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Review

The first 3500 years of aspirin history from its roots – A concise summary

Maria Rosa Montinari[a], Sergio Minelli[b], Raffaele De Caterina[c,*]

[a] Department of Biological and Environmental Science and Technology, University of Salento, Lecce, Italy
[b] ASL Lecce, D.S.S. n. 52, Lecce, Italy
[c] Cardiology, University of Pisa, Pisa, Italy

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ABSTRACT

Aspirin is currently the most widely used drug worldwide, and has been clearly one of the most important pharmacological achievements of the twentieth century. Historians of medicine have traced its birth in 1897, but the fascinating history of aspirin actually dates back > 3500 years, when willow bark was used as a painkiller and antipyretic by Sumerians and Egyptians, and then by great physicians from ancient Greece and Rome. The modern history of aspirin precursors, salicylates, began in 1763 with Reverend Stone – who first described their antipyretic effects – and continued in the 19th century with many researchers involved in their extraction and chemical synthesis. Bayer chemist Felix Hoffmann synthesized aspirin in 1897, and 70 years later the pharmacologist John Vane elucidated its mechanism of action in inhibiting prostaglandin production. Originally used as an antipyretic and anti-inflammatory drug, aspirin then became, for its antiplatelet properties, a milestone in preventing cardiovascular and cerebrovascular diseases. The aspirin story continues today with the growing evidence of its chemopreventive effect against colorectal and other types of cancer, now awaiting the results of ongoing primary prevention trials in this setting. This concise review revisits the history of aspirin with a focus on its most remote origins.

1. Aspirin – a miracle drug

Aspirin is today the most widely used drug all over the world, and in 2017, with some dispute about its real birth date, has celebrated its 120th birthday. Aspirin use in preventing cardiovascular and cerebrovascular diseases has been one of the biggest pharmaceutical achievements of the twentieth century. While most recent developments in secondary and primary cardiovascular prevention, and now in cancer chemoprevention, are still currently in the spotlight of the medical literature, the more remote roots of this miracle drug are less known. Other excellent books [1,2] or reviews [3–10] have deeply covered the history of aspirin and its precursors, as well as recent developments of its remarkable story. We have undertaken this additional historical review with a special focus on the roots of our current knowledge of aspirin and its precursors, and with particular mention of the early important contribution of Italian researchers, often neglected in the English literature.

2. The ancient history of salicylates: willow bark

The charming story of the world's best-known drug began over 3500 years ago. Salicyline – a glycoside contained in the bark of willow trees belonging to the family of *Salicaceae*, genus *Salix*, such as *Salix alba, Salix fragilis* – is indeed probably the oldest remedy still currently in use [11]. The use of willow leaves for the treatment of inflammatory rheumatic diseases was already known by the Sumerians (Table 1). The ancient Egyptians used extracts of myrtle and willow leaves to soothe joint pains. In fact, the Ebers Papyrus (1534 BCE) – a collection of 877 medical recipes in 110 pages – reports applications of myrtle and willow leaf decoctions on the abdomen and back to alleviate inflammatory conditions and painful symptoms [12].

About 1000 years later, Hippocrates from Kos (460–377 BCE), the father of medicine, and then Galen from Pergamon (129–201 CE) were aware of the medicinal properties of *Salicaceae* plants. Hippocrates prescribed willow bark to treat inflammatory pain and to relieve the pain of childbirth.

Dioscorides (40–90 CE), in *De Materia Medica*, recommended willow decoctions for the treatment of colic, gout and ear pains. Pliny the Elder (23–79 CE), in his *Natural History*, reported the use of these substances as analgesic and antipyretic remedies [1].

For centuries, there have been reports on the use of willow as an analgesic, antipyretic and anti-migraine remedy from various parts of the world even without effective contacts. In fact, indigenous populations such as the Hottentots of South Africa or the Indians of America

* Correspondence author at: Institute of Cardiology, University of Pisa, c/o Ospedale di Cisanello, Via Paradisa, 2, 56124 Pisa, Italy.
E-mail addresses: mariarosa.montinari@unisalento.it (M.R. Montinari), rdecater@unich.it (R. De Caterina).

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1537-1891/

Table 1
Chronology of the milestones in aspirin discovery and early clinical trials.

