

# Early drug discovery and the rise of pharmaceutical chemistry

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Studies in the field of forensic pharmacology and toxicology would not be complete without some knowledge of the history of drug discovery, the various personalities involved, and the events leading to the development and introduction of new therapeutic agents. The first medicinal drugs came from natural sources and existed in the form of herbs, plants, roots, vines and fungi. Until the mid-nineteenth century nature's pharmaceuticals were all that were available to relieve man's pain and suffering. The first synthetic drug, chloral hydrate, was discovered in 1869 and introduced as a sedative-hypnotic; it is still available today in some countries. The first pharmaceutical companies were spin-offs from the textiles and synthetic dye industry and owe much to the rich source of organic chemicals derived from the distillation of coal (coal-tar). The first analgesics and antipyretics, exemplified by phenacetin and acetanilide, were simple chemical derivatives of aniline and *p*-nitrophenol, both of which were byproducts from coal-tar. An extract from the bark of the white willow tree had been used for centuries to treat various fevers and inflammation. The active principle in white willow, salicin or salicylic acid, had a bitter taste and irritated the gastric mucosa, but a simple chemical modification was much more palatable. This was acetylsalicylic acid, better known as Aspirin®, the first blockbuster drug. At the start of the twentieth century, the first of the barbiturate family of drugs entered the pharmacopoeia and the rest, as they say, is history. Copyright © 2011 John Wiley & Sons, Ltd.

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## Introduction

The word 'drug' is probably of Arabic origin and first appeared in Old German as *drög*, referring to a type of powder.<sup>[1]</sup> Indeed, the first pharmaceuticals were obtained from the vegetable kingdom as the dried parts of plants, herbs, and shrubs. According to Wikipedia, the etymology of the word 'drug' is the Old French word *drogue* or the Dutch word *droog*, both of which refer to dry barrels containing herbs.

Nature has provided a rich source of pharmacologically active chemical substances produced by plants, fungi, insects, and reptiles.<sup>[2,3]</sup> Biosynthesis of these natural toxins functioned as a chemical self-defence mechanism and protected the species from being eaten by predators. Accordingly, these xenobiotics have been around since the dawn of history. The first human beings, in their continuous quest for food and survival, must have experienced the effects of these substances, for better or for worse.<sup>[4]</sup> Crude extracts from wild plants and shrubs constituted the first herbal medicines that were used for the relief of pain and suffering, to heal wounds, and to treat all types of maladies. Foremost among these natural products was the juice obtained from the opium poppy plant (*papaver somniferum*) dating from ~3000 BC that contained the all powerful painkiller, morphine.<sup>[5–7]</sup>

Perhaps the earliest written record of medical therapeutics is contained in the famous *Ebers papyrus*, a 20-metre-long, 110-page medical scroll, named after the German Egyptologist Georg Ebers, who acquired it in 1872 (Figure 1). The *Ebers papyrus* described hundreds of treatments for the many ailments inflicting ancient Egyptians ~1500 BC. These were prepared by mixing together various herbs, shrubs, leaves, minerals, and animal excreta.<sup>[1]</sup> These recipes and concoctions represented the earliest record of medicines in the ancient world and must have had a strong influence on later generations when knowledge of herbal products

became more organized, as evidence by Greek, Roman, and Indian cultures, as well as traditional Chinese medicine.<sup>[4,8]</sup>

## Nature's pharmaceuticals

Examples of pharmacologically active substances derived from plants include morphine from opium poppy, nicotine from the tobacco plant, cannabinoids from cannabis leaves, caffeine from tea and coffee, cardiac glycosides (digoxin and digitoxin) from woolly foxglove, quinine from the cinchona tree, and salicylates from the bark of the white willow tree.<sup>[8]</sup>

The first hunters learnt the trick of spiking their darts and arrows with plant toxins (poisons), such as curare to kill or stupefy wild animals.<sup>[9]</sup> The word 'toxicology' derives from the Greek word *toxikos*, which literally referred to a bow for shooting arrows.<sup>[10]</sup> Other psychoactive substances known since ancient times and which were popular in certain cultures included cocaine from coca leaves, psilocybin from mushrooms, mescaline from the peyote cactus, to name just a few.<sup>[11–13]</sup>

The isolation and characterization of the active principles in medicinal plants represented a major challenge for analytical chemists and apothecaries of the time. Morphine was the first plant alkaloid isolated in a pure state by a 23-year-old apothecary named Friedrich Wilhelm Sertürner (1783–1841). While working as an apprentice to a pharmacy in Einbeck, Germany, in 1805,

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**Figure 1.** Page from the Ebers papyrus an Egyptian medical scroll dating from ~1500 BC, which gives instructions how to prepare hundreds of purported herbal medicines and cures.

