Paths of Discovery
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# THE HISTORY OF ASPIRIN: THE DISCOVERIES THAT CHANGED CONTEMPORARY MEDICINE

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## Ancestors of Aspirin

For millennia, pain, fever, and inflammation were treated with plants containing salicylic acid glycosides: leaves of myrtle (Myrtus), bark of willow (Salix), bark of poplar (Populus), meadowsweet (Spirea). About 3500 years ago, an Egyptian papyrus recommended the application of a decoction of the dried leaves of Myrtle to the abdomen and back to expel rheumatic pains from the womb. A thousand years later, Hippocrates championed the juices of the poplar tree for treating eye diseases, and those of willow bark for pain in childbirth and for fever. Through the Middle Ages the medical use of salicylates continued. However, willows were needed for basket-making so the women grew meadowsweet (Spirea ulmaria) in their gardens and made decoctions from the flowers [1].

The first 'clinical trial' of willow bark was published by English country parson Reverend Edward Stone. He had accidentally tasted willow bark and was surprised by its bitterness, which reminded him of chinchona bark – containing quinine – then being used to treat malaria. He believed in the 'doctrine of signature' which dictated that the cures for the diseases would be found in the same location where malady occurs. Since the 'Willow delights in a moist and wet soil, where agues chiefly abound', he gathered a pound of willow bark, dried it in a baker's oven for 3 months, pulverized and administered it to 50 patients with safety and success. He reported his observations to the Royal Society [2].

In 1859 Friedrich Kolbe identified the structure of salicylic acid as an o-hydroxybenzoic acid, managed to obtain it synthetically and introduced it to therapy. However, the bitter taste of the substance and the side-effects of gastric irritation caused by acid, made long-term prescribing difficult. In

1897 Felix Hoffman at Bayer's Laboratory synthesized acetylsalicylic acid, shortly thereafter named 'aspirin' (it contained the root of spiric acid from Spirea Ulmaria, chemically identical to salicylic acid, together with 'A' as an abbreviation for acid) (Fig. 1). Hoffman had personal reasons for wanting a more acceptable salicylic acid derivative, since his father who had been taking salicylic acid for many years to treat his painful arthritis had recently discovered that he could no longer take the drug without vomiting [1].

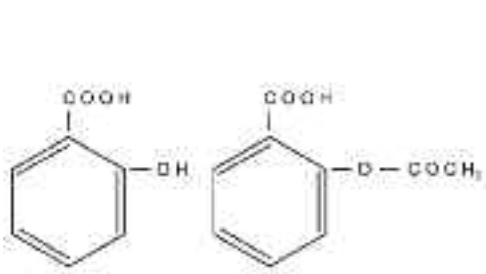



Fig. 1 Chemical structures of salicylic – and acetyl-salicylic acids.

## Use of Aspirin and its Mode of Action

Following its introduction into therapy at the beginning of 20th century, aspirin has become the extremely popular anti-pyretic, anti-inflammatory and analgesic agent. The crucial discovery of the biochemical mechanism of the action of aspirin was made by Sir John Vane in 1971 [3]. He observed that aspirin blocked the enzymatic activity of cyclooxygenase (COX), a key enzyme leading to the production of pro-inflammatory prostaglandins from arachidonic acid (Fig. 2). He thus demonstrated the reasons for the anti-inflammatory, analgesic, antipyretic and toxic effects of the most widely used remedy of all time. The discovery in part