The ancient history
Analgesic effects known by the Assyrians from the Sumerian period and described in the Ebers papyrus (1534 BCE), Hippocrates, Galen, Dioscorides and Pliny the Elder
In the 18–19th century
1763: Rev. Edward Stone uses willow bark as an antipyretic
1824: Francesco Fontana and Bartolommeo Rigatelli extract active ingredient from the willow bark
1828: Joseph Buchner identifies willow's active ingredient "Salicin"
1829: Henri Leroux refines salicin extraction process
1838: Raffaele Piria produces salicylic acid
1852: Charles Gerhardt chemically synthesizes impure and unstable acetylsalicylic acid
1855: Cesare Bertagnini discovers transient ototoxicity of salicylate
1859: Hermann Kolbe describes the chemical structure and synthesized salicylic acid
1876: First rigorous trial with salicin in rheumatism, by Thomas MacLagan
1897: Felix Hoffmann, under Eichengrün's direction, synthesizes acetylsalicylic acid in pure and stable form
1899: Bayer registers the new compound under the name "Aspirin"
In the 20th century
1900: Aspirin is patented in the United States
1904: Production of the stamped tablet form of aspirin by Bayer
1948: Paul Gibson proposes salicylic acid in treatment of coronary thrombosis
1953: Lawrence Craven uses aspirin in primary cardiovascular prevention
1971: Vane discovers the mechanism of action of aspirin
1974: First randomized trial of aspirin in secondary prevention of myocardial infarction, by Elwood et al.
1975: Aspirin found to reduce thromboxane A2 synthesis, by Samuelsson et al.
1976: Aspirin found to inhibit cyclooxygenase, by Hemler et al.
1978: Secondary prevention of stroke, The Canadian Cooperative Study Group
1982: Vane, Samuelsson and Bergström win the Nobel Prize for Medicine for topics related to aspirin mechanism of action
1983: Veterans Administration Study, the first placebo-controlled randomized trial on prophylactic use of aspirin in men with unstable angina
1988: ISIS-2 trial proves early aspirin treatment is effective on mortality from myocardial infarction

used the willow extracts to cure fever, osteoarthritis and headache. By 216 CE, with the intensification of military and commercial maritime contacts, the use of willow bark spread throughout the Western world, then to China and other eastern countries. In the Middle Ages, in the Renaissance and the following years until the 18th century, decoctions of plants containing salicylates were used to treat rheumatic pains, wounds, ulcers, headache and for dysmenorrhea [1].

3. 18th–19th century: from salicin to aspirin

3.1. Salicin

In 1758, the Reverend Edward Stone (1702–1768), from Chipping Norton, Oxfordshire, England, studied the healing properties of willow, looking for a valid and cheaper remedy than the expensive cinchona bark for treating "the agues" (i.e., malarial symptoms) [6]. He administered aqueous extract of *Salix alba* bark to 50 patients with fever, and discovered that the administration of these extracts every 4 h had a marked antipyretic action. Stone presented this study to the Royal Society of London in 1763 [13], and is now recognized as the first author to demonstrate the effectiveness of willow bark in the treatment of fever or agues with scientific rigor.

It appears [14] that the first extraction of the active component of willow bark had been performed in 1824 by two Verona Italian pharmacists, Francesco Fontana [15] and Bartolommeo Rigatelli [16]. Some literature attributes this erroneously to Luigi Brugnatelli, but he had already died in 1824 – the year when the scientific work was actually done. Rigatelli named the drug "*indigenous substitute for quinine sulfate*" [16] and then "*very bitter antipyretic saline*" [17], while Fontana [15] utilized the same term – salicin – that a few years later was to be adopted by others. In 1828, indeed, Joseph Buchner (1783–1852), a German pharmacologist, also extracted the active ingredient from

Fig. 1. Raffaele Pirìa (1814–1865).

willow, producing bitter-tasting yellow crystals, which he (re-)labeled "salicin" [18]. In 1829, the French pharmacist Henri Leroux (1795–1870) perfected the process of salicin extraction and isolated important amounts of soluble crystals of pure salicin [19].

3.2. Salicylic acid

Salicin is an alcoholic β-glucoside. When consumed, the acetalic ether bridge is broken down and the two parts of the molecule, glucose and salicyl alcohol, then are metabolized separately. By oxidizing the alcohol function, the aromatic part is finally metabolized to salicylic acid. In 1838, Raffaele Pirìa (1814–1865, Fig. 1), one of the most important Italian chemists of the nineteenth century, extracted salicylic acid from salicin separating the glucose component, and determined its molecular formula [20]. In 1855, his pupil Cesare Bertagnini (1827–1857, Fig. 2) first demonstrated the transient ototoxicity of salicylate, accurately describing tinnitus – a reversible side effect after the ingestion of high doses – which he reported after voluntarily taking massive doses himself and measuring the urinary levels of salicylic acid and its metabolites. Bertagnini repeatedly ingested 25 centigrams of salicylic acid every hour (about 6 g in two days), and described the effects as follows "... *No disturbance appeared on the first day, but in the second there was a continuous noise in the ears and a kind of stunning; because of this, I suspended the ingestion* " (translated from the original text in [21]).

