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Aspirin (I)

Discovery, Current and Potential New Therapeutic Uses, and Mechanism of Action*

Dong Han Kim**

Wyeth Research Laboratories, Philadelphia, U.S.A.

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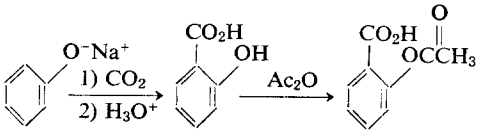
Aspirin is one of the oldest synthetic drugs and remains the most widely used medical agent. It is a household remedy effective in treating such common ailments as headache, minor muscular pain and fever. Aspirin is the drug of choice for rheumatic fever and arthritis which some five million Americans suffer. Lately it has been established by double-blind and randomized clinical studies that regular aspirin intake reduces the incidence of mild strokes and heart attacks.

Aspirin is produced by acetylation of salicylic acid with acetic anhydride using a small amount of sulfuric acid or pyridine as a catalyst. One tablet of ordinary aspirin preparation contains 300–400 mg of pure aspirin. At present salicylic acid is manufactured by carbonylation of the sodium or potassium salt of phenol with carbon dioxide under pressure and a high temperature (120–170°C).[1]

Orally ingested aspirin is rapidly absorbed in the stomach and upper small intestine. An apprecialbe plasma concentration is found in less than one-half hour after ingestion and



salicylic acid aspirin

reaches a maximum in about two hours, then fades away due to hydrolysis to salicylic acid. The most important factors controlling the rate of absorption when aspirin is ingested in tablet form are the dissociation characteristics of the formulation. The absorption of aspirin is known to occur via passive diffusion, primarily of the nondissociated lipid-soluble molecules across gastrointestinal membranes.[2]

There is little meaningful difference between the rate of absorption of aspirin and numerous buffered preparations. For example, in man the absorption half-time of unbuffered aspirin is about 30 minutes and for buffered aspirin it is about 20 minutes. The presence of food in the stomach delays the absorption.

In this paper an attempt will be made to summarize recent developments pertaining to the pharmacology of aspirin and its new

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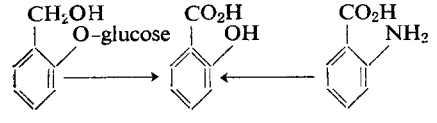
** All correspondence regarding this review should be addressed to Dr. D.H. Kim, 109 Oakford Circle, Wayne, Pa. 19087, U.S.A.

potential therapeutic uses. Also included is a brief historical survey of salicylic acid and aspirin, and current therapeutic uses of aspirin.

HISTORY[3,4]

The use of naturally occuring salicylates may be traced back to ancient days. Some 2,400 years ago, Hippocrates recommended the juice of the poplar tree for eye diseases and the leaves of the willow tree in childbirth. The use of plant salicylates as an antipyretic, however, was first reported in 1763 by Rev. E. Stone who treated malarial patients with a decoction of the bark of the white willow, thus relieving the feverish symptom. It took over sixty years until the active principle of the decoction was isolated and characterized. In 1829, Leroux isolated salicin in the pure state from willow bark, and Piria converted the salicin into salicylic acid in 1838. Gerland found that salicylic acid could be prepared by the action of nitrous acid on anthranilic acid. The current method for the preparation of salicylic acid was discovered by Kolbe in 1860.[5] In 1876, the synthetic salicylate was used first for the treatment of rheumatic fever by McLagan.[6] Aspirin was first prepared in 1853 by Gerhardt[7] who treated sodium salicylate with acetyl chloride, but forty more years passed until its therapeutic value was recognized.



salicin salicylic acid anthranilic acid

The discovery of acetyl salicylic acid as a therapeutic agent was one of chance. Hoffmann, a chemist associated with the Bayer Company at Elberfeld, Germany, gave some of the acetylsalicylic acid which he prepared to his father, who was suffering from rheumatoid arthritis, but was unable to stand the salicylic acid treatment because of severe stomach irritation. It was an extraordinary successful trial. Hoffmann reported the observation to the management of the Bayer Company which, after further study, introduced the agent to the market under the trade name "aspirin", a name adopted from the words "acetyl" and "spirsäure" (an old name for salicylic acid).

