

HISTORY

Brief History of Antipyretic Therapy

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Both external cooling and pharmacotherapy have been used to treat fever since time immemorial. In the past century such treatments have proliferated at an astonishing rate. The COX-2 inhibitors are the most recent additions to the antipyretic pharmacopoeia. Additional research is needed to determine whether they represent an important new chapter in antipyretic therapy's long history or, for that matter, if the benefits of any currently available treatment for fever outweigh its cost.

The origin of antipyretic therapy is not known. When Alexander the Great was stricken with the mysterious febrile illness that would take his life in 323 BC, the Babylonian physicians who cared for him prescribed cool baths as treatment for his unremitting fever [1]. Preceding generations almost certainly used similar external cooling measures to relieve fever, as we still do to the present day [2].

Pharmacologic treatment of fever also extends deep into the human historical record. Stone tablets dating to the Sumerian period describe the use of willow leaves by Assyrian physicians to treat inflammatory rheumatic diseases [3]. The Ebers papyrus, which has been dated to circa 1500 BC, verifies that the ancient Egyptians were also aware of the antipyretic property of willow leaves and used them to treat various inflammatory disorders. According to the papyrus, when a "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." Hippocrates, almost certainly influenced by Egyptian medical doctrine, recommended the use of extracts of willow bark to alleviate the pain of childbirth and to reduce fever [4].

The leaves and the bark of the willow tree (figure 1), like myrtle leaves and a number of other plant extracts, contain salicylic acid. The early Romans apparently used such plants to treat pain and perhaps fever, as did the ancient Chinese and the early Native Americans and Southern African Hottentots [5].

The first scientific description of the clinical application of antipyretic plant extracts is generally attributed to the Reverend

Edward Stone [6], who in 1763 submitted a letter to the Royal Society of London describing the successful treatment of agues (an archaic term for malaria and other fevers) with extracts of willow bark. Stone, a proponent of the "doctrine of signatures," believed that cures for diseases were most likely found in the same places in which the diseases arose. Thus, he reasoned that because the willow "delights in a moist or wet soil, where agues chiefly abound, the general maxim that many natural maladies carry their cures along with them and that their remedies lie not far from their causes," [6] the willow tree might be a cure for agues. His suspicions were reinforced by the results of a study of 50 patients afflicted with ague, who under his care exhibited a favorable response to a preparation of pulverized willow bark.

In 1829 the French pharmacist Henri Leroux first isolated salicin in pure form from the common white willow and demonstrated its antipyretic property [7]. Nine years later, Raffaele Piria, an Italian chemist, hydrolyzed salicin to salicylic alcohol, which, upon further chemical manipulation, produced salicylic acid [8].

In 1874 Thomas MacLagan, a Scottish physician, conducted what is believed to have been the first formal clinical trial of salicin [9]. After personally consuming an estimated 2 g of the compound without apparent ill effect, he gave it to a patient with rheumatic fever. The patient's fever, pain, and inflammation subsided, thus confirming the antipyretic effect of salicylates, as well as their analgesic and anti-inflammatory effects.

That same year, 2 Germans, Kolbe and Lautemann, perfected a procedure for synthesizing salicylic acid commercially [3, 5]. Hermann Kolbe had discovered the chemical structure of salicylic acid, which he first synthesized almost 20 years earlier in 1859 while a professor of chemistry at Marburg University. As a result of his work with Lautemann, it became possible to produce salicylic acid on an industrial scale for one-tenth the cost of extracting it from willow bark [3].

In a relatively short time, sodium salicylate, the commercial

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Figure 1. Pollarded willow trees. Reprinted with permission from Jack [3].

form of salicylic acid, gained widespread popularity as a treatment for numerous inflammatory conditions, including rheumatic fever, rheumatoid arthritis, and gout [5]. Unfortunately, the compound was plagued by a number of unpleasant side effects, not the least of which were gastric irritation and an unpleasant taste. Because of these, many patients found the drug intolerable. One such patient was the father of a young

chemist by the name of Felix Hoffman (figure 2), then employed at Friedrich Bayer and Co. in Elberfeld, Germany. Although at that time Bayer was principally a manufacturer of dyestuffs, it was beginning to appreciate and capitalize on the pharmacologic properties of some of the by-products of its dye manufacturing process. Hoffman was but one of numerous talented chemists who helped launch Bayer's pharmaceutical program. His father, who had long suffered from arthritis, provided special impetus for him to focus his initial attention on salicylic acid in the hope of producing a more palatable derivative with which to relieve his father's suffering. In August of 1897 he succeeded in doing so by acetylating the compound's phenol moiety to produce acetylsalicylic acid (figure 3). Although Charles Friedrich Gerhart had produced a crude preparation of the same compound 15 years earlier in Strasbourg [10], Gerhart's impure compound was unstable and had therefore attracted little interest [3].