In the following years, research was directed towards the chemical synthesis of salicylic acid to obtain a purer, better-tolerated and less expensive compound. In 1853, the French chemist, Charles Gerhardt (1816–1856), first demonstrated the reaction of sodium salicylate with acetyl chloride, obtaining a white substance, which he called "acide acéto-salicylique". In fact, he obtained acetylsalicylic acid – aspirin – without knowing it. The compound was, however, unstable and impure, the process was cumbersome and inconsistent in results, and for these reasons did not raise further interest [22].

The key compound for the synthesis of aspirin, salicylic acid, was chemically described and synthesized in 1859 by Hermann Kolbe (1818–1884), a professor of chemistry at Marburg University, Germany,

Fig. 2. Cesare Bertagnini (1827–1857).

through a general process now known – because it was further perfected by his assistant Rudolf Wilhelm Schmitt (1830–1898) – as the Kolbe-Schmitt reaction [23]. In Kolbe's synthesis, sodium phenoxide was heated with carbon dioxide under pressure (at 125 °C and 100 atm), and the reaction mixture was subsequently acidified with sulfuric acid to produce salicylic acid. This reaction was used to produce chemically pure salicylic acid on an industrial scale by another pupil of Kolbe, Friedrich von Heyden (1838–1926), who, in 1874, established the first factory for the production of synthetic salicylates in Dresden. Von Heyden was the first to receive a patent for this technique, and succeeded in marketing the compound at a price ten times lower than willow extracts [23].

3.3. Early studies with salicylates

The industrial production of low-cost salicylic acid favored its clinical use. In 1876, the German doctor Franz Stricker published on the efficacy of pure sodium salicylate in acute rheumatism, thus extending the indication of the drug as an agent not only with antipyretic, but also with anti-rheumatic and analgesic properties [24]. In the same year, his compatriot Ludwig Reiss independently published similar findings in the same journal [25]. Two months after Stricker, the Scottish physician Thomas MacLagan (1838–1903) published a rigorous trial on salicin in *The Lancet* [26]. He administered 12 grains of salicin every 3 h to 8 patients with acute rheumatism, and obtained a complete remission of joint pain and fever. MacLagan emphasized that salicin was "*the most effective means yet for the cure of acute articular rheumatism and it may even show itself to be a specific for the disease*", although he noted that it caused severe gastric irritation. One year later, the French doctor Germain Sée (1818–1896) proved the efficacy of sodium salicylate additionally in the treatment of chronic rheumatism and gout [27].

In the same years, salicylic acid was used also in Italy in the treatment of rheumatic fever (synonyms: "polyarthritis rheumatica", "acute articular rheumatism"). In 1877, Nemesio Bosisio from Brescia described 10 cases of acute articular rheumatism treated with dose of 0.5 g every 2 h, observing a rapid drug efficacy, no major side effects at the doses used and – interestingly – the lack of adverse effects in a woman treated during pregnancy. In 1878, Giovanni Brugnoli (Fig. 3), head of Medicine at Ospedale Maggiore in Bologna, published 26 cases of patients with rheumatic fever treated with sodium salicylate. He observed a rapid resolution of rheumatic fever and the efficacy of the drug also in preventing the relapse of the disease and on rheumatic carditis. He however reported that sodium salicylate was almost ineffective in other rheumatic diseases, in particular, on syphilitic arthritis and periostitis [28].

3.4. …and finally aspirin!