At the turn of this century the modern medical use of aspirin began. Witthauer[8] and Wohlgemut[9] in papers published in 1899, recommended its use as a substitute for sailcylic acid, citing its acceptable taste and decreased irritation of the stomach lining. In the following year, Witthauer reported its potent analgesic activity,[10] and thus the greatest use of aspirin became relief of pain, particulary muscular pain and headache.

THERAPEUTIC USES

Analgesic

As an analgesic aspirin relieves mild pain rapidly and effectively, and unlike morphine does not induce a physiologic dependence. Aspirin is especially effective for common pain such as headache, toothache, myalgia and arthraligia. Several clinical studies demonstrated that a dose of 600 mg. is preferable

to a 300 mg. dose, and a still greater result is obtained with 900 mg. Whereas the analgesic action of morphine occurs centrally, aspirin is known to work peripherally.[11]

Antipyretic

Aspirin lowers fever promptly. The antipyretic effect is accompanied by increased blood flow and sweating. Interestingly, the normaly body temperature is rarely affected by moderate doses. However, at a toxic dosage level aspirin causes a pyretic effect and heavy sweating, leading to dehydration.

Antirheumatic

Aspirin reduces the inflammation and pain in the joints of arthritic patients and permits increased mobility. In acute conditions it reduces fever as well. Although numerous new and novel antiinflammatory drugs have been introduced lately into medical practice, aspirin is still the drug of choice for the initial treatment of rheumatoid arthritis. Large daily doses (about 12 tablets) are used well dispersed throughout the day for extended periods of time. Aspirin does not alter the proliferative reaction but does suppress the acute exudative inflammatory process.

Colds

Most physicians recommend aspirin for common colds and upper respiratory infections. In such cases aspirin is used simply to comfort the patient by reducing fever and relieving headache and muscle aches. A recent double blind trial by Stanley *et al.*,[12] showed that in rhinovirus (RV 21 and RV 25) infections the overall benefit of aspirin intake was not statistically significant; aspirin treatment appeared rather to cause a highly significant increase in the rate of virus shedding and thus make cold sufferers more contagious. This finding, however, has been fervidly disputed by others, and further investigation is needed to resolve the question.

MECHANISM OF ACTION

Although aspirin has been used in medical practice for almost a century, no satisfactory explanation for its mechanism of action was offered until the turn of this decade. One of the appealing explanations proposed in the past was that aspirin works *via* interference with oxidative phosphorylation.[13] Recently, Collier called aspirin an "anti-defensive" drug and suggested that it may work by blocking the release of endogenous mediators of inflammation.[14] The newest and best theory so far regarding its mechanism of action has emerged mainly by virtue of the work carried out by Vane at the Royal College of Surgeons, London, not long ago. This work sheds new light in understanding its complex pharmacology on the molecular level.

In 1971, Vane and others concurrently discovered that aspirin and aspirin-like drugs inhibit an enzyme which catalyzes the synthesis of prostaglandins from their precursor, arachidonic acid.[15,16] This discovery was particularly important since prostaglandins had been shown to trigger inflammation. Prostaglandins are a family of lipid acids found in most mammalian tissues.[17] They behave as local hormones formed within tissue in response to some stimuli and they exert diverse physiologic effects, including inflam-

mation and fever.