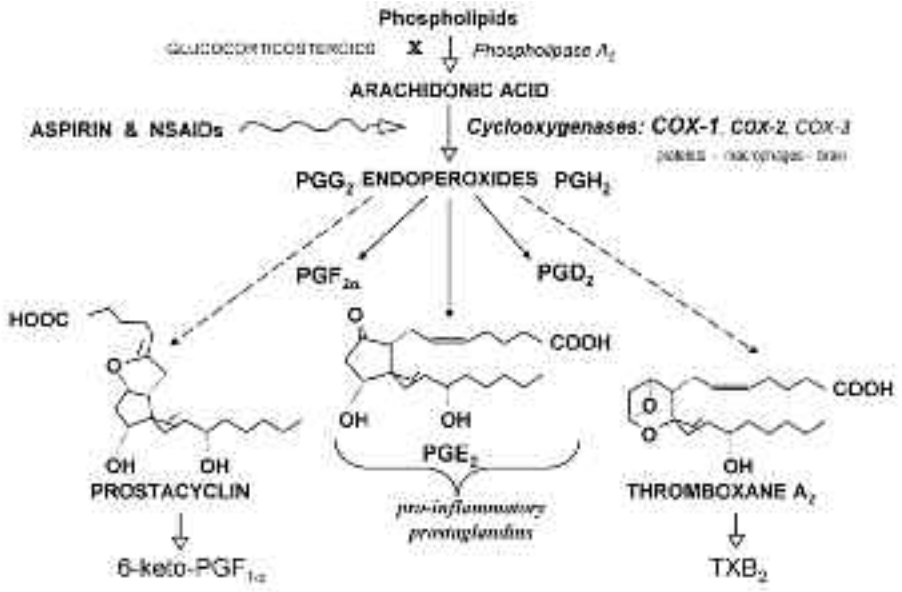


Fig. 2 Arachidonic acid metabolism, controlled by cyclooxygenases. Arachidonic acid is liberated from the cells by phospholipase $A_2$, and converted by cyclooxygenases via unstable endoperoxides to prostaglandins. In endothelial cells prostacyclin is preferentially produced, while blood platelets generate thromboxane $A_2$.

coincided with a veritable explosion of aspirin-like drugs, exemplified by phenylobutazone, indomethacin, mefenamic acid, ibuprofen and others, widely used for treating rheumatic condition. All of the so-called non-steroidal anti-inflammatory drugs (NSAIDs) inhibited prostaglandin biosynthesis, but their toxicity remained a problem and was probably caused by the same biological intervention.

Over the last twenty years, yet another use for aspirin has emerged connected with the discovery of its anti-thrombotic action [4]. The peculiar effectiveness of aspirin in thrombosis is based on its irreversible inhibition of the COX enzyme in platelets which make thromboxane $A_2$ ($TXA_2$), the potent pro-aggregatory and vasoconstrictive prostaglandin. Of all the aspirin-like drugs, only aspirin permanently inactivates the enzyme (by attaching an acetyl group close to the active site), and thus makes the

platelet incapable of synthesizing $TXA_2$ for the rest of its life (about 10 days). Regular low doses of aspirin have a cumulative effect and inactivate platelet COX without affecting much the synthesis in blood vessels of prostacyclin – which exert potent vas-dilatory and anti-platelet effects [5].

## Effectiveness of Aspirin in Cardiovascular Disease

Aspirin is the cornerstone of therapy in atherothrombosis, encompassing a wide spectrum of clinical entities. A recent meta-analysis of 287 clinical trials on aspirin in the prevention of cardiovascular disease has provided firm evidence that antiplatelet therapy, mainly aspirin, can reduce by approximately 25% the risk of nonfatal myocardial infarction (MI), nonfatal stroke, or vascular death in high-risk patients, regardless of sex, age, presence of arterial hypertension or diabetes [6]. An absolute reduction in the risk of having a serious vascular event was 36 per 1000 MI survivors treated for two years [6]. Undoubtedly, the clinical benefits of aspirin are most apparent in patients with acute myocardial infarction, which has been convincingly demonstrated in the landmark infarction trial, ISIS-2 [7]. Administration of 162mg aspirin within 24 hours following the onset of acute coronary symptoms resulted in significant reductions in the risk of cardiovascular mortality (by 23%), nonfatal reinfarction (by 49%), and nonfatal stroke (by 46%) in the 5-week follow-up, without any increase in major bleeding complications [7]. The magnitude of the effect attributed to aspirin was almost equivalent to that produced by streptokinase [7]. This study showed that aspirin has the best benefit-to-risk ratio of any known therapy for AMI. Aspirin is also effective in reducing the risk of MI or sudden death by about 30% in patients with stable angina [8]. Current state of evidence favors the use of aspirin as the first-line agent for the majority of patients with vascular disease [9]. Although recommended by existing guidelines in diabetes, its efficacy appears to be substantially lower than in non-diabetic individuals [10]. Data on a role of aspirin among low-risk patients are inconsistent. In 2001, the first randomized controlled trial, PPP (the Primary Prevention Project) [11], conducted in men and women aged 50 years or more, provided the direct evidence of aspirin's efficacy in prevention of cardiovascular events such as angina, peripheral artery disease, and transient ischemic attacks (TIA) and demonstrated a reduction in the relative risk of death to 0.56 among individuals taking 100mg aspirin daily. Based on the meta-analysis of four primary prevention trials, including the