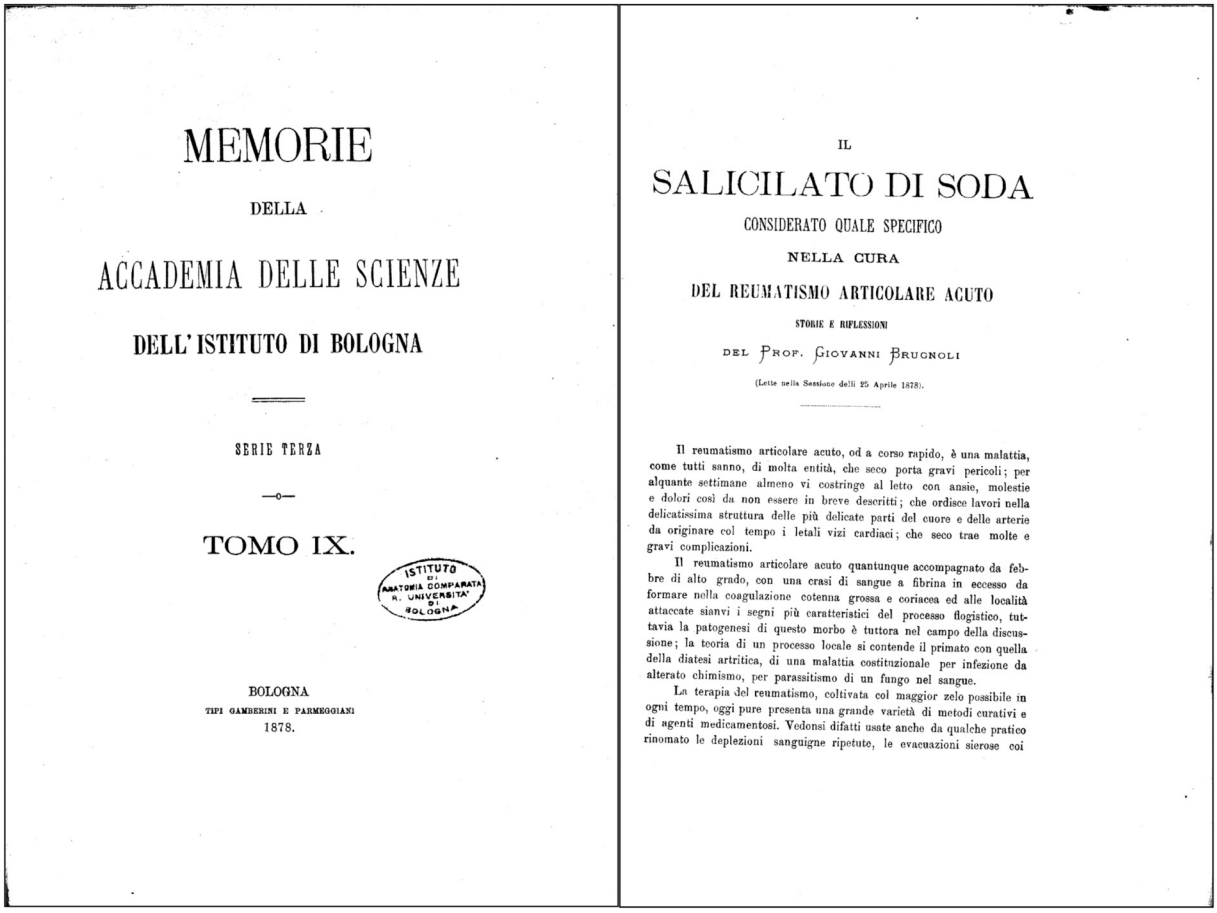
The development of salicylates resumed in Bayer's laboratories, founded in 1863 by Friedrich Bayer and William Weskott, and initially specialized for the production of dyes. In 1888, the company decided to establish a drug division headed by Carl Duisberg (1861–1935), consisting of a pharmaceutical branch headed by Arthur Eichengrün (1867–1949, Fig. 4) and a pharmacological branch, headed by Heinrich Dreser (1860–1924) [1]. They wanted to synthesize a derivative of salicylates that did not cause the adverse effects (mainly nausea, gastric irritation and tinnitus) common with the use of sodium salicylate. This task was assigned to Felix Hoffmann (1868–1946, Fig. 5), a young pharmaceutical chemist who graduated at the University of Munich [29]. On August 10, 1897, according to his laboratory notebook, Hoffmann was able to acetylate the phenol group from salicylic acid refluxed with acetic anhydride (acetylation reaction, Fig. 6), obtaining acetylsalicylic acid in its purest form with a relatively simple, reliable and efficient method. That date, August 10, 1897, has since then been credited as the birthday of aspirin. Acetyl-salicylic acid had immediate therapeutic success and received praise among medical practitioners, but initially Dreser was skeptical of the clinical validity of the molecule for its possible cardiotoxicity [11]. Responsible for Bayer's clinical trials, after the initial animal experiments he promoted the initial clinical experimentation of the drug and tested it on himself [1]. In 1899, Dreser published the first essay on the pharmacology of aspirin, without even mentioning the names of Hoffmann and Eichengrün. Moreover, he was the only one to obtain economic benefits for the discovery of the molecule [30].

The new drug received the name "aspirin", composed from acetyl and *Spiraea ulmaria,* the tree from which salicylic acid was extracted. On February 1, 1899, Bayer registered the trademark name in Berlin. Aspirin was then patented in the United States in 1900.

Initially marketed in a powder form, the drug was made available in 1904 also in tablets, and as such was the first industrial drug available in tablet form worldwide [1], with immediate commercial success. The first clinical studies on aspirin were published in 1899 in Germany by Witthauer [31] and Wohlgemut [32], and in the United States by Floeckinger [33].