Heinrich Dreser (figure 2) was the head of the pharmacology laboratories at Bayer when Hoffman succeeded in synthesizing acetylsalicylic acid. He was well aware of the fact that acetylation of certain drugs could both enhance their efficacy and reduce their toxicity; earlier, he had succeeded in producing heroin by acetylating codeine and morphine [11]. Consequently, he was quick to recognize the vast potential of Hoffman's creation and registered the new drug under the name "Aspirin" on 1 February 1899 [5]. Dreser's reason for so naming the drug is uncertain. The most plausible explanation is that the initial

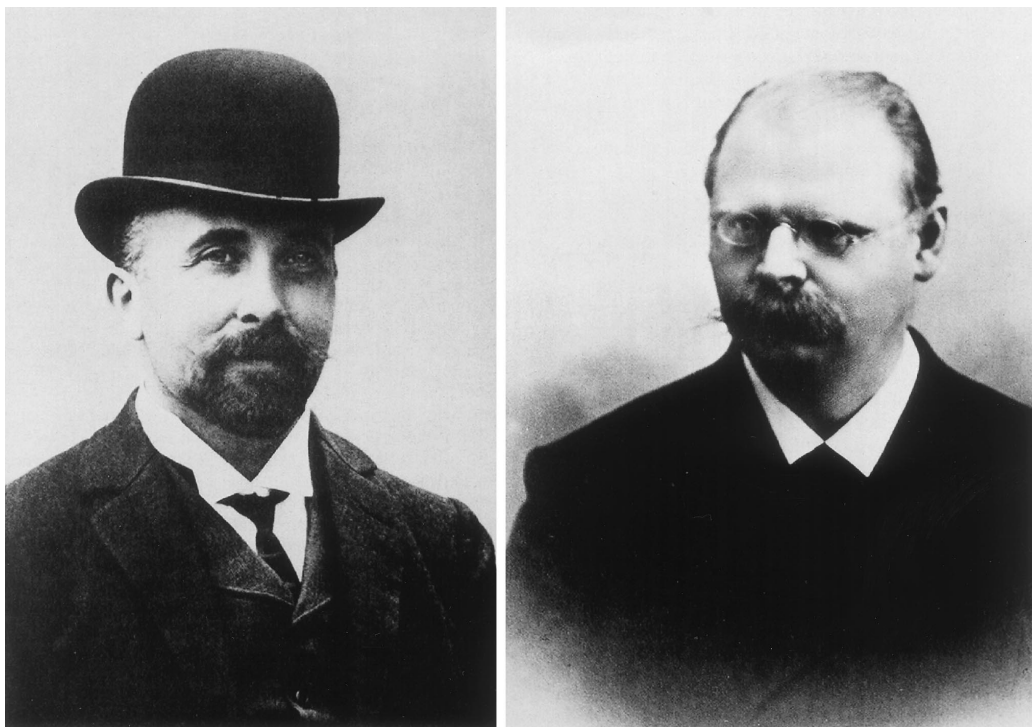


Figure 2. Felix Hoffman (*left*) and Heinrich Dreser (*right*). Reprinted with permission from Vane et al. [5].

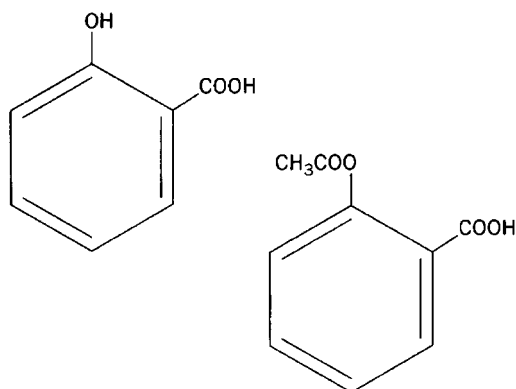


Figure 3. The chemical structures of salicylic acid (*left*) and acetylsalicylic acid (*right*).

“a” of the name was derived from acetyl and “spirin” from *Spirea*, the genus to which meadowsweets (a source of salicylaldehyde) belong. Another theory is that he named the drug after St. Aspirinius, the patron saint of headaches [5].

By the early 1900s an expanding array of antipyretic compounds had been discovered and incorporated into the clinical pharmacopoeia [5]. These included antipyrine (1884), antifebrin (1886), phenacetin (1887), acetaminophen (1888), and pyramidon (1896) [12]. These were followed shortly thereafter by phenylbutazone (1949), the fenamates (1950s), and indomethacin (1963).

Before 1971 little was known of the mechanisms by which drugs such as aspirin exerted their antipyretic and anti-inflammatory effects. Early theories held that such drugs functioned in some way by stabilizing cell membranes or by inhibiting certain proteases involved in the inflammatory process [5]. Eventually research into the mechanism of action of aspirinlike drugs focused on the effects of these agents on prostaglandin synthesis.

In a series of experiments conducted during the late 1960s and early 1970s, Vane [13] showed that aspirinlike drugs limit the formation of prostaglandins by interfering with the cyclooxygenase (COX) activity of prostaglandin endoperoxidase synthase. In 1972 Flower and Vane [14] hypothesized the ex-

istence of multiple forms of COX with differing tissue distributions on the basis of the observation that acetaminophen blocks prostaglandin synthesis in the central nervous system but not in peripheral tissues. This hypothesis was confirmed in 1991 when investigators working in D. L. Simmons' laboratory proved the existence of an isoform distinct from the one previously identified [15].

As the history of antipyretic therapy gives way to its future, new drugs are being developed that inhibit the inflammatory COX isoform, COX-2, while leaving undisturbed the isoform linked to the toxicity of aspirinlike drugs. Time will tell whether these agents represent an important new chapter in antipyretic therapy's long history.

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