Sertürner isolated meconic acid from raw opium. The following year he obtained a substance with the properties of a weak base.<sup>[11]</sup> When this base was administered to a dog, the animal fell into a deep sleep and Sertürner felt that he had discovered *der eigentliche betäubende Grundstoff* of raw opium (the specific narcotic element of opium).<sup>[11]</sup> The new substance was christened 'morphine' after *Morpheus* the Greek god of dreams.<sup>[10]</sup> Sertürner tested the pharmacological effects on himself and some young friends and took unusually large doses (1.5 grains ~100 mg in three divided doses).<sup>[11]</sup> Not long afterwards other alkaloids were isolated from opium, including codeine and papaverine.

When available in a pure form, the pharmacological activity and toxicity of these alkaloids increased considerably and many were deadly poisons.<sup>[14]</sup> These toxins were incriminated in crimes of murder by poisoning and development of suitable methods for extraction and identification of the poison in biological specimens marked the beginning of forensic pharmacology and toxicology.<sup>[9,15]</sup>

## Animal chemistry and pharmacology

Apothecaries probably represent the first pharmaceutical chemists charged with mixing and dispensing all kinds of herbal remedies in the hope of finding a cure for their customer's medical complaints. Foremost among the early apothecaries was the Swede Carl Wilhelm Scheele (1742–1786), who is known and admired by all historians of chemistry as a veritable pioneer.<sup>[16]</sup> Another pioneer chemist was Jöns Jacob Berzelius (1779–1848), who was born in the vicinity of Linköping in Sweden, and made enormous contributions to the chemical sciences, even writing the first book on animal (physiological) chemistry.<sup>[17,18]</sup>

By the mid-1800s, German scientists began to dominate the field of analytical and organic chemistry, with such luminaries as

Friedrich Wöhler (1800–1882), famed for the synthesis of urea 'without the help of a kidney' simply by heating ammonium cyanate.<sup>[19]</sup> A contemporary, close friend and sometimes scientific rival of Wöhler was the celebrated Justus von Liebig (1803–1873), whose chemical discoveries are legendary. Liebig is considered by many as the founding father of organic and clinical chemistry (Figure 2).<sup>[20]</sup>

The subject of pharmacology (*Materia Medica*) was established as a scientific discipline in the latter half of the nineteenth century by people such as Rudolf Buchheim (1820–1879), Oswald Schmiedeberg (1838–1921), Paul Ehrlich (1854–1915), and Henry Dale (1875–1968).<sup>[11]</sup> Another venerable pioneer in pharmacology and toxicology was Louis Lewin (1850–1929), who was one of the founding fathers of psychopharmacology as evidenced by his many published papers and the textbook *Phantastica*.<sup>[21]</sup> He also wrote the first book devoted to adverse drug reactions.<sup>[22]</sup>

