of their pregnancies and notified Chemie Grünenthal and the authorities. The report of thalidomide teratogenicity was immediately picked up and publicised by a German newspaper, forcing the manufacturer to withdraw the drug. Like most others introduced up till then, it had never been tested for teratogenicity.

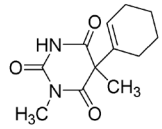
By the time thalidomide was withdrawn, 3000 deformed babies had already been born in Germany and at least twice that number elsewhere.[75] The United States was spared because Frances Kelsey at the Food and Drug Administration had not approved a new drug application, having been dissatisfied with the limited safety data that had been submitted. At that time, it was only the United States that required manufacturers to seek government approval before launching a new drug. Within a few years of the thalidomide disaster, countries around the world had quickly emulated the American system.

Barbiturate Anaesthetics

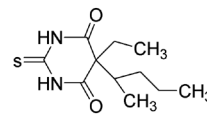
Intravenous medication did not become feasible until after the development of the hypodermic syringe by Alexander Wood of Edinburgh in 1853. The earliest attempt at intravenous anaesthesia was due to the work of Pierre Oré of Bordeaux, who reported to the Surgical Society of Paris in 1872 that he had injected a solution of chloral hydrate and achieved deep enough anaesthesia to remove a fingernail.[76] Oré published a detailed report of a further 36 operations in which he had used the technique with some success, but in one case the patient died.[77] It was not until 1905 that further development occurred when N.P. Krawkow of St Petersburg successfully administered a saline solution containing the Bayer Company's recently introduced urethane analogue Hedonal®. Fedoroff subsequently used this method in more than 500 operations.[78] The technique was taken up in Russia and some parts of Europe, where it stimulated others to seek more suitable drugs.

Daniel Bardet reported in 1921 that he had anaesthetised patients with injections of Somnifen®, a water-soluble formulation of barbital and allobarbital.[79] He found that recovery was too slow, and patients awoke with headaches. Amobarbital, butallylonal and pentobarbital were occasionally used in the latter half of the decade. Particularly disconcerting, however, was a tendency for anaesthesia to deepen alarmingly without warning. This was because the delay in its onset prevented the anaesthetist from knowing how much drug was required to render the patient unconscious. Not until I.G. Farben introduced hexobarbital in 1931 did a safe intravenous anaesthetic become available. With it, the onset of action was rapid and so the anaesthetist could control the level of anaesthesia by giving the injection slowly.

Hexobarbital was synthesised by the chemists Kropp and Traub at Elberfeld.[80] Its rapid onset of anaesthesia was due to the replacement of a hydrogen atom on one of the barbiturate ring nitrogen atoms by a methyl group. This rendered the molecule less water soluble and more lipophilic. Small though this molecular change may have been, it ensured rapid transposition of the drug from the blood into the brain cells. As a consequence, patients fell unconscious in the few seconds it took for the blood to carry the anaesthetic to the brain from the site of injection.[81] Hexobarbital was deservedly successful, and it is estimated that over the next 12 years some 10 million injections of it were administered.



hexobarbital



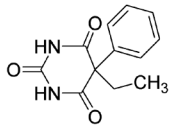
thiopental

Even before the first reports of the success of hexobarbital had begun to circulate, Donalee Tabern and Ernest Volwiler of Abbott Laboratories were on the trail of the drug that was ultimately to render it obsolete. Their work on pentobarbital encouraged them to seek very short-acting barbiturates, probably with a view to introducing them as hypnotics free from any tendency to produce a hangover. They followed up old reports stating that