The concentration of aspirin needed for the inhibition of prostaglandin synthesis was, importantly, well within the range of that found in the plasma of people who had taken normal doses of aspirin. Furthermore, Smith and Willis showed that platelets in the blood of volunteers who had taken aspirin can no longer produce prostaglandins.[18] Very recently, Kuehl *et al.*,[19] during a search for potential nonsteroidal antiinflammatory drugs, observed that MK-447 (2-aminomethyl-4-*t*-butyl-6-idophenon) exhibited good antiinflammatory activity when tested in rat foot edema. To their surprise, however, the compound failed to inhibit the synthesis of prostaglandins; rather it stimulated overall prostaglandin synthesis when tested in a microsomal preparation derived from ram seminal vesicles. This intriguing observation led these investigators to conclude that rather than the primary prostaglandins (PGE_2 and PGF_2), prostaglandin G_2 (PGG_2), an unstable intermediate in the biosynthesis of prostaglandin (see later discussion), is the major causative factor of inflammation.[19]

Aspirin works by blocking the formation of the endoperoxide PGG_2 through interference with an enzyme which catalyzes its formation from arachidonic acid, whereas MK-447 alleviates the inflammatory symptom through elimination of the endoperoxide PGG_2 by

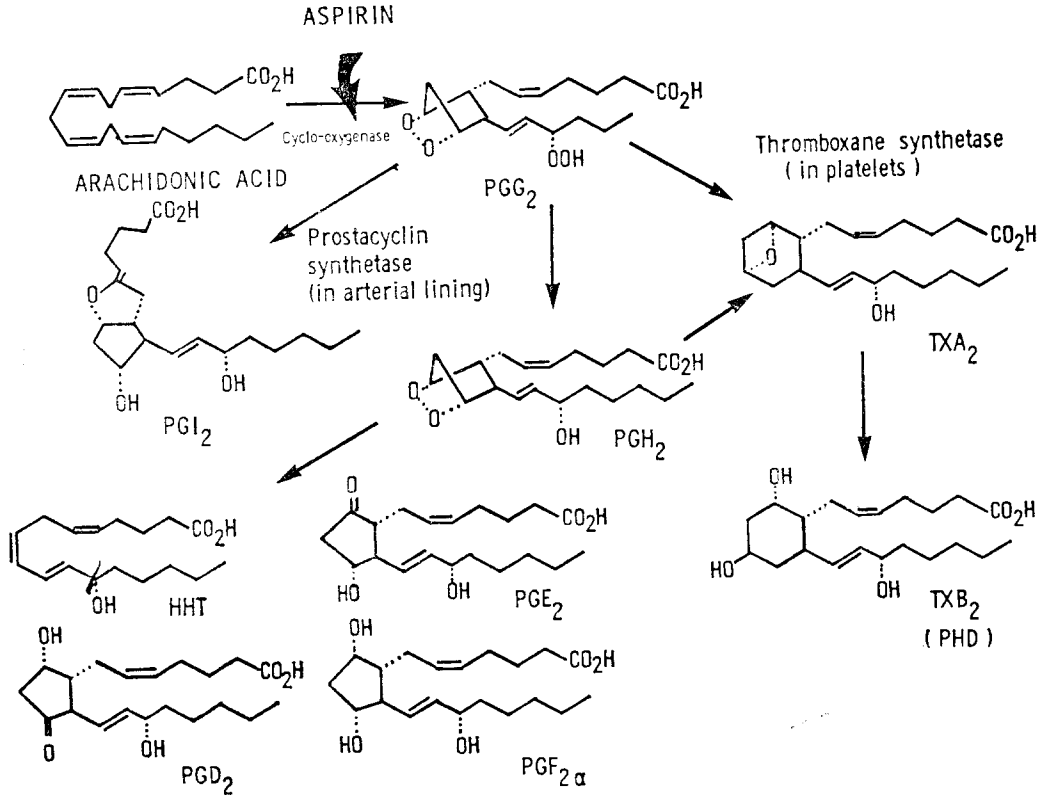


Fig. 1: Biologically important transformations of arachidonic acid.

facilitating its conversion into the primary prostaglandins[19] (see Fig 1).

Prostaglndins have been reported to cause headache and overt pain on intravenous infusion or intramuscular injection, lending support to the hypothesis that the inhibition of prostaglndin biosynthesis is linked to the analgesic effect of aspirin. At the beginning, however, the attempted explanation of aspirin's analgesic effect in terms of prostaglandin synthesis met some difficulties, as prostaglandins failed to produce much pain when injected intradermally unless given in abnormally high concentration.