US Physicians' Health Study and the British Doctors' Trial, it has been concluded that the use of low-dose aspirin is safe and effective in subjects with coronary event risk of at least 1.5 % per year [12].

Both European and American guidelines recommend aspirin administration at a daily dose of 75 to 100mg in high-risk patients [13, 14]. In contrast, a small absolute benefit in terms of cardiovascular morbidity and mortality does not justify a routine use of aspirin among low- risk individuals, in whom potential protective effects could be offset by exposure of thousands of apparently healthy individuals to hemorrhagic complications, and in asthmatics to aggravation of their disease [14, 15]. The FDA has not approved aspirin for primary prevention of cardiovascular disease.

## Aspirin Resistance

Treatment failures occur with any drug and aspirin is no exception. Evidence is growing to indicate there are subpopulations that do not respond to the antithrombotic action of aspirin. The term 'aspirin resistance' has been used to describe a number of different phenomena, including inability of aspirin to: 1) protect against cardiovascular events despite its regular intake; 2) affect various laboratory tests, reflecting platelet activity. Research on aspirin resistance yielded interesting results in clinical pharmacology and pharmacogenetics [11, 16]. Future studies will show whether genotyping for polymorphisms might be of value in everyday clinical use of aspirin. Present data indicate that in survivors of recent myocardial infarction or unstable angina, patients receiving coronary artery bypass grafts, as well as in subjects with hypercholesterolemia, aspirin resistance has to be considered when implementing anti-thrombotic therapy (table 1). However, in individual patients the available laboratory tests are of no particular use to predict reliably the clinical outcome or to guide in making therapeutic decision. Prospective clinical trials seem necessary to reach such conclusions.

## Attempts to Develop a Better Aspirin

Although aspirin and other NSAIDs effectively relieve symptoms, such as pain, the relief comes at the expense of important side effects, most notably upper gastrointestinal toxicity and exacerbation of existing asthma [14, 15] (Fig. 3). So when in early 1990, it was discovered that there

TABLE 1. Possible mechanisms of aspirin resistance

*Reduced bioavailability*

- Poor compliance[20]
- Concurrent intake of certain NSAIDs[21]

*Enhanced platelet function*

- Hypercholesterolemia, usually accompanied by increased thrombin generation[22]
- Hypercoagulable states following MI[23] and unstable angina[24]
- Biosynthesis of $TXA_2$ by pathways that are not blocked by aspirin, e.g. by COX-2 in monocytes and macrophages[25]
- Increased release of platelets from bone marrow in response to stress, i.e. after coronary artery bypass surgery[25]
- Transcellular arachidonate metabolism between aspirinated platelets and endothelial cells[26]

*Genetic polymorphisms*

- Polymorphism of platelet glycoprotein IIb/IIIa; carriers of $PlA^2$ allele are less sensitive to anti-thrombotic action of aspirin in vivo[27,28]
- COX-2 variants in patients after coronary artery bypass surgery[29]