## Alkaloids

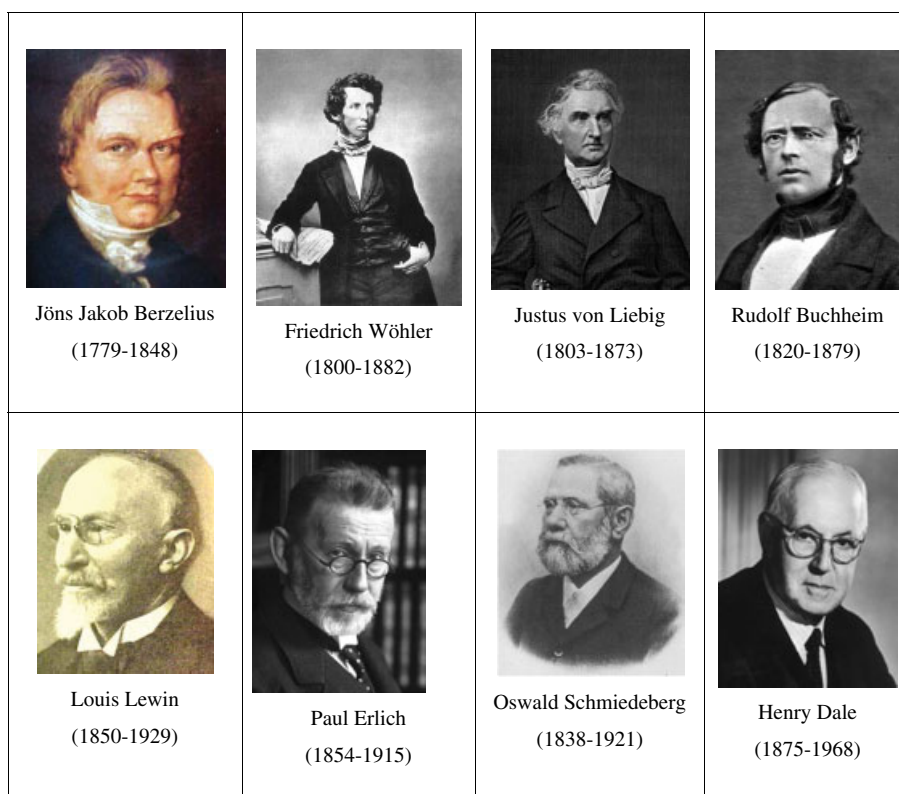
The word 'alkaloid' (Figure 3) was coined in 1819 by a German chemist Carl F. Wilhelm Meissner (1792–1853) and this class of organic compounds played a prominent role in the development of forensic toxicology as a scientific discipline.<sup>[23]</sup> These bitter-tasting (alkaline) substances produced by nature contain one or more nitrogen atoms in the molecule and are deadly poisonous in a pure state.<sup>[24]</sup> One notorious alkaloid, strychnine, derived from the plant *strychnos nux-vomica* has been implicated in murder by poisoning in many criminal prosecutions.<sup>[14]</sup> The complex chemical structure of alkaloids meant they were difficult to extract from body organs and tissue, a daunting task for the first analytical chemists. Without being able to extract and identify a poison from the body, it was not possible to prove its use in the crime of murder.

A major preoccupation of analytical chemists and early toxicologists was to develop methods that allowed the identification of plant alkaloids in blood and human viscera as evidence of poisoning. Foremost among these pioneers was Mathieu JB Orfila (1787–1853), born on the Spanish island of Minorca but who lived and worked in Paris as Professor of Medical Jurisprudence and later Dean of the Medical Faculty.<sup>[25]</sup> Orfila is considered as the father of forensic toxicology as a scientific discipline and he also wrote the first textbook on drugs and poisons in 1814 (Figure 4).<sup>[26]</sup> Many of the first forensic chemists and toxicologists began their careers by visiting and studying under Orfila. These individuals included Jean-Servais Stas (1813–1881) in Belgium,<sup>[27]</sup> Robert Christison (1797–1882) in Scotland,<sup>[28]</sup> and Alfred Swaine Taylor (1806–1880) from London.<sup>[29]</sup>

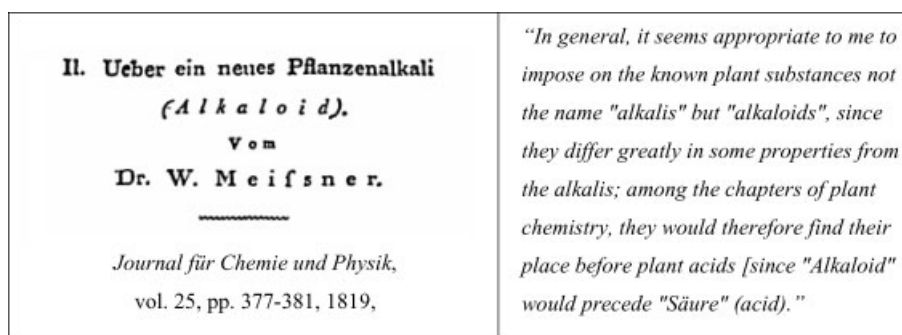
Examples of common alkaloids and their botanical plant origin include morphine (*papaver somniferum*), LSD (*ergot fungus*), emetine (*cephaelis ipecacuanha*) strychnine (*strychnos nux-vomica*), physostigmine (*calabar beans*), scopolamine (*scopolia carniolica*), atropine (*atropa belladonna*), ricinine (*castor oil beans*), and coniine (*spotted hemlock*).