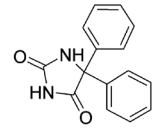
sulfur-containing thiobarbiturates were chemically less stable than the familiar oxobarbiturates. Thiobarbiturates had been among the earliest barbiturates examined in 1903 by Fischer and von Mering, but had been rejected after an oral dose of the sulfur analogue of barbital had killed a dog. Notwithstanding, Tabern and Volwiler pursued their idea that a chemically unstable thiobarbiturate might decompose fast enough in the body to ensure that its effects quickly wore off. By 1934 they were convinced that thiopental, the sulfur analogue of pentobarbital, was a promising agent.[82] Doubtlessly inspired by the recent success of hexobarbital, they arranged for thiopental to be investigated by Ralph Waters,[83] who had just completed his pioneering investigations into cyclopropane anaesthesia, at the University of Wisconsin Medical School, Madison, and by John Lundy[84] of the Mayo Clinic in Rochester, Minnesota. Both confirmed the superiority of thiopental over existing intravenous anaesthetics. It ultimately achieved recognition as the single most useful agent for the induction of anaesthesia prior to the administration of an inhalational anaesthetic. It was only in the 1990s that it was rivalled by propofol. It also became widely used as an intravenous anaesthetic for short operations.

Anticonvulsants

Phenobarbital was one of the compounds reported by Fischer and Dilthey in their paper of 1904. It was later found to be superior to barbital and was marketed by F. Bayer & Company under the proprietary name of Luminal®.[85] For half a century it was a commonly prescribed hypnotic and sedative, but it remains in use today principally on account of its anticonvulsant activity. This was discovered by chance shortly after its introduction into the clinic, when a young doctor, Alfred Hauptmann, supplied it to epileptic patients in his ward who kept awakening him at night due to their fits. He expected the hypnotic to keep them asleep during the night, but did not expect that the incidence of their fits would decline during the day, particularly in those with grand mal epilepsy.[86] At first, there were few who believed Hauptmann's claims that he had stumbled upon the first truly anti-epileptic drug that did not produce the severe sedation hitherto associated with the use of bromides. Only after the First World War was there general recognition of this valuable property of phenobarbital.



phenobarbital



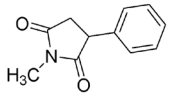
phenytoin

Tracy Putnam, the Director of the Neurological Unit of the Boston City Hospital, initiated experiments in 1934 aimed at finding a less sedating anticonvulsant than phenobarbital. He and Frederick Gibbs established the first electroencephalographic laboratory in the world designed for routine clinical studies of brain waves. An important observation to emerge from the new laboratory was that epileptic seizures were accompanied by an electrical 'storm' in the brain. This led Putnam to conclude that it might be possible to induce convulsions in laboratory animals by applying an electrical current to the brain. Furthermore, it might also be possible to quantify the strength of current required, thereby affording a method of recognising whether a drug was able to give some degree of protection to the animal. Having then set up an improvised piece of apparatus, Putnam and Gibbs demonstrated that phenobarbital markedly raised the convulsive threshold in cats.

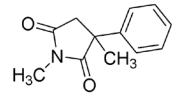
Putnam next sought a wide variety of phenyl compounds from several chemical manufacturers, believing that the phenyl group in phenobarbital was somehow responsible

for its efficacy. Only Parke, Davis and Company responded. They provided 19 analogues of phenobarbital, all of which had been found to be inactive as hypnotics. Putnam screened these, as well as over a hundred other available chemicals. A few were active but, with one exception, were too toxic for clinical use. The exception was one of the Parke, Davis and Company compounds, phenytoin, which was more effective in protecting cats from electrically induced convulsions than even phenobarbital. As it was known to have no hypnotic or other untoward effects, this seemed to be just what Putnam had been seeking.

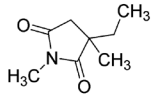
Putnam gave phenytoin to Houston Merritt for clinical evaluation in 1936. The first patient to receive the drug had suffered from seizures every day for many years, but as soon as his treatment began these ceased permanently. Subsequent studies confirmed that phenytoin was at least as effective as phenobarbital, with the added advantage of causing less sedation.[87] Paradoxically, this absence of marked sedation initially prejudiced many physicians against accepting the new drug!



