Scanned and you know what that means!

One hundred years of aspirin

Lancet 1997; 350: 437-39

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August 10, 1997, marks the centenary of the first, and most commercially successful, synthetic drug the world has seen: acetylsalicylic acid (aspirin). Unlike many other centenaries, this is a time to look forward as well as back since acetylsalicylic acid has recently been given another lease of life and seems set to go into the next millennium with a new set of indications.

The early history of salicylates

Human beings have suffered from inflammatory rheumatic disease since ancient times. The Assyrians left behind stone tablets from the Sumerian period describing the use of willow leaves for this condition. The Egyptians were aware of 100-year-old pollarded willow trees the analgesic effects of a decoction of myrtle or willow leaves for joint pain and the Ebers papyrus has a very accurate description of an inflammatory condition: "When you examine a man with an irregular wound . . . and that wound is inflamed . . . [there is] a concentration of heat; the lips of that wound are reddened and that man is hot in consequence . . . then you must make cooling substances for him to draw the heat out . . . leaves of the willow". Other remedies were also advanced and the papyrus suggests alternatives such as onion crushed in honey and taken in beer; a poultice of chopped bat, wasp dung, and fresh milk; or application of a poultice containing a fragment of lead mixed with cat and dog dung. Dioscorides favoured coriander *(Coriandrum sativam)* whereas Hippocrates of Kos followed the Ancient Egyptians in recommending extract of willow bark.

The 18 19th century

Willow leaves and its bark, myrtle leaves, and a number of other plant extracts rely for their effect on the presence of the very simple organic acid, salicylic acid. The Reverend Edward Stone, from Chipping Norton, Oxfordshire, UK, is generally recognised as giving the first scientific description in 1763 of the beneficial effects of willow bark in a letter to the Earl of Macclesfield, President of The Royal Society, in which he describes successfully treating patients with ague (fever, usually taken to be malaria) with 20 grains (about 1 g) of powdered willow bark in a dram of water every 4 hours. Stone had become

interested in willow bark because, at least partly, of the ancient Doctrine of Signatures whereby the cause of disease offers a clue to its treatment. According to Stone: "As this tree delights in a moist or wet soil, where agues chiefly abound, the general maxim that many natural maladies carry their cures along with them or that their remedies lie not far from their causes was so very apposite to this particular case that I could not help applying it; and that this might be the intention of Providence here, I must own, had some - little weight with me"

However, the first proper clinical trial is usually credited to the Dundee physician, Thomas MacLagan, who took 2 g of salicin and, experiencing no ill-effects, gave it to patients with acute rheumatism. He obtained complete remission of the fever and joint inflammation. [3] MacLagan was also influenced by the Doctrine of Signatures for he wrote in his report to *The Lancet* in 1876:

It seemed to me that a remedy for that disease would most hopefully be looked for among those plants and trees whose favourite habitat presented conditions analogous to those under which the rheumatic miasma seemed most to prevail. A low-lying damp locality, with a cold rather than warm climate, gives the conditions under which rheumatic fever is most readily produced. On reflection, it seemed to me that plants whose haunts best corresponded to such a description were those belonging to the natural order Salicaceae, the various forms of willow. Among the Salicaceae, therefore, I determined to search for a remedy for acute rheumatism. The bark of many species of willow contains a bitter principle called salicin. This principle was exactly what I wanted.

In continental Europe, willow bark became much sought after when supplies of Peruvian bark stopped as a result of the continental blockade imposed by Napoleon at the beginning of the 19th century in his disastrous attempt to destroy British trade. In 1828, the professor of pharmacy at the University of Munich, Johann Andreas Buchner, managed to obtain a small amount of yellow material, salicin, by purifying an extract of willow bark. [4] A year later the French pharmacist, Henri Leroux, improved the purification process and obtained salicin in crystalline form for the first time.5 Soon after, in 1838, the Italian chemist, Raffaele Piria, showed that salicin was actually a glycoside and succeeded in splitting it to obtain salicylic acid. [6] Reports of the beneficial properties of salicylic acid spread quickly and demand grew. Hermann Kolbe, professor of chemistry at Marburg University, discovered its chemical structure and succeeded in synthesising it in 1859. This allowed salicylic acid to be produced on

an industrial scale and by 1874 a factory in Dresden was able to offer it for sale at a tenth of the price of material extracted from willow bark.'

However, salicylic acid, or strictly speaking its commercial form sodium salicylate, has unpleasant side-effects: most notably it irritates the stomach and many patients were unable to tolerate its unpleasant taste. One such patient was Herr Hoffmann, whose young son, Felix, was a chemist with Friedrich Bayer & Co, Elberfeld, Germany. Although it was principally a manufacturer of dyestuffs, Bayer had appointed a pharmacologist, Wilhelm Siebel, in 1890. Siebel was a former assistant to Robert Koch and he was interested in salicylatesj in 1892 he published an account of his investigations on Salophen. [8] Although Siebel had to retire from the company the following year because of tuberculosis, his salicylate research was helpful to the 29 year-old Felix who decided to try and help his father by modifying the structure of salicylic acid in an attempt to make it more easily tolerated.