## The first synthetic drugs

The doyen among German organic chemists during much of the nineteenth century was Justus von Liebig (1803–1872), the renowned Professor of Chemistry in Munich.<sup>[30]</sup> One of his many discoveries was the volatile liquid chloroform (CHCl<sub>3</sub>), which



**Figure 2.** Some early scientific luminaries in the field of chemistry, pharmacology, and toxicology.



**Figure 3.** Title of Meissner's article in which he coined the word 'alkaloid' and his reasoning for the choice of this word.

later became important as a general anesthetic drug. The use of chloroform as a volatile anesthetic in surgery is credited to a Scottish physician James Young Simpson (1811–1870). Simpson demonstrated the benefits of chloroform to deaden the pain associated with child birth and one of his first patients in 1872 was none other than Queen Victoria of England.<sup>[11]</sup>

In 1832, Liebig also prepared chloral hydrate and showed that in alkaline solution it was converted into chloroform and formic acid. This prompted the German physician and pharmacologist Oscar Liebreich (1839–1908) to investigate whether the same reaction might occur directly in the blood, which would mean that chloral hydrate might also be useful anesthetic in the same way as chloroform.<sup>[11]</sup> The results of these investigations were reported in a classic monograph (Figure 5).

Administration of chloral hydrate to animals put them into a deep sleep, but without loss of pain sensation, which meant its pharmacological effects differed from that of chloroform. Further

studies showed that chloral hydrate was a relatively safe sleeping aid (hypnotic) and entered the pharmacopeia as early as 1869 and still exists today (Noctec®) in some countries. Indeed, chloral hydrate was incriminated in the accidental death of the Playboy model Anna-Nicole Smith (1967–2007), who overdosed on a mixture of pharmaceuticals. Other early drugs used as sedative-hypnotic include bromide salts, paraldehyde, and urethanes, although these were made more or less redundant when the barbiturate class of drugs appeared in the first decade of the twentieth century.

## Barbiturates

Barbiturates represent a remarkable class of therapeutic agents and function as sleeping aids, anaesthetics, and anticonvulsants. They entered the pharmacopoeia in the first decade of the twentieth century.<sup>[31]</sup> The parent compound of barbiturates,

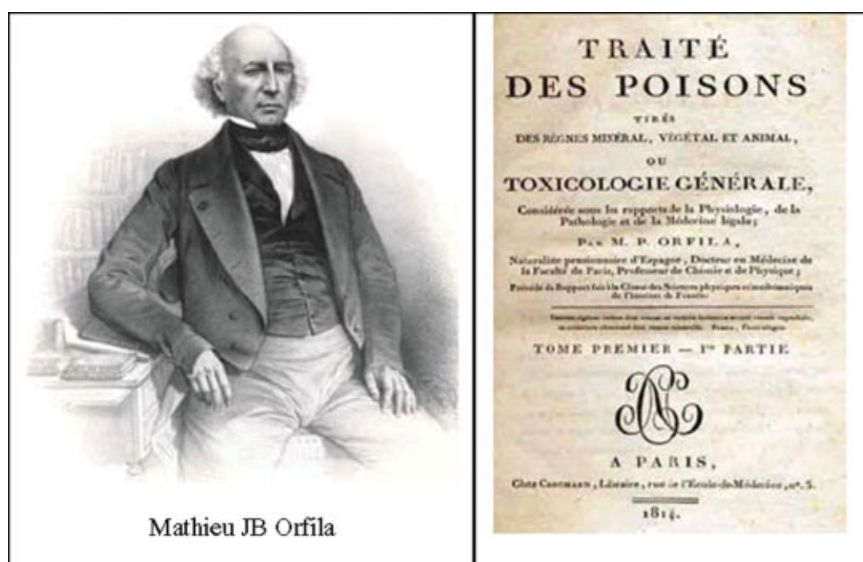


Figure 4. Portrait of Mathieu JB Orfila alongside the first page of his famous 1814 treatise on the general toxicology of poisons.