Ferreira[20] discovered that slow subdermal infusion of prostaglandin E_1 (PGE_1) into the volar surface of the arms of volunterrs in concentrations as weak as those found at the site of an inflammation reaction caused a long lasting hyperalgesia (pain elicited when only slight pressure is applied to the infusion area) and increase in pain sensitivity to chemical stimuli such as histamine or bradykinin. The hyperalgesia was dependent not only on the concentration infused but also on the duration of infusion. The pain of gradually increasing intensity, developed when histamine, and particularly bradykinin was infused into the hyperalgesic site caused by an infusion of PGE_1. Ferreira then suggested that the hyperalgesia might be due to a sensitization of the pain receptors: Prostaglandins sensitize pain receptors such as afferent nerve endings to the algesic action of endogenous pain-producing substances, i.e., histamine or bradykinin and to mechanical stimuli. Aspirin blocks the synthesis of prostaglandins and thus prevents the sensitization action on the pain receptors.[21]

Even before Vane discovered that aspirin inhibits prostaglandin biosynthesis, Milton and Wendlandt, in 1970, hypothesized that pyrogens (the causative agents of fever) might produce fever by causing the release of prostaglandins especially PGE_1, and that antipyretic drugs might work by preventing the release of PGE_1.[22] The speculation was based on the following observations: The fever produced by the intracerebral injection of pyrogen into a conscious cat was abolished by the antipyretic agent 4-acetaminophenol; and when PGE_1 was injected into the third ventricle of a cat in a very minute amount, the body temperature rose immediately in dose-dependdent fashion, but the fever thus produced was not affected by the antipyretic.[23] The observation was soon confirmed by Feldberg and Saxema who noticed the hyperthermia produced is sustained for only as long as the infusion lasts; moreover, they found that the site of action of the prostaglandin is the preoptic area of the anterior hypothalamus, the area of the brain considered to be the center for thermoregulation.[24]

It is now generally accepted that aspirin and aspirin-like durgs produce their antipyretic effects by inhibiting the endogenous formation of prostaglandins, especially PGE_1 caused by pyrogens.[25,26]

In 1969, by using new assay methods, Piper and Vane[27] discovered that anaphylaxis of islolated perfused lungs of guinea pigs caused release of a new unstable compound and its releasing factor, along with other known

chemical mediators. Since the new substance had a strong rabbit aorta-contracting property, they called it RCS (rabbit aorta-contracting substance). RCS-releasing factor (RCS-RF), which was much more stable, induced the release of RCS when injected into the pulmonary artery of perfused lungs from unsensitized guinea pigs. These investigators also discovered that the release of RCS was impaired by aspirin and aspirin-like drugs.[27] Subsequently, Gryglewski and Vane observed that the release of RCS is decreasing as prostaglandin generation increases when slices of rabbit spleen was stimulated mechanically. This observation led them to suggest that RCS may be an unstable intermediate in the biosynthesis of prostablandins.[21] Recently, RCS-RF was shown to be a small peptide.[28]

A cyclic endoperoxide had been postulated as early as 1965 by Samuelsson as an intermediate in the prostaglandin biosynthesis from arachidonic acid.[29] Independently, in 1973, Hamberg and Samuelsson[30,31] and Nugteren and Hazelhof,[32] succeeded in the isolation and characterization of two unstable intermediates, i.e., prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2).[33] Both endoperoxides exert pronounced biologic effects. As described earlier, PGG_2 and PGH_2 were found to have an extremely potent platelet-aggregation property in the concentrations of 10–300 ng/ml., and were released in similar concentrations during aggregation of platelets by thrombin. The first intermediate (PGG_2) was three times more potent than PGH_2 as a platelet aggregation. Consequently the antiaggregation property of aspirin is considered to be due to its inhibitory effect on the endoperoxide formation from arachidonic acid.[34,35]