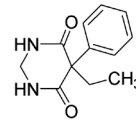
phensuximide



methsuximide



ethosuximide



primidone

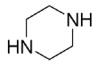
After the Second World War ended, Parke, Davis and Company initiated a major research project to find a less toxic drug to replace Abbott's troxidone in petit mal. This involved the synthesis and testing of over 1000 aliphatic and heterocyclic amides. This resulted in the discovery of three useful anticonvulsants, namely phensuximide,[88] methsuximide[88] and ethosuximide. The last of these was originally synthesised in 1927[89] and was put on the market in 1958. It remains in use for the treatment of petit mal absence seizures in children.

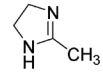
ICI scientists also tried to find improved anticonvulsants in the early 1950s. Herbert Carrington at the company's research laboratories in Manchester considered that the new hydantoins being developed by Parke, Davis and Company, although relatively free of sedating properties, produced too many side effects. Barbiturates, in contrast, were usually free from these, but instead caused sedation. However, as not all sedating barbiturates were anticonvulsants, Carrington concluded that it should be possible to find a barbiturate analogue in which this separation of activity was reversed. This led on to the development of primidone by Charles Vasey and William Booth.[90] It was given its first clinical trial in 1952 and results were satisfactory in grand mal epilepsy.[91] How much of its efficacy is due to phenobarbital formed from it and how much is due to unchanged primidone is uncertain, but primidone is prescribed when neither phenytoin nor carbamazepine is acceptable.

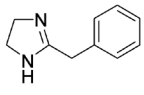
IMIDAZOLINES

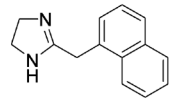
Piperazine was synthesised at the University of Breslau in 1888 by Alfred Ladenburg.[92] When he discovered that it formed a soluble salt with uric acid, he suggested that this might dissolve the deposits of uric acid that caused much pain in patients with gout.[93] Piperazine was immediately marketed for this purpose and remained in use well into the twentieth century

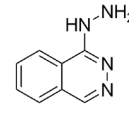
despite repeated criticism on the grounds that it was ineffective. The same situation arose with 2-methylimidazoline, which Ladenburg synthesised in 1894.[94] After clinical studies were conducted at his suggestion, it was marketed for the treatment of gout on the grounds that it dissolved uric acid.


piperazine


methylimidazoline


tolazoline


naphazoline


hydralazine

In 1935, Henry Chitwood and Emmet Reid at the Chemistry Department in Johns Hopkins University decided to reinvestigate 2-methylimidazoline and its homologues.[95] Only the methyl homologue had any effect on the acidity of the urine, a pointer to increased excretion of uric acid – which was the usual mode of action of drugs that relieved gout. Toxicity decreased as the methyl group was replaced with longer alkyl groups. As this was the reverse of the tendency usually found in a series of homologues, it prompted researchers at the Ciba laboratories in Basle to re-examine the series of compounds. They obtained the opposite effect so far as the influence of chain length on toxicity was concerned, contradicting the earlier claims. In the course of this investigation of the toxicity of imidazolines, a drop in blood pressure caused by dilation of peripheral blood vessels was observed. When Ciba chemists introduced cyclic substituents such as benzene and naphthalene rings at the 2-position of the imidazoline ring, the toxicity decreased. The most potent of these compounds, tolazoline,[96] was found to have weak adrenergic blocking activity and was introduced clinically.[97] Its use had to be limited to the treatment of Raynaud's disease and certain spastic vascular disorders since it stimulated the heart. Unexpectedly, the naphthyl analogue increased blood pressure by acting as a vasoconstrictor. It was introduced into clinical practice in the early 1940s as a long-acting nasal decongestant called 'naphazoline'.

In an expansion of their studies on imidazolines, Ciba researchers investigated other heterocyclic compounds containing two nitrogen atoms. A series of phthalazines were found to be active in screens for hypotensive activity, from which hydralazine emerged as a long-acting peripheral dilator.[98] It became the first orally active peripheral vasodilator to be introduced for the treatment of high blood pressure. With regular use, patients experienced side effects and became tolerant to it. As a result, other drugs superseded it. However, hydralazine became popular once again when it was found that tolerance was due to physiological compensatory mechanisms that could be overcome by combining it with a beta-blocker and a diuretic. Since the dose of hydralazine required in such a combination was smaller than that when used on its own, patients experienced fewer side effects. It continues to be widely used.