3.5. Disputes on the discovery of aspirin

The discovery of aspirin has been the subject of considerable controversy. It has been said that Hoffmann, in August 1897, achieved the synthesis of aspirin in a pure form and suitable for clinical use in a search for an innovative and well-tolerated molecule to treat his father's arthritis, who was at that time being treated with high doses of sodium salicylate. In 1949, Eichengrün complained that his role in the discovery of aspirin, directing Hoffmann's work as the head of pharmaceutical research at Bayer, had been obscured [34]. His contribution would have been deleted from Bayer's archives during the Nazi period, possibly because of Eichengrün's Jewish origins. This thesis was supported by Sneader [4,35]. However, the American patent of 1900 attributes the invention of aspirin exclusively to Hoffmann. This document, certainly known and accepted by his supervisors, testifies that they indeed considered Hoffmann as the inventor of the drug. Today Hoffmann is officially considered the discoverer of aspirin: we should however acknowledge that Duisberg, Eichengrün and Dreser, with different roles, were certainly important co-protagonists in this story.



MEMORIE

DELLA

ACCADEMIA DELLE SCIENZE

DELL'ISTITUTO DI BOLOGNA

SERIE TERZA

TOMO IX.

BOLOGNA
TIPI GAMBERINI E PARMEGGIANI
1878.

IL

SALICILATO DI SODA

CONSIDERATO QUALE SPECIFICO

NELLA CURA

DEL REUMATISMO ARTICOLARE ACUTO

STORIE E RIFLESSIONI

DEL PROF. GIOVANNI BRUGNOLI

(Lette nella Sessione delli 25 Aprile 1878).

Il reumatismo articolare acuto, od a corso rapido, è una malattia, come tutti sanno, di molta entità, che seco porta gravi pericoli; per alquante settimane almeno vi costringe al letto con ansie, molestie e dolori così da non essere in breve descritti; che ordisce lavori nella delicatissima struttura delle più delicate parti del cuore e delle arterie da originare col tempo i letali vizi cardiaci; che seco trae molte e gravi complicazioni.

Il reumatismo articolare acuto quantunque accompagnato da febbre di alto grado, con una crasi di sangue a fibrina in eccesso da formare nella coagulazione cotenna grossa e coriacea ed alle località attaccate sianvi i segni più caratteristici del processo flogistico, tuttavia la patogenesi di questo morbo è tuttora nel campo della discussione; la teoria di un processo locale si contende il primato con quella della diatesi artritica, di una malattia costituzionale per infezione da alterato chimismo, per parassitismo di un fungo nel sangue.

La terapia del reumatismo, coltivata col maggior zelo possibile in ogni tempo, oggi pure presenta una grande varietà di metodi curativi e di agenti medicamentosi. Vedonsi difatti usate anche da qualche pratico rinomato le deplezioni sanguigne ripetute, le evacuazioni sierose coi

Fig. 3. Frontispiece and first page of the Memoirs of the Academy of Sciences, Bologna, reporting the first observations by Giovanni Brugnoli on the efficacy of sodium salicylate in acute rheumatic fever.

Fig. 4. Arthur Eichengrün (1867–1949).

Fig. 5. Felix Hoffmann (1868–1946).

4. The 20th century: from mechanism of action to indications in cardiovascular disease

After its commercialization, aspirin use spread rapidly throughout the world, and became so famous as to be cited by several writers, including Franz Kafka, Thomas Mann, Henry Miller, José Ortega y Gasset

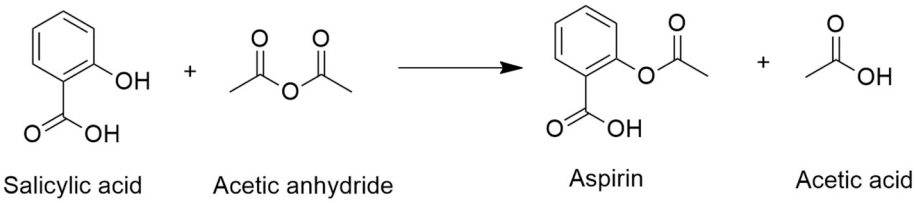


Fig. 6. Hoffmann's aspirin synthesis, from salicylic acid and acetic anhydride.

and Gabriel Garcìa Marquez in their literary works. It was soon also used by illustrious personalities, from the son of Tsar Nicholas II (inappropriately, because he was hemophiliac) to Winston Churchill after his first stroke. In 1950, aspirin entered the Guinness World Records for being the most frequently sold painkiller. Mashkovsky's manual [36], a standard reference textbook on drugs for doctors in the former Soviet Union, lists about 50 synonyms of aspirin with the following footnote: "*The multitude of synonyms indicates the prevalence of this drug*". Aspirin and drugs that contained it in combination with various other substances were produced by dozens of manufacturers from different countries. Seventy years after its discovery the mechanism of action of aspirin had not yet been clarified: indeed in 1966, the New York Times called aspirin "*the wonder drug that nobody understands*" [1].

4.1. Mechanism of action of aspirin

The mechanism of action of aspirin began to be investigated later in the 20th century with the progress of pharmacological techniques. There were many attempts to link the anti-inflammatory actions of aspirin and of non-steroidal anti-inflammatory drugs with their ability to inhibit the activity of endogenous substances.