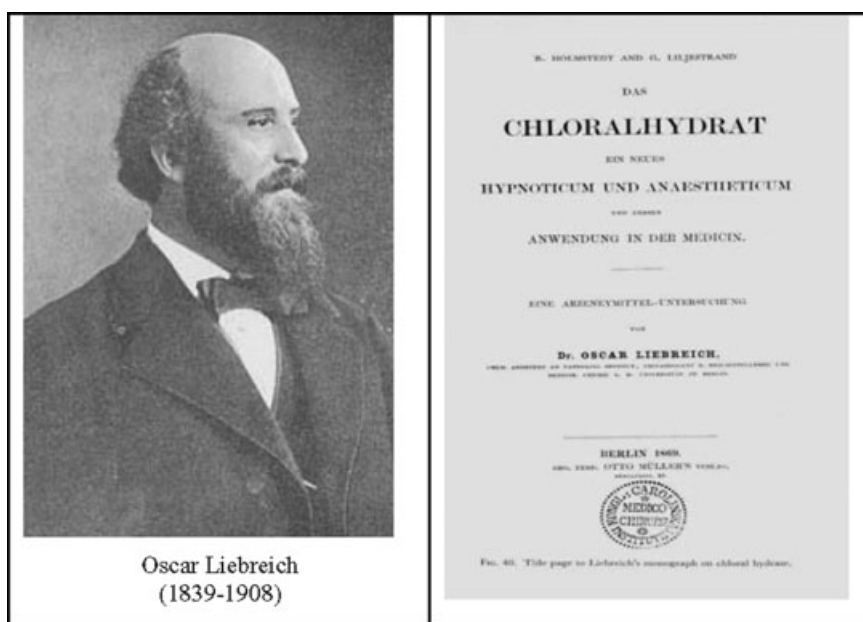


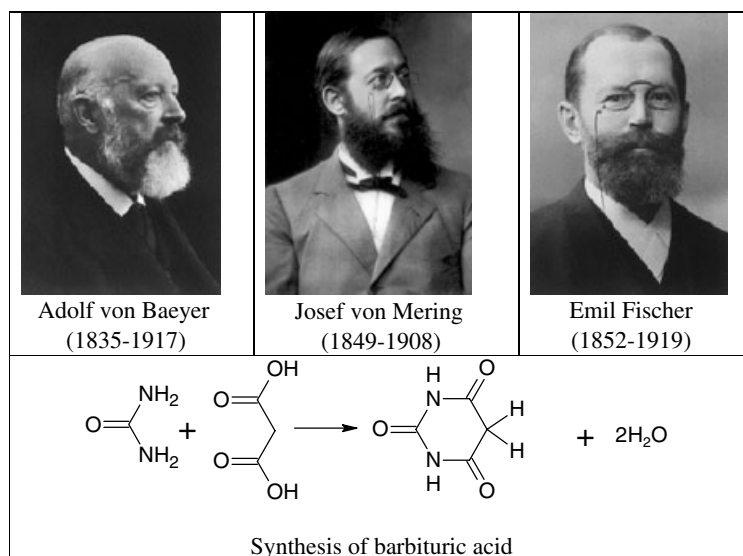
Figure 5. Portrait of Oscar Liebreich alongside the first page of his 1869 monograph on chloral hydrate and its use as a hypnotic.

barbituric acid, was synthesized in 1864 by Adolf von Baeyer (1835–1917) as part of research for his thesis (habilitation).<sup>[32]</sup> He reacted uric acid, an animal waste product, with malonic acid (from apples) to produce a new compound with empirical formula of  $C_4H_4N_2O_3$ , although its chemical structure was unknown at the time. The development of structural formulae, including aromatic and aliphatic rings, had to await the work of August Kekulé (1829–1896) from Germany<sup>[33]</sup> and Archibald Scott Couper (1831–1892) from Scotland.<sup>[34]</sup> In 1857–1858, more or less simultaneously, these structural chemists published novel ideas about the tetravalent nature of the carbon atom and its ability to self-link into chains and ring structures

The synthesis of barbituric acid was only a very small fraction of the many contributions to organic chemistry made by Adolf Von Baeyer and he justifiably received a Nobel Prize in 1905, mainly for

work he had done on synthetic indigo dyes.<sup>[35]</sup> Whether the name barbituric acid was coined in honour of a lady named Barbara that von Baeyer was allegedly dating at the time or if it comes from St Barbara the patron saint of artillery officers, we will never know.<sup>[36,37]</sup>

Later work showed that barbituric acid contained a 6-membered pyrimidine ring (Figure 6), although it was pharmacologically inactive, owing to the low pKa of 4.12, which meant that it was poorly absorbed from the gut. After the chemical structure of barbituric acid was elucidated, the physician and pharmacologist Josef von Mering (1849–1908) had the idea of replacing two adjacent hydrogen atoms in the pyrimidine ring with ethyl groups. He knew from earlier research that two alkyl groups bonded to the same carbon atom imparted pharmacological activity so he synthesized diethyl barbituric acid. With a higher pKa (7.9), this



**Figure 6.** Scientists credited with the development of barbiturates and the synthesis of barbituric acid by Adolf von Baeyer in a condensation reaction between urea and malonic acid.

diethyl derivative of barbituric acid was more easily absorbed from the gut, it had a greater solubility in lipids, which meant that it more easily crossed the blood-brain barrier.<sup>[38]</sup>