REFERENCES

1. S. Garfield, *Mauve: How One Man Invented a Colour that Changed the World*. London: Faber and Faber; 2000.

2. J.P. Swazey, *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation*. Cambridge, Massachusetts: The MIT Press; 1974, pp. 23–33.
3. F.F. Runge, Ueber einige Produkte der Steinkohlendestillation (*Poggendorff's*) *Ann. Phys. Chem.*, 1834; **31**: 65–78, and 1835; **32**: 308–33.
4. H.A. Kelly, Jules Lemaire: the first to recognise the true nature of wound infection, and the first to use carbolic acid in medicine and surgery. *J. Am. Med. Ass.*, 1901; **36**: 1083–8.
5. J.K. Crellin, The disinfectant studies by F. Crace Calvert and the introduction of phenol as a germicide. *Veroef. Int. Ges.Gesch. Pharm.*, 1966; **28**: 61.
6. F.C. Calvert, *C.R. Acad. Sci.*, 1859; **49**: 262.
7. F. Küchenmeister, *Deutsche Klinik am Eingange des zwanzigsten Jahrhunderts*, 1860; **12**: 123.
8. D.C. Schecter, H. Swan, Jules Lemaire: a forgotten hero of surgery. *Surgery*, 1991: **49**: 817–26.
9. R. Godlee, *Lord Lister*. London: Macmillan; 1917.
10. J. Lister, On a new method of treating compound fracture, abscess, etc. With observations on the conditions of suppuration. *Lancet*, 1867; **1**: 387–9.
11. A.E. Sansom, On the uses of septicidal agents in disease. *Retrospect. Med.*, 1868; **57**: 6–11.
12. A.E. Sansom, *The Antiseptic System: a Treatise on Carbolic Acid and its Compounds*. London: 1871, p. 324.
13. H. Bechhold, P. Ehrlich, Beziehungen zwischen chemischer Konstitution und Desinfektionswirkung – Ein Beitrag zum Studium der inneren Antisepsis. *Z. Physiol. Chem.*, 1906; **47**: 173.
14. H.J. Kolbe, E. Lautemann, Über die Constitution und Basicitat der Salicylsäure. *Ann. Chem.*, 1860; **115**: 157–9.
15. C.E. Buss, Über die Anwendung der Salicylsäure als Antipyreticum. *Deutsches Arch. Klin. Med.*, 1875; **15**: 457–501.
16. S. Stricker, Über die Resultate der Behandlung der Polyarthritis rheumatica mit Salicylsäure. *Berl. Klin. Wochenschr.*, 1876; **13**: 1–2, 15–16, 99–103.
17. T.J. MacLagan, The treatment of acute rheumatism by salicin and salicylic acid. *Lancet*, 1876; **1**: 342–3.
18. G. Sée, Études sur l'acide salicylique et les salicylates: traitement du rhumatisme aigu et chronique de la goutte, et de diverses affections du système nerveux sensitif par les salicylates. *Bull. Acad. Med. Paris*, 1877; **6**: 689, 897.