In 1960, Harry Collier (1912–1983) proposed a mechanism of action of aspirin after examining the antagonism between bradykinin and aspirin, measuring the bronchoconstrictive response in guinea pigs in vivo. He found that aspirin prevented bronchospasm if given before – but not after – the administration of bradykinin, inferring that aspirin could antagonize bradykinin [1,37]. By realizing that this was just a hint to the essential mechanism of action, in 1963 he spurred his collaborator Priscilla Piper (1939–1995), to learn new bioassay techniques at John Vane's laboratory.

In 1969, John Vane (1927–2004, Fig. 7) and Priscilla Piper, repeating Collier's experiments, demonstrated that, in guinea-pig isolated lungs, a variety of stimuli (such as anaphylaxis, the infusion of bradykinin and other substances, or the shock perfusate) caused the release of a "rabbit aorta contracting substance" (RCS) – later identified as a prostaglandin – which was blocked by aspirin [38]. In a later 1971 study, Vane proposed the dose-dependent inhibition of prostaglandin biosynthesis as the mechanism of action of aspirin and all non-steroidal anti-inflammatory drugs [39]. With this important discovery, Vane first demonstrated that a single mechanism of action – the inhibition of prostaglandin synthesis – satisfactorily explained the anti-inflammatory properties of aspirin and aspirin-like drugs. For these refined studies and for the subsequent discovery of prostacyclin with Salvador Moncada (1944-) in 1976, Vane was awarded the Nobel Prize for Medicine in 1982.

In 1975, the Swedish biochemist Bengt Samuelsson (1934-) and his group showed that the major component of the RCS was an unstable prostanoid, thromboxane A_2, a potent vasoconstrictor and stimulator of platelet aggregation [40]. Aspirin was then found to inhibit thromboxane A_2 synthesis and, by this mechanism, increase the bleeding time and platelet aggregation. This inhibition was accompanied by a sharp reduction of the aggregation-dependent release of adenosine diphosphate (ADP). A few years laterresearch by Hemler et al. [41] completed knowledge of the mechanism of action of aspirin through the identification of cyclooxygenase (COX), the enzyme irreversibly inhibited by aspirin. COX is a monotopic integral protein that currently is known to exist in 2 main isoforms (COX-1 and -2), endowed with both a

Fig. 7. Sir John Vane (1927–2004).

fatty acid oxygenase and a peroxidase activity. Aspirin blocks the synthesis of prostaglandins and thromboxane A_2 by irreversible acetylation of a serine in position 530 in COX-1, as the group of Philip Majerus (1936–2016) showed first in 1975, (42, 1994 #37) and in position 516 in COX-2 [43], limiting the access of arachidonic acid to the catalytic active site of the enzyme. The irreversibility of COX inhibition through the acetylation of the enzyme renders aspirin truly unique among non-steroidal anti-inflammatory drugs, and is the basis for its long-term inhibition of platelet function. In 1982, Bengt Samuelsson shared the Nobel Prize for Medicine and Physiology with John Vane and the Swedish biochemist Sune Bergström (1916–2004), who had been the first to isolate, purify and identify the chemical structures of two prostaglandins. The discoveries by Vane, Samuelsson and Bergström of the inhibition of prostaglandin synthesis by aspirin explain – in a unitary and coherent way – its multiple pharmacological actions, and favored the development of other nonsteroidal anti-inflammatory drugs.

4.2. Aspirin as an antiplatelet agent

In the late 1960s and early 1970s, scientists became more and more interested in mechanisms of thrombosis, a final common pathway for most acute coronary syndromes. It became apparent that aspirin prolonged the bleeding time, an overall test for primary hemostasis, mostly affected by the status of blood platelets [44]. The introduction of the aggregometer by Gustav Born (1921–2018) [45,46] confirmed that aspirin inhibited platelet aggregation induced by a variety of agents, such as ADP and epinephrine [47–49], opening the door to a huge amount of subsequent research. A PubMed search run on October 19, 2018 with the terms "aspirin" and "platelet aggregation" yielded

15,662 citations on the topic. It also became apparent that very low doses of aspirin inhibit both platelet thromboxane production and platelet aggregation [50], in healthy volunteers [51] and in patients after a myocardial infarction [52,53]. Indeed, low-dose aspirin is able to inhibit platelet aggregation effectively, without significantly affecting endothelial cell prostacyclin synthesis, due to the inability of the anucleated platelets to resynthesize COX-1. On the contrary, inhibition of inflammatory cell function requires a higher and more frequent dosage. The unique property of aspirin to acetylate platelet COX-1 irreversibly, thus inhibiting thromboxane production, accounts entirely, to the best of our understanding, for aspirin's antiplatelet properties [54], while acetylation of other proteins may account for a variety of additional effects, including anti-cancer activity [55,56]. The anti-inflammatory effects of salicylates are perhaps in part due to competitive inhibition of COX-1 and COX-2, but also to other unrelated mechanisms [57].