The endoperoxides were found to transform to a variety of stable compounds, depending on the enzymes present and the conditions of the medium. Whereas the endoperoxides were converted into prostaglandin E_2 in a nearly quantitative yield by the enzyme present in a sheep vesicular gland homogenate, biologically inactive prostaglandin D was the main product formed by the enzyme present in the supernatant of many rat tissues.[32] PGG_2, generated upon the aggregation of washed platelets by thrombin, was metabolized almost exclusively to the biologically inactive nonprostaglandin substances, HHT and TXB_2, and only to a small extent to the classical PGE_2 and PGF_2.[36,37]

Initially, it seemed that the properties of the endoperoxides could account for the activity of RCS of Piper and Vane, but a careful comparison of the properties of the two materials, especially of the breakdown rates, made this identity less likely. The half-life of the endoperoxides in aqueous medium (ca. 5 minutes) was considerably longer than that of RCS. Thus, in addition to the endoperoxides there appeared to be at least one more biologically active intermediate in the prostaglandin synthesis. Indeed, in 1975, Hamberg *et al.*[38] discovered that the breakdown of PGG_2 to stable PHD goes through an unstable, biologically active oxane intermediate (see Fig. 1). They proposed "thromboxanes" as the name for this new group of compounds on the basis of their thrombus formation property and

basic chemical structure, oxane. The unstable intermediate is called thus thromboxane A_2 (TXA_2) and the stable metabolite previously called PHD is then called thromboxane B_2 (TXB_2). TXA_2 had a $t_{1/2}=34$ seconds (in aqueous solution) and showed a potent platelet-aggregating activity and rabbit aorta contracting effect. It is a much more potent inducer of platelet-aggregation than the endoperoxide. These properties of TXA_2 resembled very closely the properties of RCS of Piper and Vane, and it was concluded that the activities of RCS is mainly due to TXA_2.[38] An enzyme which is responsible for the generation of TXA_2 from the endoperoxides was subsequently isolated from the human platelet microsome. Subsequently, Needleman *et al.* claimed that the potent vasoconstricting property of the thromboxanes could be dissociated from the capacity to produce platelet aggregation; the primary physiological function of TXA is presumably its potent localized vasoconstricting property which enhances hemostasis, primarily by sharply reducing the blood vessel lumen, and perhaps secondarily by augmenting aggregation.[39]

Very lately a new type of unstable prostaglandin named prostacyclin (PGI_2) was discovered by the Vane's group.[40] Prostacyclin is synthesized from PGG_2 in blood vessel linings, and has the property of counteracting TXA_2 action, i.e., it prevents or reverses platelet aggregation and relaxes blood vessels.[40] PGI_2 is the most potent platelet-aggregation inhibitor known today.

As described earlier aspirin inhibits prostaglandin biosynthesis through interference with the cyclo-oxygenase responsible for the formation of PGG_2.[31,37] Using radioactive aspirin labeled in the acetyl moiety, Roth *et al.*, showed that aspirin inactivates the cyclo-oxygenase by irreversible acetylation presumably on an amino group at the active site. The particulate acetylation took place within minutes (*ca.* 20) at a concentration in the micromolar range (30 M) which is accessible with an oral dose of aspirin as low as 150 mg. Arachidonic acid, the substrate of the cyclo-oxygenase, was shown to compete with aspirin for the enzyme and to inhibit the acetylation reaction. Other cyclo-oxygenase inhibitors, including the fatty acid analogs and indomethacin, inhibit the enzyme activity and acetylation reaction in parallel.[41,42,43] It was also shown by them that the acetylation may depend upon an essential functional group or conformation of groups in the peptide chains of the oxygenase enzyme.[43]

NEW POTENTIAL THERAPEUTIC USES

As the mechanism of action of aspirin is being uncovered, other discoveries are being made of new therapeutic uses of the drug.