19. J.S. Goodwin, J.M. Goodwin, Failure to recognize efficacious treatments: a history of salicylate therapy in rheumatoid arthritis. *Persp. Biol. Med.*, 1981; **25**: 78–92.
20. M. Nencki, *Arch. Exp. Path. Pharmakol.*, 1886; **20**: 396.
21. H. Sahli, Ueber die Spaltung des Salols mit Rücksicht auf dessen therapeutische Verwerthung zu innerlichem und äusserlichem Gebrauch. *Therap. Monatsch.*, 1887: s. 333–9.
22. C.F. von Gerhardt, Untersuchungen über die wasserfreien organischen Säuren. *Annalen*, 1853; **87**: 149–79.
23. K. Witthauer, Aspirin, eine neues Salicylpräparat. *Die Heilkunde*, 1899; **3**: 396–8.
24. J. Wohlgemuth, Über Aspirin (Acetylsalicylsäure). *Therap. Monatshefte*, 1899; **3**: 276–8.
25. H. Dreser, Pharmacologisches über Aspirin (acetylsalicylsäure). *Pflüger's Archiv. Anat. Physiol.*, 1899; **76**: 306–18.
26. A. Schmidt, *Die industrielle Chemie in ihrer Bedeutung im Wetbild und Errinnerungen an ihren Aufban*. Berlin: De Gruyter; 1934, p. 775.
27. A. Eichengrün, 50 Jahre Aspirin. *Pharmazie*, 1949; **4**: 582–4.
28. W. Sneader, The discovery of aspirin: a reappraisal. *Br. Med. J.*, 2000; **321**: 1591–4.
29. J.R. Vane, Inhibition of prostaglandin synthesis as a mechanism of action for Aspirin-like drugs. *Nature New. Biol.*, 1971; **231**: 232–5.
30. G.J. Roth, P.W. Majerus, The mechanism of the effect of Aspirin on human platelets: 1. Acetylation of a particulate fraction protein. *J. Clin. Invest.*, 1975; **56**: 624–32.
31. P.C. Gibson, Aspirin in the treatment of vascular disease. *Lancet*, 1949; **2**: 1172–4.
32. L.L. Craven, Acetylsalicylic acid, possible preventive of coronary thrombosis. *Ann. West. Med. Surg.*, 1950; **4**: 95.
33. L.L. Craven, Experiences with aspirin (acetylsalicylic acid) in the non-specific prophylaxis of coronary thrombosis. *Miss. Valley Med. J.*, 1953; **75**: 38–44.
34. H.J. Weiss, L.M. Aledort, Impaired platelet-connective-tissue reaction in man after aspirin ingestion. *Lancet*, 1967; **2**: 495–7.
35. P.C. Elwood, A.L. Cochrane, M.L. Burr, *et al.*, A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. *Br. Med. J.*, 1974; **1**: 436–40.
36. C.V. Winder, J. Wax, L. Scott, *et al.*, Anti-inflammatory, antipyretic and antinociceptive properties of *N*-(2,3-xylyl)anthranilic acid (mefenamic acid). *J. Pharmacol. Exp. Ther.*, 1962; **138**: 405–13.