4.3. The developments of aspirin as an anti-thrombotic drug

In parallel with the increasing knowledge of the antiplatelet and antithrombotic effects, aspirin gradually became the current milestone in therapies used to prevent or treat patients with acute coronary syndromes [58–61]. However, this route was very long and not without initial scepticism.

Already in 1940 Karl Paul Link (1901–1978) – the American biochemist best known for his discovery of dicumarol and warfarin – documented a prolongation of the bleeding time caused by aspirin [62]; and in 1945 the American doctor Rudolf Singer described more frequent bleeding in patients treated with aspirin after tonsillectomy. Neither at that time hypothesized the possible use of aspirin as an antithrombotic drug [63]. It was then Paul Gibson who – in 1948 – proposed the use of aspirin in the treatment of coronary thrombosis, and in the next year presented case reports detailing the potential role of aspirin in the treatment of angina pectoris and vascular diseases [64].

In 1953 Lawrence Craven – a Los Angeles doctor – noticed, similarly to Singer, that tonsillectomy patients experienced increased bleeding after using aspirin for pain relief; but he went on to hypothesize the potential efficacy of aspirin in preventing coronary thrombosis, considering aspirin as a safer and better tolerated substitute to warfarin ("warfarin-light"), already used at that time in this clinical setting [65]. He conducted clinical investigations with aspirin with "positive" results, prescribing it in primary prevention to males aged 45 to 65 years who were overweight and with a sedentary lifestyle. He reported to have treated about 8000 patients, and that "*not one of these patients experienced a myocardial infarction over a several-year period*" and no patient suffered from a stroke [65]. Interestingly, Craven's recommendations are very similar to several – albeit not all – current guidelines for the use of aspirin in primary cardiovascular prevention [66,67]. Craven's pioneering studies, being uncontrolled and published in secondary journals, did not have the clinical interest they deserved, and were long forgotten.

In 1967, Harvey Weiss [47] first experimentally demonstrated that aspirin bleeding diathesis was due to inhibition of platelet activation by collagen, without however explaining the mechanism of action. The scientist who solved this question was, as we have seen, the great pharmacologist John Vane.

4.4. The first studies in cardiovascular diseases

The above evidence of aspirin's ability to inhibit platelet aggregation stimulated large multicenter trials to test its antithrombotic efficacy. In 1974 Peter Elwood, epidemiologist at the UK Medical Research Council, led the first such clinical trial of aspirin in the prevention of myocardial infarction. The results of this study, with a single dose of 300 mg daily of aspirin in the prevention of re-infarction in 1239 men who had had a recent myocardial infarction, were statistically inconclusive. However, they showed a non-statistically significant reduction in total mortality (by 12% at 6 months and 25% at 12 months after enrollment) [68]. It took 6 more years and 5 more trials, all individually inconclusive until, in 1980, Richard Peto (1943-) published a meta-analysis of these 6 clinical trials, in a total of over 10,000 patients with a myocardial infarction, recruited at variable time distance from the acute event, but all strictly randomized, in a double-blind fashion, to aspirin or a placebo control. His analysis demonstrated that aspirin reduced the risk of re-infarction by 21%. There were also overall fewer strokes in the aspirin compared with the control groups [69]. This short paper was also the introduction of the meta-analysis in the cardiovascular literature [69].

In 1983, a report from the Veterans Administration Cooperative Study on Aspirin in men with unstable angina showed that aspirin was protective against acute myocardial infarction also in subjects before the occurrence of the index event, suggesting a similar effect on mortality in the setting of what was at that time called pre-infarction or unstable angina [70]. The ISIS-2 study, 1988, conducted on 17,187 patients, was a further milestone on the use of aspirin in acute myocardial infarction. Patients were randomized – this time within 24 h of symptom onset – to the intravenous fibrinolytic drug streptokinase (1.5 million Units in 1 h) and oral aspirin (162 mg daily for 1 month) versus placebo. Among patients in the aspirin group there was a 50% reduction in re-infarctions and a 23% reduction in mortality at 5 weeks compared with the placebo group, and this effect was additive to that of streptokinase. Subsequent studies confirmed that the initial benefits of aspirin treatment persisted for at least 10 years [71]. These and other observed benefits led health authorities, such as the American Food and Drug Administration (FDA) in 1985, to approve the use of aspirin both in the treatment of acute myocardial infarction and in its secondary prevention.