Bartter's syndrome is an disorder characterized by hypokalemia, hyperreninemia, and hyperaldosteronism, the treatment of which has been largely unsatisfactory. It has been suggested that overproduction of renal prostaglandins is of pathophysiologic importance. Lately Norby *et al.*, reported the successful treatment of a patient with this disorder by giving aspirin at a dose of 100 mg/day for 3

months.[44]

In 1971, it was postulated that cholera toxin might act by releasing prostaglandins,[45] and since then several animal studies have showed that the cholera-toxin-induced secretion can be inhibited by aspirin when given before, with, or immediately after toxin.[46,47] However, the therapeutic efficacy of aspirin in cholera is thought to be poor.

Patent ductus arteriosus is a congenital anomaly which is relatively common in preterm infants and requires early surgical treatment.[48] Recently it was found that prostaglandins play an important role in keeping the ductus arteriosus open by relaxing ductal musculature, and it was suggested that such anomalous openings of ductus arteriosus in premature babies might be closed by a prostaglandin synthesis inhibitor.[49,50] Indeed, Heymann *et al.*, have reported successful treatment of preterm infants with patent ductus arteriosus by administration of aspirin or indomethacin.[51]

PROPHYLATIC EFFECT AGAINST STROKE AND MYOCARDIAL INFARCTION

Aspirin inhibits platelet aggregation and prolongs bleeding time. The effect lasts for several days. Zucker and Peterson[52] and O'Brien[53] showed that aspirin exerts the antiaggregation effect through preventing the release of endogenous ADP from platelet granules, thereby inhibiting collagen-induced platelet aggregation (secondary aggregation). Recently Smith *et al.*, proposed that the release of ADP may be induced by an endoperoxide intermediate most likely PGG_2 in the prostaglandin synthesis. Later study by Smith *et al.*, however, showed that the endoperoxides and thromboxanes can cause aggregation of normal human platelets without secretion of ADP.[54]

As discussed earlier, thromboxane A_2 (TXA_2), formed in platelets has platelet aggregation property, whereas prostacycline (PGI_2) which is known to be synthesized in vascular tissues shows the opposite effect. Under normal hemostatic conditions there exists a delicate balance between the two opposing prostaglandins. Inhibition of TXA_2 synthesis might be expected to cause an antithrombic effect, and prohibition of PGI_2 synthesis in the vascular vessel wall would bring about thromboembolic events. Consequenly a question arises as to the possible effectiveness of aspirin as an antithrombic agent, for aspirin is known to inhibit the first stage of the prostaglandin synthesis, i.e., the formation of prostaglandin G_2 which serves as the common intermediate for TXA_2 and PGI_2, and thus block the formation of both the PGI_2 and TXA_2. In order to answer this perplexing question, Livio, *et al.*,[55] investigated the relative prostaglandin inhibitory activities of aspirin in different parts of the body. They found that in rats the prostaglandin synthesis is inhibited for longer in platelets than it is in vascular tissues. It took approximately 120 hours for platelets to recover their TXA_2 synthetic activities, after given a single intraperitoneal dose of aspirin (200 mg/Kg). The PGI_2-like activities were returned to normal

within 24 hours in arterial vascular tissues.[55]

Atherosclerosis is a major cause of potentially fatal myocardial and cerebral infarction, and it is believed that platelets play a major role in the initiation and growth of thrombosis in arteries. The potential benefit of aspirin as a prophylaxis of the arterial thrombosis thus became obvious. Accordingly, many doctors started to prescribe aspirin for cardiac patients. In a variety of animal models aspirin was effective in preventing arterial thrombosis.

Elwood *et al.*[56] tested over one thousand recent myocardial infarction patients by administering a single daily dose of 300 mg. of aspirin. The results of this study were inconclusive. Patients who took aspirin had a mortality rate of 8.3% compared with 10.9% for those taking placebo; the difference is not statistically significant. The aspirin-taking group, nevertheless, had a reduction in mortality of 12% at 6 months, and 25% at 12 months after admission to the trial.