37. C.V. Winder, J. Wax, B.S. Querubin, *et al*., Anti-inflammatory and antipyretic properties of *N*-(alpha,alpha,alpha-trifluoro-*m*-tolyl) anthranilic acid (CI-440; flufenamic acid). *Arthritis Rheum*., 1963; **6**: 36–47.
38. A.R. Sallmann, The history of diclofenac. *Am. J. Med*., 1986; **80** (Suppl. 4B): 29–33.
39. J. Hannah, W.V. Ruyle, H. Jones, *et al*., Novel analgesic–antiinflammatory salicylates. *J. Med. Chem*., 1978; **21**: 1093–100.
40. F. Bernheim, The effect of salicylate on the oxygen uptake of the tubercle bacillus. *Science*, 1940; **92**: 204.
41. A.K. Saz, F. Bernheim, Effect of 2,3,5-triiodobenzoate on growth of tubercle bacilli. *Science*, 1941: **93**; 622–3.
42. Cited in F. Ryan, *Tuberculosis: The Greatest Story Never Told*. Bromsgrove: Swift; 1992, p. 244.
43. J. Lehmann, Para-aminosalicylic treatment of tuberculosis. *Lancet*, 1946; **1**: 15–16.
44. O. Schmiedeberg, Über die pharmakoligischen Wirkungen und therapeutischen Anwendung einiger Carbaminosäuren. *Arch. Exp. Path. Pharmakol*., 1886; **20**: 203–16.
45. K. Laubenheimer, *Phenol und seine Derivate als Desinfektionsmittel*. Berlin: Urban Schwartzenberg; 1909.
46. E.G. Klarmann, V.A. Shternov, L.W. Gates, *J. Lab. Clin. Med*., 1934; **19**: 835.
47. L. Colebrook, M. Kenny, Treatment of human puerperal infections, and of experimental infections in mice, with Prontosill. *Lancet*, 1936; **1**: 1279–86.
48. US Pat. 1941: 2250480 (to Burton T. Bush).
49. H.C. Powell, O. Swarner, L. Gluck, P. Lampert, Hexachlorophene myelinopathy in premature infants. *J. Pediat*., 1973; **82**: 976–81.
50. J. Liebig, *Annalen*, 1832; **1**: 182.
51. T.C. Butler, The introduction of chloral hydrate into medical practice. *Bull. Hist. Med*., 1970; **44**: 168–72.
52. R. Buchheim, *Arch. Path. Anat*., 1872; **56**: 1.
53. O. Liebreich, Das Chloral, ein neues Hypnotikum und Anästhetikum. *Berl. Klin. Wochenschr*., 1869; **6**: 325.
54. O. Liebreich, *Das Chloralhydrat, ein Neues Hypnotikum*. Berlin: G.F.O. Müller; 1869.
55. J.F. von Mering, F. Musculus, *Ber*., 1875; **8**: 662.
56. T.C. Butler, *J. Pharmacol. Exp. Ther*., 1948; **9**2: 49.
57. B. Hems, R.M. Atkinson, M. Early, E.G. Tomich, Trichloroethyl phosphate. *Br. Med. J*., 1962; **1**: 1834.
58. J.F. von Mering, *Pharm. Central*., 1889; **484**: 494.
59. E. Baumann, *Ber*., 1885; **18**: 883.
60. A. Kast, Sulfonal, ein Neues Schlafmittel. *Berl. Klin. Wochenschr*., 1888; **25**: 309–14.
61. E. Fischer, J. von Mering, Über eine neue Klasse von Schlafmitteln. *Therap. Gegenw*., 1903; **44**: 97.
62. Ger. Pat. 1910: 225710 (to F. Bayer & Co.).
63. M. Conrad, M. Guthzeit, Über Barbitursäure-derivate. *Ber*., 1882; **15**: 2844.
64. G.B. Kauffman, Adolf von Baeyer and the naming of barbituric acid. *J. Chem. Educ*., 1980; **57**: 222.
65. G.W. Collins, P.N. Leech, The indispensable uses of narcotics. Chemistry of barbital and its derivatives. *J. Am. Med. Ass*., 1931; **96**: 1869.
66. E. Fischer, A. Dilthey, Ueber C-Dialkylbarbitursäuren und über die Ureide der Dialkylessigsäuren. *Annalen*, 1904; **335**: 334–68.
67. R. Adams, C. Marvel, Organic chemical reagents. VI. Reagents from *n*-butyl alcohol. *J. Am. Chem. Soc*., 1920; **42**: 310–20.
68. A. Dox, L. Yoder, Some derivatives of normal-butyl-malonic acid. *J. Am. Chem. Soc*., 1922; **44**: 1578–81.
69. H.A. Shonle, A. Moment, Some new hypnotics of the barbituric acid series. *J. Am. Chem. Soc*., 1923; **45**: 243–9.
70. E. Tagmann, E. Sury, K. Hoffmann, *Helv. Chim. Acta*, 1952; **35**: 1541.
71. US Pat. 1958: 2848455 (to Ciba).
72. R. Cash, A.J. Brough, M.N.P. Cohen, P.S. Satoh, Aminoglutethimide (Elipten–Ciba) as an inhibitor of adrenal steroidogenesis: mechanism of action and therapeutic trial. *J. Clin. Endocrin. Metab*., 1967; **27**: 1239–48.
73. C.T. Griffiths, T.C. Hall, Z. Saba, Preliminary trial of aminoglutethimide in breast cancer. *Cancer*, 1973; **32**: 31–7.
74. W. Kunz, H. Keller, H. Muckter, *N*-Phthalyl-glutaminic imide. *Arzneimittel.-Forsch*., 1956; **6**: 426–30.
75. Sunday Times Insight Team, *Suffer the Children. The Story of Thalidomide*. London: Andre Deutsch; 1979.