As von Mering was a pharmacologist and not a chemist, he contacted Emil Fischer (1852–1919), the acknowledged authority in organic chemistry in Germany at the time, and asked him to verify the structure and check the purity of the new compound.<sup>[39]</sup> Together with his students, Fischer succeeded in making a more potent derivative of barbituric acid, which he patented in 1903 under the trade name Veronal®, allegedly named after the peaceful Italian city of Verona.<sup>[40]</sup> Fischer and von Mering also conducted clinical trials with barbital as a sleeping aid and published their findings in 1903.<sup>[11,40]</sup> The success of barbital as a hypnotic led to the synthesis of scores of other derivatives of barbituric acid with the two hydrogen atoms on the 5,5-position of the pyrimidine ring being replaced with alkyl, aryl, allyl or aromatic groups. Many of these compounds were further developed into useful pharmaceutical products, notable phenobarbital (Luminal®) which appeared in 1909 and is still in use today as an anticonvulsant.<sup>[36–38]</sup>

After prescribing the barbiturate group of drugs on a large-scale, problems arose, with reports of acute toxicity when used as sleeping aids; there was a narrow margin between a therapeutic dose and a lethal dose.<sup>[41]</sup> Moreover, barbiturates carry a high abuse potential and some people develop tolerance and dependence on their medication. Toxicity is enhanced if taken together with other depressant drugs, such as alcohol.<sup>[41]</sup> Among other famous names, the pop star Jimi Hendrix (1943–1970) died from asphyxia after inhalation of vomit when sedated after a night of heavy drinking and the prescription sleeping aid Vesparax®, a mixture of two barbiturates, namely brallobarbitol and secobarbital, as well as a small amount of hydroxyzine.

The barbiturate family of drugs, without any shadow of a doubt, represented a major advance in pharmacotherapy and some, such as thiopental an intravenous anaesthetic agent (e.g. sodium pentothal), are still in use today. Thiopental is one of a three-drug cocktail used in connection with capital punishment by lethal injection in several US states.<sup>[42]</sup> The development of methods for

extraction, identification, and quantitative analysis of barbiturates in blood and liver tissue belong to classic procedures in the field of analytical and forensic toxicology.<sup>[43]</sup>

## The first analgesics and antipyretics

The first synthetic drugs and, indeed, the entire pharmaceutical industry can be traced to the manufacture of textiles and synthetic dyes, as exemplified by mauveine (mauve), which was discovered by a young British chemist William Henry Perkin (1838–1907).<sup>[44]</sup> One of the first German chemical firms to show an interest in pharmaceuticals was the Friedrich Bayer Company, founded in 1863, and originally located in Barmen, Germany (today in Leverkusen). The black sticky mass (tar) remaining after distillation of coal under a vacuum provided a rich source of aromatic chemicals, including benzene, naphthalene, phenol and aniline.<sup>[45]</sup>

An example of one of the many aromatic compounds derived from coal-tar was naphthalene, which was used as an intestinal antiseptic for, among other things, the irradiation of worms. When a patient with this condition who also happened to be suffering from a fever received naphthalene, the fever was cured but not the worms.<sup>[45]</sup> On closer inspection it turned out that the pharmacist had made a mistake and instead of naphthalene, another derivative of coal-tar, acetanilide (Figure 7) had been prescribed. This led the Bayer Company to develop and market acetanilide as the first synthetic antipyretic drug, which became known commercially as Antifebrin® (fever-reducing).

The success of Antifebrin prompted the Bayer Company to search for other chemicals in the waste products from the dye-works for possible use as pharmaceuticals. One such substance was *p*-nitrophenol, which was easily converted into the ethyl ester derivative of acetanilide (Figure 7) to give another commercial product phenacetin®. In 1887, the Bayer Company began to manufacture phenacetin® which eventually became more successful as an analgesic-antipyretic agent than acetanilide.<sup>[45]</sup> Another derivative of acetanilide prepared around the same time was *N*-acetyl-*p*-aminophenol (paracetamol), but as a commercial product this was overlooked in favour of phenacetin.

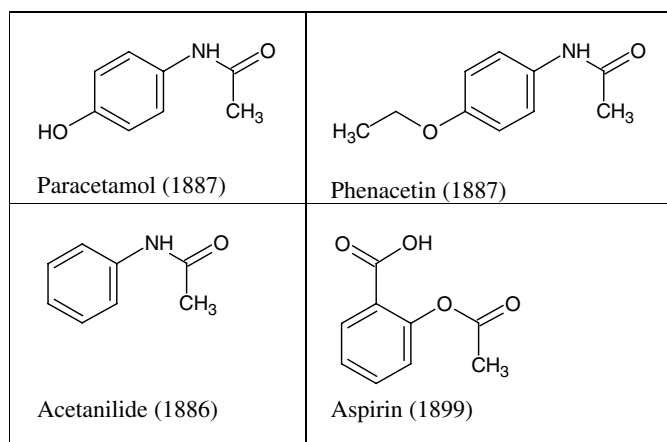


Figure 7. Chemical structures of early analgesic and anti-pyretic drugs.