4.5. The first studies in cerebrovascular diseases

At the turn of the '70s and '80s, studies on aspirin for cerebrovascular prevention were also performed. The first large randomized clinical trial concerned secondary prevention in stroke. The Canadian Cooperative Study Group in 1978 randomized 585 stroke patients to receive aspirin or sulfinpyrazone, alone or in combination for 26 months, and showed that aspirin can reduce the risk of stroke or death by 31% [72]. In 1980, the FDA authorized the use of aspirin after ischemic stroke.

In the early 1990s, trials were designed to test the efficacy of lower doses of aspirin in the prevention of cerebrovascular ischemia. The Dutch TIA (*transient ischemic attack*) Trial Study Group showed that 30 mg/day of aspirin was no less effective in the prevention of vascular events than a 283 mg/day dose in patients with a TIA or minor stroke [54]. Similarly, the SALT Collaborative Group found that 75 mg/day significantly reduced the risk of stroke or death in patients with cerebrovascular ischemic events [73,74].

Since then, the use of aspirin, especially, in modern times, at low doses, as elucidated by Patrono's group [50], has become increasingly common. Inhibition of platelet COX-1 fully accounts for the antithrombotic effects of low-dose aspirin. However, the inhibition of platelet activation at sites of vascular lesions might also have indirect effects, such as reducing the release of inflammatory cytokines, oxygen radicals, growth factors, and other proteins.

5. Aspirin today

Although the benefit of aspirin treatment, beyond its analgesic, antipyretic and anti-inflammatory effects, is now clear for acute coronary syndromes and for secondary cardiovascular prevention, the evidence in patients without prior cardiovascular disease (primary prevention) remains less clear [54,66,67]. Evidence-based guidelines recommend aspirin patients at cardiovascular risk, defined as ≥1–2

major cardiovascular events (death, myocardial infarction, or stroke) per 100 person-years, who are not at increased risk of bleeding [54,66,67]. While the results of 3 further primary prevention trials have just been published [75–77] these have not, due to the recruitment of relatively low-risk populations, resolved the controversy. In secondary cardiovascular prevention, its use also remotely after an acute coronary syndrome appears recommendable [78], also on the light of recent evidence about the increased rate of cardiovascular events documented upon its withdrawal [79]. In 2017, further evidence has also accrued on the value of its use in women at high risk for preterm preeclampsia [80,81]. One of the ongoing disputes is now whether a dose-adjustment based on body weight should be adopted [82]. Finally, the favorable results of low-dose aspirin in combination with a low dose of the non-vitamin K antagonist rivaroxaban in comparison with rivaroxaban alone in patients with stable coronary, peripheral or carotid artery disease in the recently published COMPASS trial [83] further support the cardiovascular benefit of the aspirin component in what appears to be now the most effective antithrombotic treatment for such patients long-term. Cardiovascular benefits may also expand in the future to the prevention of dementia, possibly beyond its cardiovascular component [84].

Pathways related to cyclooxygenase activity have now also been proposed in the development of carcinogenesis, based on the relationship with the inflammatory processes precursors of tumorigenesis, which could be partially inhibited by aspirin, administered for a long time [85]. It is now known that platelets are involved not only in the processes of hemostasis and thrombosis, but also in inflammatory and immune responses, and probably in carcinogenesis [85]. The possible role of low-dose aspirin in reducing the long-term risk of several cancers has opened a new era of aspirin use [86]. The recent recommendation of the U.S. Preventive Services Task Force on low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer reflects increasing attention to its chemopreventive effects [67]. Further evidence in this area is being now analyzed in 3 recently completed primary prevention trials [75–77]. Furthermore, several adjuvant studies of various low-dose aspirin regimens have recently been initiated in patients with newly diagnosed tumors, including colorectal cancer, gastro-esophageal, breast and prostate cancer [85].

6. Conclusion

The charming history of aspirin goes thus back to Egyptian healers who used the willow bark to cure joint pain. Synthesized as it is today in 1897 and marketed in 1899 as an analgesic, antipyretic and anti-inflammatory agent, aspirin continues to attract research and debate related to its antiplatelet properties. It is now the most commonly used drug worldwide and has proved to be lifesaving in the prevention of cardiovascular disease. Its future, possibly for the entire millennium, still seems bright and full of promises, awaiting the completion of trials in the chemoprevention of colorectal and other cancers, and in reducing the risk of dementia. No drug has received such scientific attention now at 120 years after its industrial synthesis, in the cardiovascular area and beyond.

Disclaimer

Aspirin, as shown here, has many fathers. As any short summary of such an immense story, the authors have been obliged to make a selection of what appeared to them most relevant. As a result, they did not cite a huge number of very relevant contributions and contributors especially in modern times, when claims have not yet withstood the test of time. They ask for understanding and forgiveness in such – in their opinion not unreasonable – choices.

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