76. P.C. Oré, Études cliniques sur l'anesthésie chirurgicale par la methode des injections de chloral dans les veines. *Bull. Soc. Chir. (Paris)*, 1872; **1**: 400.
77. P.C. Oré, *Études Cliniques sur l'Anesthésie Chirurgicale par la Methode des Injections de Chloral dans les veines*. Paris: J.B. Baillie; 1875.
78. I. Kissin I, A.J. Wright, The introduction of Hedonal: a Russian contribution to intravenous anesthesia. *Anesthesiology*, 1988; **69**: 242–5.
79. D. Bardet, G. Bardet, Contribution l'étude des hypnotiques ureiques. Action et utilisation du diethyl-diallyl-barbiturate de diethylamine, *Bull. Gen. de Therap.*, 1921; **172**: 173.
80. Br. Pat. 1931: 401693 (to I.G. Farben).
81. H. Weese, W. Scharpff, Evipan, ein neuartiges Einschlafmittel. *Deut. Med. Wochenschr.*, 1932; **58**: 1205.
82. D.L. Tabern, E.H. Volwiler, Sulfur-containing barbiturate hypnotics. *J. Am. Chem. Soc.*, 1935; **57**: 1961–3.
83. T.W. Pratt, A.L. Tatum, H.R. Hathaway, R.M. Waters, Preliminary experimental and clinical study. *Am. J. Surg.*, 1936; **31**: 464.
84 J.S. Lundy, Intravenous anesthesia: preliminary report of the use of two new thiobarbiturates. *Proc. Staff Meet. Mayo Clinic*, 1935; **10**: 534–43.
85. Ger. Pat. 1911: 247952 (to F. Bayer & Co.).
86. A. Hauptmann, Luminal bei Epilepsie. *Munch. Med. Wochenschr.*, 1912; **59**: 1907.
87. T.J. Putnam, in *Discoveries in Biological Psychiatry*, eds F. Ayd and B. Blackwell, Philadelphia: Lippincott; 1970.
88. C.A. Miller, L. Anticonvulsants. I. An investigation of *N*-*R*-α-*R*1-α-phenylsuccinimides. *J. Am. Chem. Soc.*, 1951; **73**: 4895–8.
89. S.S.G. Sircar, The influence of groups and associated rings on the stability of certain heterocyclic systems. Part II. The substituted succinimides. *J. Chem. Soc.*, 1927: 1252.
90. Br. Pat. 1952: 666027 (to ICI).
91. J.Y. Bogue, H.C. Carrington, The evaluation of Mysoline – a new anticonvulsant drug. *Br. J. Pharmacol.*, 1953; **8**: 230–6.
92. A. Ladenburg, *Ber.*, 1888: **21**: 758.
93. F.S. Kipping, Ladenburg Memorial Lecture. *J. Chem. Soc.*, 1913: 1871–95.
94. A. Ladenburg, *Ber.*, 1894; **27**: 2952.
95. H. Chitwood, E. Reid, Some alkyl-glyoxalidines. *J. Am. Chem. Soc.*, 1935; **57**: 2424–6.
96. M. Hartmann, H. Isler, Chemische Konstitution und pharmakologische Wirksamkeit von in 2-Stellung substituierten Imidazolinen. *Arch. Exp. Path. Pharm.*, 1939; **192**: 141.
97. R. Meier, R. Müller, *Schweiz. Med. Wochenschr.*, 1939; **69**: 1271.
98. J. Druey, B.H. Ringier, Hydrazinederivate der Phthalazin- und Pyridazinreihe. *Helv. Chim. Acta*, 1951; **34**: 195–210.