*Other factors*

- Smoking[30] or increased levels of noradrenaline (excessive physical exercise, mental stress)[31]

are two COXs, COX-1 and COX-2, coded by two different genes, an effort was made to design drugs that would inhibit specifically COX-2. Their development was based on the hypothesis that COX-2 was the source of prostaglandins $E_2$ which mediates inflammation, and that COX-1 was the source of the same prostaglandins in gastric epithelium, where they afford cytoprotection. Indeed, coxibs, as they came to be called, proved to be much safer on gastro-intestinal tract than aspirin and other NSAIDs; moreover, they were perfectly well tolerated by adult asthmatics in whom aspirin precipitated asthmatic attacks [17, 18]. Coxibs have been aggres-

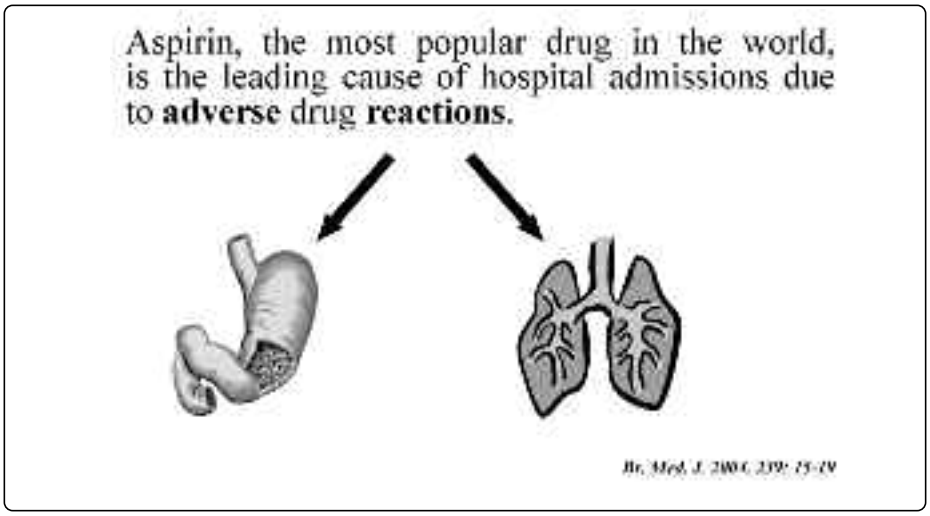


Fig. 3. Common side-effects of aspirin therapy: gastric ulcer and exacerbation of existing asthma.

sively marketed and have rapidly dominated the prescription-drug market for NSAIDs, accounting for worldwide sales of roughly $10 billion. However, in 2004, five years after its introduction, the leading coxib, rofecoxib (VIOXX), was withdrawn because its use was associated with unexpected but significant increase in myocardial infarction. The most likely explanation of this serious side-effect is that rofecoxib and probably other coxibs suppress the formation of prostacyclin in the endothelial cell of arteries, without affecting $TXA_2$ production in platelets. Thus, a single mechanism, depression of prostacyclin might be expected to elevate blood pressure, accelerate atherogenesis and predispose patients receiving coxibs to an exaggerated thrombotic response and to the rupture of an atherosclerotic plaque. How could it happen? Why did it take five years of the drug on the market to realize its dangerous side-effects? When the drug was introduced it was assumed that prostacyclin was derived mainly from COX-1 in endothelial cells. This assumption later proved incorrect, since studies in mice and humans showed that COX-2 was the dominant source [19]. The rofecoxib story also reflects poorly on the process that leads to drug approval [17].

SUMMARY

Slightly one hundred years after its introduction to therapy, aspirin remains the most popular drug in the world. Its medical indication have been increasing constantly, and now cover large areas beyond inflammation, including anti-thrombotic effects, and most recently anti-cancer activity. Yet, the recent story with coxibs teach us how careful we have to be in trying to improve actions of an extraordinary and well-known drug such as aspirin.

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