Lately, the well designed Canadian Cooperative Study[57] headed by Barnett presented the definitive conclusion that aspirin taken regularly four tablets a day can reduce substantially the risk of stroke in men experiencing transient ischemic attacks (TIA). Transient cerebral ischemic attacks are not serious in themselves since, by definition, they cease spontaneously within 24 hours. Their importance lies in the fact that they often given warning of an impending stroke. It is believed that about a third of the TIA patients will have stroke most probably within a couple of months after the first TIA incidence. Five hundred and eighty five patients with threatened stroke were involved in the study. In a randomized clinical trial, they were examined for an average of 26 months. The study showed that aspirin reduces the risk of continuing ischemic attacks, stroke, or death by 19% compared with a control group given placebo, and the risk of major stroke or death was reduced by 31% compared with controls. The favorable effect of aspirin was found to be sex dependent: thus among men, the risk reduction for stroke or death was as high as 48%, whereas no significant trend was observed among women. The result on the sex dependent was not totally unexpected, for Harris, *et al.*[58] also reported recently that only men showed a beneficial response to aspirin in the prevention of thromboembolism after total hip replacement.

The favorable prophylactic value of aspirin against mild stroke were also reported lately by Fields, *et al.*[59] who randomly allocated 178 patients who had carotid transient ischemic attack to aspirin or placebo and followed to determine the incidence of subsequent TIAs, death, cerebral infarction or retinal infarction. This study revealed that the aspirin treatment is significantly favorable for patients with a history of multiple TIAs, and most evident in those individuals having carotid lesions appropriate to the TIA symptoms.[59]

In the case of deep vein thrombosis, some early studies appeared to be encouraging, but an extensive double blind, randomized trial carried out by the British Medical Research Council involving some 300 patients failed to show significant difference between the treated and placebo groups.[60]

ASPIRIN AND LABOR

In 1972, Aiken observed that aspirin or indomethacin prolongs parturition in rats. Furthermore, female rats treated with indomethacin or aspirin showed excessive bleeding during parturition and there was a high incidence of fetal mortality. At the same time uterine prostaglandin production and motility were decreased. When aspirin was added to a tissue bath containing spontaneously contracting uterine smooth muscle from a 20 day pregnant rat, the contractions were diminished and prostaglandin release into the bath was reduced. Aiken attributed the fetal deaths to a reduced ability to expel the fetus due to decreased uterine motility resulting from diminished release of prostaglandins.[61] In the same year, Chester *et al.*, reported that the onset of parturition in rats was delayed by aspirin and other non-steroidal anti-inflammatory agents.[62]

Prostaglandins play an important role in the initiation of normal labor at term and in the pathogensis of premature labor.[63] In 1967, Karim and Devlin found $PGF_{2\alpha}$ in the amniotic fluid of women, but only during labor.[64] This discovery was confirmed by many researchers.[65,66,67] Hamberg, by measuring the levels of 5α, 7α-dihydroxy-11-ketotetranorprostane-1, 16-dioic acid, the major urine metabolite of both $PGF_{1\alpha}$ and $PGF_{2\alpha}$ in three pregnant women showed that the prostaglandin synthesis increased steadily as the pregnancies progressed with maximum towards the end of pregnancy, then fell abruptly to the pre-pregnancy level.[68]

Prolongation of gestation as well as prevention of the normal initiation of parturition was observed when indomethacin was administered to rhesus monkeys in the last week of pregnancy.[69] Conversely, in cases of premature labor rectal or oral administration of indomethacin postponed deliveries until greater fetal maturity could be achieved.[70,71]

A retrospective survey carried out by Lewis and Schulman of 103 women who had taken high doses of aspirin during the later stage of pregnancy showed a striking increase in frequency of postmaturity, a nearly 70% longer duration of labor and a significantly increased loss of blood at delivery compared to controls.[72] This and other studies indicated that aspirin ingestion in the later stage of pregnancy is potentially hazardous.