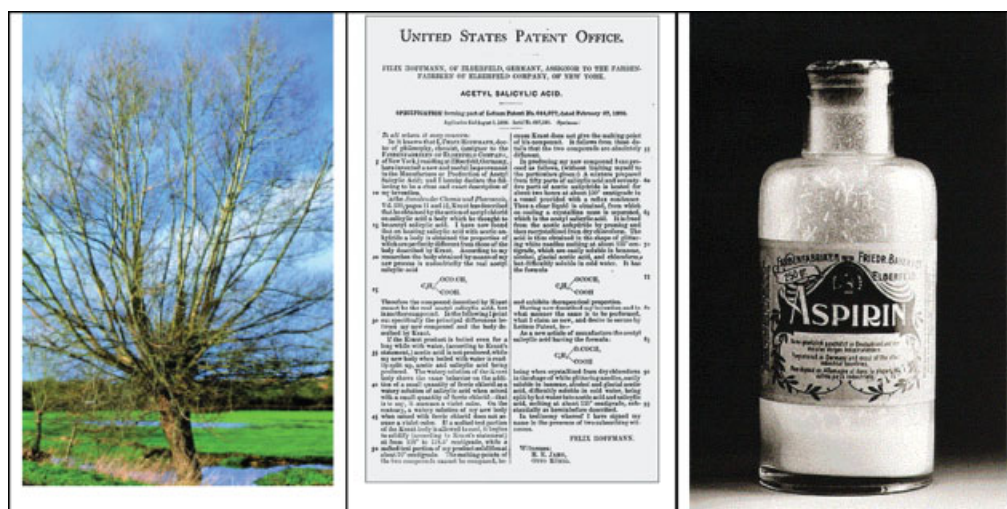


Figure 8. The white willow tree (*Salix alba*), the bark of which is rich in salicylates (left), US patent 1900 granted to Bayer's Felix Hoffmann for the synthesis of acetylsalicylic acid (middle) and an old bottle of aspirin (right).

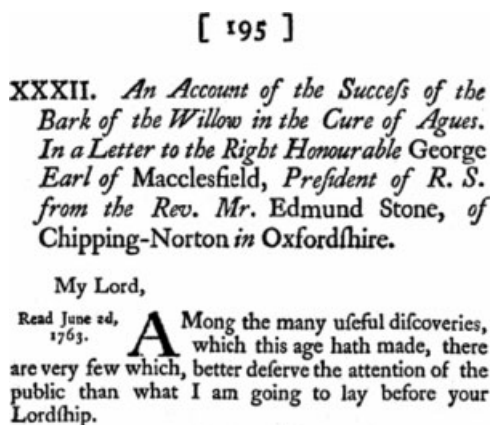
Phenacetin was not without its problems because some patients, after long-term use of the drug, developed a medical condition known as methemoglobinemia. The ability of red blood cells to distribute oxygen is lost and as a result the patient's skin turns a blue-purple color (cyanosis). This problem was investigated by two Americans, namely Julius Axelrod (1912–2004) and Bernard B Brodie (1907–1989) who identified aniline, a minor metabolite of phenacetin, as the cause of the problem.<sup>[45]</sup> Another metabolite they identified was *N*-acetyl-*p*-aminophenol, better known today as acetaminophen (USA) or paracetamol (Europe), which retained the antipyretic and analgesic properties of the parent drug but was lacking the methemoglobinemia side-effect.<sup>[45]</sup>

In the 1950s, a small US drug firm, McNeil laboratories, began to develop *N*-acetyl-*p*-aminophenol as a new pharmaceutical product, named Tylenol Elixir.<sup>[45]</sup> This liquid formulation was especially suitable for children and the elderly and was approved for this purpose by the Food and Drug Administration (FDA) in 1955. Shortly afterwards, Tylenol was also manufactured in tablet form (500 mg), becoming a blockbuster drug available over-the-counter and found in bathroom cabinets of virtually every home.