Salicylic acid is simply a benzene ring with a phenol (HO) group at position 1 and a carboxylic acid (COOH) group at position 2. Earlier workers had experimented by changing the carboxylic acid group (eg, to an amide to give salicylamide), but Hoffmann decided to concentrate on the phenol group. After some experimentation, he managed, on August 10, 1897, to acetylate the phenol group and he obtained acetylsalicylic acid in a pure and stable form. However, this was not the first time the compound had been prepared. Charles Friedrich Gerhardt had made an impure form in Strasbourg in 1853, but the compound, being impure, was unstable and soon decomposed; it attracted no interest at the time. [9]

The head of the pharmacology laboratories of Bayer, Elberfeld, was Heinrich Dreser and he quickly tested Hoffmann's new compound on himself; he also set up a series of animal experiments—the first time this had been done in an industrial setting. He soon showed the anti-inflammatory and analgesic effects of the acetylsalicylic acid and reported his findings in 1899 in *Pflugers Archiv fur die gesamte Physiologie"2°* The compound was also tested on patients in the Deaconess Hospital, Halle an der Saale, and \ /COOH compared with salicylic acid. The senior doctor, Kurt Witthauer, was sceptical of the new drug because he had seen so many others launched with great expectations only for them to disappear quickly. However, acetylsalicylic acid was different and in his report he enthused: "The drug never failed in its effect on pain, inflammation or fever and there were no unpleasant effects on the heart or stomach, even in severely ill patients". [11]

Bayer was quick to recognise the potential of Hoffmann's discovery and the new compound was registered under the name "Aspirin" on Feb 1, 1899. The "a" came from acetyl and "spir" came from the first part of *Spirea ulmania,* the plant from which salicylic acid had originally been isolated. Interestingly, the first name proposed was "euspirin", following Bayer's enthusiasm at that time for taking its tradenames from the Greek. This suggestion was rejected because it was felt that "eu" was generally used to indicate an improvement in taste and smell.

Bayer quickly ran into problems with other companies making the original salicylic acid, but Bayer argued that if a physician actually wrote a prescription for "Aspirin" their product had to be dispensed by the pharmacist. Its addition to the trademark role of the Imperial Patent Office in Berlin (no 36433) on March 6, 1899, marked the start of its success. According to Sneader, Bayer circulated information about the new drug to more than 30 000 doctors—the first mass marketing of a pharmaceutical agent. [?] However, the German Patent Office refused to grant a patent for the acetylation of salicylic acid on the grounds that the process was not sufficiently novel. This decision had important consequences for Felix Hoffmann and Artur Eichengrun, the head of Bayer's chemical research laboratories, since both men had contracts by which they were to receive a royalty on any patentable product they invented, whereas Dreser's contract paid him a royalty on any product introduced. Hoffmann and Eichengrun received no royalties on the sale of aspirin in Germany, whereas Dreser retired early, a rich man.

The 20th century

In 1904, the original powder form of aspirin was replaced with a stamped tablet to allow exact dosage and prevent adulteration. The drug quickly became part of everyday life and it began to be mentioned in novels by authors such as Thomas Mann, Graham Greene, Edgar Wallace, Kafka, Ortega y Gasset, and Giovanni Guareschi. In 1950, aspirin earned a place in the *Guinness Book of Records* as the most popular painkiller in the world, and in 1969 the on-board first-aid cabinet of the Apollo spaceship that took the first US astronauts to the Moon contained Bayer Aspirin. In the USA about 35 000 kg aspirin is now consumed daily;' the corresponding figure for the UK is about 6000 kg.

The rise of aspirin was not entirely smooth and untroubled. At the end of World War I, Bayer lost its exclusive right to the name "Aspirin" when its property was sequestrated by the allies, and the US Patent Office cancelled Bayer's right to the name aspirin claiming it was improperly registered. When challenged by the company, the US Supreme Court ruled that Bayer Aspirin had been so widely advertised

that it had become a common name. Although the company's monopoly of the name was broken in the USA and the UK, it has remained a tradename in many other countries. The rights to the name Bayer Aspirin in the USA were bought by Sterling Drug Inc for $53 million in the 1920s and it was only when Bayer's US affiliate Miles bought the OTC business of Sterling Winthrop in 1994 that the German company was able to regain its right to the name aspirin in the USA.

The future

Unlike many centenarians, aspirin is not ready to retire. In fact, its future seems assured following the publication of numerous major trials showing its efficacy as an antiplatelet agent, [12] and in prevention of myocardial infarction, [13] stroke, [14] migraine, [15] dementia, [16] and even colon cancer." In April, 1997, over 300 researchers and journalists attended a major scientific symposium in Venice to review the latest data on this remarkable drug which seems poised to continue its blockbuster career well into the next century.

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A chronology of the salicylates

. Pre-lSth century

Described in the Ebers papyrus, by Hippocrates, Celsus, Pliny, Dioscorides , and Galen

The bark Salix alba 1763 *Rev* Edward Stone, Chipping Norton
Saix *latifolia* 1792 Samual James, surgeon, Hoddesdon
1798 William White, apothecary, Bath
1803 G Wilkinson, Sunderland

Pharmacology

Antipyretic 1763 Stone
Anti rheumatic 1874-76 MacLagan and Stricker Uricosuric 1877 See

Chemical structure

Salicin 1826-29 Leroux
Salicylic acid 1835-38 Lowig and Piria Synthesis 1860 Kolbe and Lautemann

Synthesis of impure acetyl salicylic acid 1853 Gerhardt

Synthesis of pure, stable acetyl salicylic acid 1897.

Salicylate. In common use at the start of the 20th century

Salicylic acid	Acidum salicylicum
Sodium salicylate	Natrium salicylicum
Salol, Phenylsalol Salolum,	Phenylum salicylicum
Salophen, Acetylamidosalol	Salophenum
Aspirin, acetylsalicylic acid	Aspirinum, Acidum
Salicylic acid methyl ester,	acetylosalicylicum
Oil of Wintergreen	Methylium salicylicum
Salit salicylic acid-borneol ester	Salitum, Borneolum
salicylicum	

(From Kobert *R.* Lehrbuch der Pharmakotherapie Stuttgart: Verlag