SIDE EFFECTS AND TOXICITY

Two kinds of gastrointestinal problems due to aspirin have been realized. The first is dyspepsia, which is common but only rarely leads to peptic ulceration. The much more common and probably most serious side effect associated with aspirin is damage to the gastric system. It has been shown that even a single aspirin tablet may lead to development of a small focal erosion on direct contact with the gastric mucosa. Some 60–70% of the people who take 1–3 grams of aspirin daily are known to experience gastrointestinal blood loss in amounts of 2–6 ml. daily. People with gastrointestinal problems should be cautious in using aspirin. Other non-steroidal antiinflammatory drugs such as phenylbutz-

zone and indomethacin have other side effects that mitigate against their long-term use in the treatment of arthritic conditions. It has been shown that concurrent administration of antacids such as sodium bicarbonate with aspirin possibly reduce the gastric damage significantly.

Aspirin intake along with alcohol causes much greater damage than the injury produced by aspirin along;[73,74,75] accordingly, it is not advisable to take aspirin after an alcohol intake. Even effervescent aspirin preparation, which is known to cause much less bleeding than plain aspirin alone, may be harmful when taken after excessive drinking for relief of alcohol hangover.[76]

To minimize the gastrointestinal irritation any aspirin tablet should be taken with a full glass of water. The large amount of water enhances the absorption of aspirin from the stomach by making it available in dissolved form. Aspirin is rather poorly soluble in water (3.3. g. of aspirin per liter of water).

Studies in rats indicated that gastric irritancy is primarily associated with the carboxylic acid group in case of aspirin.[77] Although the occurrence of gastric damage by aspirin was known about the same time as when it was introduced to clinical use, it in only within the last few years that some knowledge of its possible mechanism have been acquired. The process of the development of chronic ulcer is far more poorly understood, and remains the subject of further study. The recent development in the biochemical pathology of aspirin-induced gastric damage has been reviewed lately by Rainsord.[78] Although animal experiments showed that under prolonged oral administration, aspirin develops tolerance to the initial gastric erosion, leading to a complete recovery,[79,80,81] no such tolerance development was observed in human studies.[82]

Its ready availability and the misconception that aspirin is a harmless household remedy have resulted in numerous incidents of aspirin intoxication due to overdose. Mild, chronic intoxication (salicylism), which develops upon repeated administration of large doses, consists of headache, dizziness, tinnitus, difficulty in hearing, dimness in vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomitting and occasional diarrhea, and may even lead to convulsions and coma upon further intoxication. Epigastric distress and occasional abdominal pain are also experienced. These symptoms serve as a useful warning that the dosage given must be reduced. Direct stimulation of the respiratory center and the hyperventilation that follows leads to alkalosis. At this stage the urine is alkaline. With increasing toxicity there is direct poisoning of the cells, particularly of the liver and kidneys with loss of glycogen, increased cellular metabolic rate, and a number of other changes which affect acid base balance as well as disturbing the regulatory function of the kidney itself.

In acute intoxication due to accidental overdose, hyperthermia and dehydration are the immediate threats to life, and the initial therapy should be directed toward their correction and to the maintenance of adequate renal function. External sponging with luke-

warm water should be applied quickly to any child whose rectal temperature reads over 104°F resulting from accidental overdose of aspirin. Adequate amounts of intravenous fluids must also be given promptly. Emergency hospitalization is strongly advised.

About 0.2–0.9% of the general population is known to show acute allergic responses to aspirin. People who have a history of allergic disease, especially asthma and nasal polyps, are prone to exhibit a hypersensitivity response. Attacks are often precipitated by even minute amount of aspirin. Skin rashes and anaphylactic phenomena such as angioedema and asthma are common. Death may even occur within minutes after ingestion of the drug unless appropriate measures are instituted immediately. The cause of the anaphylaxis is not known and it cannot be predicted by an *in vitro* test. Interestingly, no such allergic reactions are experienced when sodium salicylate, salicylic acid ester, or choline salicylate are given to people who are sensitive to aspirin.

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