## Aspirin - a wonder drug

This historical account of early drug discovery of mild analgesics and antipyretics would not be complete without mentioning acetylsalicylic acid, better known around the world as Aspirin®. Aspirin was marketed as a highly successful pharmaceutical product by the Bayer Company in 1897, although plant extracts rich in salicylates enjoy a much longer history and were used for the treatment of fevers and other ailments since ancient times.<sup>[46]</sup> Many plants, shrubs, and trees of the *Spiraea* genus contain salicin, a naturally occurring glycoside of salicyl alcohol, which after hydrolysis and oxidation gives salicylic acid.

The first well-documented clinical trial of salicylates in medicine is credited to an English clergyman, the Reverend Edward Stone (1702–1768).<sup>[47]</sup> Reverend Stone, who lived in Chipping Norton, Oxfordshire, had an inquisitive mind and was interested in the health and well-being of the rural community where he lived. He was well aware of the rumours that circulated for years about the curative properties of extracts of bark from the white willow, a tree that flourishes in wet or damp environments and grows close to river banks and streams in many countries (Figure 8). Willow-bark extracts had been used with great benefit in the treatment of a



**Figure 9.** Title and opening paragraph of the letter sent in 1765 by the Reverend Edward Stone to the Royal Society of London to inform them of the usefulness of extracts of willow bark as a cure for various fevers.

host of medical complaints, including aches and pains, fevers and chills.

Around 1763, Reverend Stone decided to undertake a scientific experiment to test the efficacy and curative properties of white willow bark (*Salix alba*) as a herbal medicine. In a clinical trial, he gave extracts of willow bark to a total of 50 patients suffering from agues (fevers), albeit without a control or placebo treatment, to verify any beneficial effects for this condition. The results were communicated to the Royal Society of London and published in its *Philosophical Transactions* (Figure 9), and this represented the first peer-reviewed documentation of the medicinal properties of willow bark. The article was entitled *An account of the success of the bark of the willow in the cure of agues*.<sup>[47]</sup>

During the first decades of the nineteenth century, French, Italian, and German chemists attempted to isolate the active principle contained in willow bark (salicin or salicylic acid), but the crude substances they obtained were not much better than the raw material, because of a lack of chemical purity.<sup>[48]</sup> In 1853, a French chemist Charles Frederic Gerhardt (1816–1856) heated an extract of willow bark with acetyl chloride and in this reaction he succeeded in producing, for the first time, acetylsalicylic acid.<sup>[49]</sup> However, the chemical structure of this derivative was unknown and acetylsalicylic acid was ignored as a potential therapeutic agent. A major breakthrough in research on salicylates occurred in 1860 when Hermann Kolbe (1818–1884), a Professor of Chemistry first in Marburg and later in Leipzig, discovered an efficient way to synthesize salicylic acid also establishing its correct structure.<sup>[50]</sup> By 1874, Kolbe, in association with his student Fredrich von Heyden, began to produce salicylic acid on an industrial scale and this synthetic product was much cheaper than that derived from willow bark.<sup>[49]</sup>

The Bayer Company, already the manufacturer of phenacetin, was naturally much interested in this rival compound salicylic acid and its sodium salt. Two of the movers and shakers in the development of Bayer's Aspirin® were Heinrich Dreser (1860–1924), who was head of pharmacology, and a young chemist Felix Hoffmann (1868–1946).<sup>[49,50]</sup> Legend has it that Hoffmann was inspired to make an improved form of salicylic acid because his father was a long-time sufferer of rheumatism and often complained about the bitter taste of his medicine and the irritation it caused to the mucosa surfaces of his stomach.<sup>[50]</sup> Hoffmann succeeded in preparing acetylsalicylic acid in a chemically pure form and on behalf of the Bayer Company

even filed a patent for the discovery, which was granted in 1899 in Germany and the following year in the USA (Figure 8).

The world-famous name Aspirin gets the 'a' from acetyl, the 'spir' from the Latin genus *spiraea*, the botanical name of the meadowsweet plant rich in salicin, and the 'in' was added as a common ending for drug names at the time.<sup>[49,51]</sup> Besides its usefulness for the treatment of rheumatic pain, headaches, and fever, aspirin has found many other medical uses, most notably as an anti-clotting agent and a prophylactic treatment for thrombosis and stroke.<sup>[52]</sup> Hundreds or even thousands of scientific articles appear each year dealing with one or other aspect of Aspirin and its usefulness in medicine and therapeutics.

## Concluding remarks

This account of early drug discovery has highlighted the human side of pharmacology including the various chemists, physicians and other scientists involved. To paraphrase the famous French chemist and microbiologist Louis Pasteur (1822–1895) *It is by reading what discoverers have done that we lift and maintain the sacred flame of discovery*.

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